REPORT NO.
72

PARLIAMENT OF INDIA
RAJYA SABHA

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE

SEVENTY-SECOND REPORT

On

ALLEGED IRREGULARITIES IN THE CONDUCT OF STUDIES USING HUMAN PAPILLOMA VIRUS (HPV) VACCINE BY PATH IN INDIA

(DEPARTMENT OF HEALTH RESEARCH, MINISTRY OF HEALTH AND FAMILY WELFARE)

(*Presented to the Rajya Sabha on* 30th August, 2013)

(*Laid on the Table of Lok Sabha on 30th August*, 2013)

Rajya Sabha Secretariat, New Delhi
August, 2013/Bhadra, 1935 (SAKA)

PARLIAMENT OF INDIA

RAJYA SABHA

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE

SEVENTY-SECOND REPORT

On

ALLEGED IRREGULARITIES IN THE CONDUCT OF STUDIES USING HUMAN PAPILLOMA VIRUS (HPV) VACCINE BY PATH IN INDIA

(DEPARTMENT OF HEALTH RESEARCH, MINISTRY OF HEALTH AND FAMILY WELFARE)

(*Presented to the Rajya Sabha on* 30th August, 2013)

(*Laid on the Table of Lok Sabha on* 30th August, 2013)

ON HEALTH AND FAMILY WELFARE

Rajya Sabha Secretariat, New Delhi
August, 2013/Bhadra, 1935 (SAKA)

CONTENTS

*to be appended at printing stage

COMPOSITION OF THE COMMITTEE
(2009-10)

RAJYA SABHA

1. Shri Amar Singh - **Chairman**
2. Shrimati Viplove Thakur
3. Dr. Radhakant Nayak
4. Shri Janardan Dwivedi
5. Shri Balbir Punj
6. Dr. Prabhakar Kore
7. Shrimati Brinda Karat
8. Shrimati Vasanthi Stanley
9. Dr. M.A.M. Ramaswamy
10. Dr. Anbumani Ramadoss

LOK SABHA

11. Shri J. M. Aaron Rashid
12. Shri Ashok Argal
13. Shrimati Sarika Devendra Singh Baghel
14. Shri Vijay Bahuguna
15. Dr. Chinta Mohan
16. Shrimati Tabassum Hasan
17. Dr. Sanjay Jaiswal
18. Shri S. R. Jeyadurai
19. Dr. (Shrimati) Kruparani Killi
20. Shri N. Kristappa
21. Dr. Tarun Mandal
22. Shri Datta Meghe
23. Dr. Jyoti Mirdha
24. Shrimati Jayshreeben Patel
25. Shri R.K. Singh Patel
26. Shri M. K Raghavan
27. Dr. Anup Kumar Saha
28. Shrimati Meena Singh
29. Dr. Arvind Kumar Sharma
30. Shri Pradeep Kumar Singh
31. Shri Ratan Singh

SECRETARIAT

Shrimati Vandana Garg	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Committee Officer

COMPOSITION OF THE COMMITTEE
(2010-2011)

RAJYA SABHA

1. Shri Brajesh Pathak **- Chairman**
2. Shri Janardan Dwivedi
3. Shrimati Viplove Thakur
4. Dr. Vijaylaxmi Sadho
5. Shri Balbir Punj
6. Dr. Prabhakar Kore
@7. Shrimati Brinda Karat
8. Shrimati Vasanthi Stanley
9. Shri Rasheed Masood
*10. Shrimati B. Jayashree

LOK SABHA

11. Shri Ashok Argal
12. Shrimati Sarika Devendra Baghel Singh
13. Shri Vijay Bahuguna
14. Shrimati Tabassum Hasan
15. Dr. Sanjay Jaiswal
16. Shri S. R. Jeyadurai
17. Dr. Kruparani Killi
18. Shri Nimmala Kristappa
19. Dr. Tarun Mandal
20. Shri Datta Meghe
21. Dr. Jyoti Mirdha
22. Dr. Chinta Mohan
23. Shrimati Jayshreeben Patel
24. Shri R.K. Singh Patel
25. Shri M. K Raghavan
26. Shri J. M. Aaron Rashid
27. Dr. Anup Kumar Saha
28. Dr. Arvind Kumar Sharma
29. Shrimati Meena Singh
30. Shri Pradeep Kumar Singh
31. Shri Ratan Singh

SECRETARIAT

Shrimati Vandana Garg, Additional Secretary
Shri R.B.Gupta, Director
Shrimati Arpana Mendiratta, Joint Director
Shri Dinesh Singh, Assistant Director
Shri Satis Mesra Committee Officer

***** nominated to the Committee w.e.f 21/9/2010.
@ceased to be a member w.e.f 18th August, 2011.

COMPOSITION OF THE COMMITTEE
(2011-12)

RAJYA SABHA

1. Shri Brajesh Pathak - Chairman
*2 Shri Janardhan Dwivedi
%3. Shrimati Viplove Thakur
4. Dr. Vijaylaxmi Sadho
5. Shri Balbir Punj
6. Dr. Prabhakar Kore..
7. Shrimati Vasanthi Stanley
^ 8. Shri Rasheed Masood
9. Shrimati B. Jayashree
10. Shri Derek O'Brien

LOK SABHA

11. Shri Ashok Argal
&&12. Shrimati Harsimrat Kaur Badal
@ 13. Shri Vijay Bahuguna
14. Shrimati Raj Kumari Chauhan
15. Shrimati Bhavana Gawali
16. Dr. Sucharu Ranjan Haldar
17. Dr. Monazir Hassan
18. Dr. Sanjay Jaiswal
19. Shri S. R. Jeyadurai
20. Shri P. Lingam
21. Shri Datta Meghe
22. Dr. Jyoti Mirdha
23. Dr. Chinta Mohan
24. Shri Sidhant Mohapatra
25. Shrimati Jayshreeben Kanubhai Patel
26. Shri M. K Raghavan
27. Shri J. M. Aaron Rashid
28. Dr. Arvind Kumar Sharma
29. Shri Radhe Mohan Singh
30. Shri Ratan Singh
31. Dr. Kirit Premjibhai Solanki

SECRETARIAT

Shrimati Vandana Garg	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Deputy Director

***** ceased to be a Member w.e.f 27th January, 2012 and re-nominated to the Committee on 2nd February, 2012
% Vacant vide resignation w.e.f. 2nd April, 2012.
^ Vacant vide resignation w.e.f 9th March, 2012 and renominated as Member w.e.f 04th May, 2012 and Member of Sub Committee II on CGHS W.E.F. 01st June,2012.
&& ceased to be a member w.e.f 29th June, 20112
@ vacant vide resignation w.e.f. 30th April, 2012

COMPOSITION OF THE COMMITTEE ON HEALTH AND FAMILY WELFARE
(2012-13)

RAJYA SABHA

1.	Shri Brajesh Pathak	-	**Chairman**
2.	Dr. Vijaylaxmi Sadho		
*3.	Dr. K. Chiranjeevi		
4.	Shri Rasheed Masood		
5.	Dr. Prabhakar Kore		
6.	Shri Jagat Prakash Nadda		
7.	Shri Arvind Kumar Singh		
&8.	Shri D. Raja		
9.	Shri H. K. Dua		
10.	Shrimati B. Jayashree		

LOK SABHA

@11.	Shri Ashok Argal
12.	Shri Kirti Azad
13.	Shri Mohd. Azharuddin
14.	Shrimati Sarika Devendra Singh Baghel
15.	Shri Kuvarjibhai M. Bavalia
16.	Shrimati Priya Dutt
17.	Dr. Sucharu Ranjan Haldar
18.	Mohd. Asrarul Haque
19.	Dr. Monazir Hassan
20.	Dr. Sanjay Jaiswal
21.	Dr. Tarun Mandal
22.	Shri Mahabal Mishra
23.	Shri Zafar Ali Naqvi
24.	Shrimati Jayshreeben Patel
25.	Shri Harin Pathak
26.	Shri Ramkishun
27.	Dr. Anup Kumar Saha
28.	Dr. Arvind Kumar Sharma
29.	Dr. Raghuvansh Prasad Singh
30.	Shri P.T. Thomas
#31.	Shri Chowdhury Mohan Jatua

SECRETARIAT

Shri P.P.K. Ramacharyulu	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Deputy Director
Shri Pratap Shenoy	Committee Officer

---

* ceased to be Member of the Committee w.e.f. 28th October, 2012.
@ ceased to be Member of the Committee w.e.f. 9th January, 2013.
# nominated as a Member to the Committee w.e.f. 14th December, 2012.
& ceased to be Member of the Committee w.e.f. 24th July, 2013..

PREFACE

I, the Chairman of the Department-related Parliamentary Standing Committee on Health and Family Welfare, having been authorized by the Committee to present the Report on its behalf, do hereby present this Seventy-Second Report of the Committee on the "Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health(PATH) in India.

2. The Committee first took up the issue about the trial of HPV vaccine on the children in Khammam district of Andhra Pradesh and Vadodra district of Gujarat and reported deaths of the children therefrom in its meeting held on 06th April, 2010 during the course of examination of Demands for Grants (2010-11) of Department of Health Research and sought exact status in this regard from the Secretary, Department of Health Research. Subsequently, taking serious view of the procedural and ethical lapses on the part of the Ministry, the Committee sought the matter of allowing trial of the vaccine as also the approval for its marketing in the country to be enquired into. The Committee also desired the Ministry to take further appropriate action in the matter and apprise it of the follow-up action taken in this regard at the earliest. As a sequel to the Committee's recommendation, a Committee was appointed by the Government of India to enquire into"Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health (PATH) in India on 15th April,2010. The Final Report of the Committee appointed by the Government of India to enquire into"Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health(PATH) in India was made on 15th February,2011.

3. The Committee thereafter deliberated on the subject in its meetings held on 25th July, 2011 and 24th May, 2013.

4. During the course of examination of the subject, the Committee heard the views of the Secretary, Department of Health Research and other officials of the Department on 25th July,2011 and Secretary, Department of Health Research and Drug Controller General of India(DCGI) on 24th May, 2013.

5. During the finalization of its Report, the Committee relied upon the following documents/papers:-

(i) Background note received from the Ministry;

(ii) Final Report of the Committee Appointed by the Government of India to enquire into"Alleged Irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine" by Programme for Appropriate Technology in Health(PATH) in India;

(iii) Oral Evidences tendered by Secretary, Department of Health Research and DCGI; and

(iv) Replies to the questionnaires received from the Department of Health Research.

6. The Committee considered the Draft Report and adopted the same in its meeting held on 29th August, 2013.

7. For facility of reference and convenience, observations and recommendations of the Committee have been printed in bold letters in the body of the Report.

NEW DELHI;
29th August, 2013
Bhadra7, 1935 (Saka)

Brajesh Pathak
Chairman,
Department-related Parliamentary
Standing Committee on Health and Family Welfare

ACRONYMS

1. AE- Adverse Event.
2. AEFI- Adverse Event Following Immunization.
3. ANM- Auxiliary Nurse Midwife.
4. AP- Andhra Pradesh.
5. AIIMS- All India Institute of Medical Sciences
6. CDSCO-Central Drugs Standard Control Organisation.
7. CTRI- Clinical Trials Registry- India.
8. CORT- Centre for operations Research and Training
9. DCGI- Drug Controller General of India.
10. DG, ICMR- Director General, Indian Council of Medical Research
11. FCRA-Foreign Currency Regulation Act
12. FERA- Foreign Exchange Regulation Act
13. FEMA- Foreign Exchange Management Act
14. GCP-Good Clinical Practice
15. GAVI- Global Alliance for Vaccines and Immunization
16. MEA-Ministry of External Affairs
17. MHA- Ministry of Home Affairs
18. HPV- Human Papilloma Virus.
19. HMSC- Health Ministry Screening Committee
20. ICMR- Indian Council of Medical Research.
21. MoU- Memorandum of Understanding.
22. MEA-Ministry of External Affairs
23. MHA- Ministry of Home Affairs
24. NGO- Non-Governmental Organization
25. NTAGI- National Technical Advisory Group on Immunization
26. O&G- Obstetrics and Gynaecology
27. PATH-Programme for Appropriate Technology in Health.
28. PBC-Public Benefit Corporation
29. ROC- Registrar of Companies
30. RBI- Reserve Bank of India
31. SAE- Serious Adverse Event.
32. UIP- Universal Immunization Programme.
33. USFDA-United States Food and Drug Administration

REPORT

I. BACKGROUND

1.1 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.

1.2 Several questions were asked and concerns expressed in the media and well meaning quarters on the role of government agencies including Indian Council of Medical Research (ICMR) and Drugs Controller General of India (DCGI) in approving and facilitating the trials, which was against all laws of the land and even international ethical norms and rules; misuse of government funds, man-power, facilities and infrastructure for a private project of dubious nature; use of logo of National Rural Health Mission (NRHM), an official programme of the Union Government during these vaccination drives to give it respectability and official endorsement; and above all the blatant violation by PATH of all regulatory and ethical norms laid down by the Government of India for the purpose as also possible violations of such norms prescribed and very scrupulously enforced in the Country of its origin *viz.* United States of America.

1.3 Taking cognizance of these reports, the Committee (2009-10) which was examining the Demand for Grants (2010-11) of the Department of Health Research at that point of time sought a detailed clarification from the Government in the matter. In response the Secretary of the Department of Health Research and DG, ICMR informed the Committee that it was a vaccine against the Human Papilloma Virus which causes cervical cancer in women. The Drugs Controller General, India had given approval for marketing of HPV vaccines in India as a vaccine to be prescribed by the clinicians as per schedule 'Y' of the Drugs and Cosmetics Rules and then for a post-marketing surveillance trial. The Committee was informed that the proposal for trial came two years earlier (though later on during the

Committee's examination it was proved that it began in 2006) before the ICMR through PATH, an American agency, and the logic for allowing the trial was to see acceptability of this vaccine on Indian population. Besides, these trials were approved by the National Ethical Committee and the State Ethical Committee.

1.4 Attention of the Secretary was drawn to DCGI guidelines wherein Phase III trials cannot be conducted on children until a similar trial was conducted on adults. It was admitted by the Secretary that the DCGI guidelines were not adhered to in the present case but this vaccine is given before the sexual activity begins and then it protects against cancer. That was the reason for allowing trials on girls of the age of 10-14 years. The Committee was assured that State Governments of Andhra Pradesh and Gujarat would be asked to get the ongoing clinical trial stopped immediately.

1.5 Hugely perturbed by these blatant violations, the Committee in its Forty first Report on Demands for Grants (2010-11) of the Department of Health Research made the following recommendations on this issue:

> "Taking serious view of procedural and ethical lapses on the part of the Ministry, the Committee sought the matter of allowing trial of the vaccine as also the approval for its marketing in the country to be enquired into by a premier investigating agency and to take further appropriate follow-up action in the matter. It also asked that findings of the investigating agency and the follow-up action taken in this regard may be furnished to the Committee at the earliest. The Committee, taking a serious view in the matter, recommends to the Department of Health Research that in future all guidelines and norms should be adhered to before allowing trials of any drug including vaccines on Indian population. The Committee also recommends that the DCGI should observe optimum precautions and follow all norms and guidelines while allowing marketing of any drug including the vaccines in the Indian market".

1.6 The Department of Health Research in its Action Taken Note on the above recommendations submitted the following:

"PATH in partnership with State Governments of Gujarat and Andhra Pradesh was implementing an operational research study related to cancer of cervix prevention in India. ICMR is providing technical support & consultation for development of protocol and plan of monitoring.

The study utilized both the brands of HPV vaccines available in the market (Gardasil by Merck in Andhra Pradesh; and Cervarix by GSK in Gujarat). In view of certain complaints received, the State Governments have been advised not to carry out further vaccination till further orders. To ascertain the facts of the matter, Minister for Health & Family Welfare appointed a Committee comprising of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer, Dr. S.P. Aggarwal, former DGHS and Dr. Sunita Mittal, HoD, Obstetrics & Gynaecology, AIIMS to investigate ethical issues raised in the matter."

1.7 Not being satisfied with the action taken by the Government on its Recommendations, the Committee in its Forty eighth Report further recommended the following:

The Committee observes that as a result of its intervention, the State Governments have been advised by the Department not to carry out HPV vaccinations and a Committee has been appointed to investigate ethical issues raised in the matter. The Committee is not aware about the date of setting up of the Committee. However, the absence of any specific time-line for submission of Report of the Committee in the Action Taken Note given by the Department makes the Committee somewhat apprehensive. Like so many Committees set up by the Government, findings of this Committee, as and when received, may remain on paper only. The Committee, therefore, recommends that every effort should be made to expedite the Report of this Committee so that real facts about the HPV Vaccine trial are made known without any further delay and corrective measures not only in respect of this case but for all such ongoing/proposed clinical trials of drugs/vaccines are taken. The Committee also recommends that the Department should at least now work in close coordination with other concerned departments/organizations to undertake a comprehensive

analysis of the process of granting permission to research studies having hazardous effects on health and put in place a fool-proof system for pre-empting unethical research studies.

1.8 Considering the enormity of the wrong doing/criminality involved, and the dilly-dallying attitude of the Government in taking exemplary corrective action, the Committee took it up for detailed examination. The succeeding paragraphs contain the details of the matter, Committee's findings and recommendations.

1.9 Cancer of the cervix (mouth of uterus) popularly called Cervical Cancer has been there ever since the dawn of human race. Over the years, preventive and treatment protocols have been developed by medical experts.

1.10 The Committee was given to understand that on June 1, 2006 the American drug regulator, the U. S. Food and Drug Administration (USFDA) approved the first vaccine to prevent HPV virus that is claimed to cause 70% of cervical cancers, under the brand name of Gardasil by a US drug company namely, Merck.

1.11 In the very same month, an American organization called Program for Appropriate Technology in Health (PATH) embarked upon a large scale, 5-year long (June 2006 to May 2011) project with "the main objective …..to generate and disseminate evidence for informed public sector introduction of HPV vaccines" in four countries, India, Uganda, Peru and Vietnam. Interestingly these four countries have different ethnic populations: India (Indo-Aryans, Dravidians, Tribals etc.), Uganda (Negroid), Peru (Hispanics) and Vietnam (Mongoloids). The Committee has been given to understand that ethnicity is relevant in the determination of safety and efficacy of some drugs. What would be of further interest, as per World Health Organization (WHO) is that all these countries have state-funded national vaccine immunization programs, which if expanded to include Gardasil, would mean tremendous financial benefit to the then sole manufacturer.

1.12 With this background 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.

II. NATURE OF PROJECT

2.1 Given the controversy surrounding the project, the Committee was keen to know from the Government the exact nature of the project. The Committee noticed that there was fundamental difference between the perceptions of Drugs Controller General of India (DCGI) and Department of Health Research (DHR) / Indian Council of Medical Research (ICMR) on the actual nature of the project. The DCGI was of the opinion that since human subjects, as part of the research, were receiving invasive intervention like vaccines, the clinical trial rules must be enforced. Experts also upheld these views and were very clear about it. However, PATH described the project as an "observational study" since "it did not conform to the definition of clinical trial".

2.2 The Committee found from the information furnished to it that ICMR representative on the Project Advisory Committee not only opposed DCGI but also argued that the nature of the project does not require them to follow the clinical trial rules, including reporting of serious adverse effects within a specific time frame.

2.3 The Committee in this regard took note of the expert opinion given in the Inquiry Committee report which questioned the PATH description of the project and observed that since "the demonstration project is a study of a pharmaceutical product carried out on humans and since the primary objectives include the study of serious adverse effects, it is clear that clinical trial rules and guidelines should apply".

2.4 In fact, the Inquiry Committee in one of its findings very pointedly stated that the investigators had variously labeled the research project carried out by them as

"Observational Study/Demonstrational Study," etc. to establish that the study was not a clinical trial. But, since the project had been carried as research on human participants, it had to follow all the guidelines and statutory requirements applicable for research on human participants.

2.5 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. The Committee is not aware about the strategy followed by PATH in the remaining three countries *viz.* Uganda, Vietnam and Peru. The Government should take up the matter with the Governments of these countries through diplomatic channels to know the truth of the matter and take appropriate necessary action, accordingly. The Committee would also like to be apprised of the responses of these countries in the matter.

III. ROLE OF DEPARTMENT OF HEALTH RESEARCH/INDIAN COUNCIL OF MEDICAL RESEARCH

3.1 One of the functions mandated to the Department of Health Research/ICMR is promotion and coordination of basic, applied, clinical and operational research in medical, health and bio-medical field through development of infrastructure, manpower and skills. Uniform Ethical Guidelines for bio-medical Research on human subjects are incorporated in Good Clinical Practice (GCP) and ICMR documents. These guidelines outline the procedure for Ethics Committees review of clinical trials in India using the human beings as participants. All institutions and investigators in the country which carry out any form of biomedical research involving human beings are obliged to follow these guidelines in letter and spirit to protect participants.

3.2 As per the records made available to the Committee, the first documented contact made by PATH with ICMR took place, as early as, on 5th October 2006. An employee of PATH India sent an e-mail to Deputy Director of National AIDS Research Institute, ICMR expressing sorrow that she could not travel to Seattle, United States for "Formative Research Workshop" (on HPV vaccine) scheduled for October 24-26, 2006. Apparently, PATH functionaries were in touch with ICMR officials on an informal basis in the past.

3.3 Within a few days, a meeting took place between PATH and ICMR officials on 13 October, 2006 at PATH office in New Delhi where it was stated that "HPV vaccine, when available (in India), can prevent HPV and cervical cancer." The possibility of Global Alliance for Vaccines and Immunizations (GAVI) subsidizing the cost of vaccine for the first 2 - 4 years was also mentioned. Evidence (on role, utility of vaccine) made available to Government of India and States would "help to decide on public sector (state funded) introduction of the vaccine."

3.4 On 16 November, 2006, a draft Memorandum of Understanding (MoU) between PATH and ICMR was circulated by PATH which stated that "Parties (PATH and ICMR) desiring to explore collaboration to support public sector decision regarding HPV vaccine introduction in India and… to generate necessary evidence to

allow…..the possible introduction of HPV vaccine into India's Universal Immunization Programme."

3.5 Thus as early as October-November 2006, it was clear that the main objective of PATH project was to generate evidence that would facilitate the introduction of HPV vaccine Gardasil into government-funded immunization program in India. This appears to be a promotional activity for the benefit of manufacturing company because at that time only one HPV vaccine, Gardasil had been approved abroad, though not in India. Indeed "the key object of the project activities in India is to gather information and help the government make a decision about the introduction of HPV vaccine". The Country Director of PATH in India emphasized that "this needs to be our consistent message throughout the project."

In the formal proposal submitted by PATH to the ICMR on Project Proposals involving Foreign Collaboration/Assistance, the applicant clearly stated under Para 9. Objectives of the Project: "…….Introduction of HPV vaccines into Universal Immunization Program." The Committee found repeated mention of similar objectives at several places in various documents submitted by the Ministry. The Memorandum of Understanding (MoU) was signed by PATH and ICMR on 20 February, 2007. At that time only Gardasil was marketed in some countries in the world though not approved for use in India. The MoU stated that the purpose of the project was:

(i) Increasing understanding of HPV vaccine (i.e. Gardasil) introduction.
(ii) To help in decision-making related to the use of HPV (i.e. Gardasil) vaccine in the public and private sector.

3.6 The Committee enquired from the Secretary of Department of Health Research (DHR) and DG, ICMR, as to whether the Department or CDSCO, before approving the project had really reviewed its actual design. The Committee highlighted the observations of the experts of the Inquiry Committee who have opined that the design of the project itself was faulty. For instance, in the documents there was no column whatsoever for

Serious Adverse Events (SAE) and no diary was to be maintained as part of the protocol.

3.7 Moreover, much before the trials started, many expected side effects including anaphylaxis (severe allergic reaction), syncope, convulsions, asthma, central demyelinating diseases, acute disseminated encephalomyelitis, Idiopathic Thrombopenia Purpura, etc. were known. And astonishingly, as the records stated, while ICMR functionary was worried of bad publicity in case of side effects, PATH did not provide for urgent expert medical attention in case of serious adverse events whether known or unexpected.

3.8 After going through the final report and interactions with the Secretaries of the Department of Health and Family Welfare and the Department of Health Research/ICMR and DCGI, the Committee felt that it needs clarification as to under what category, permission was given to PATH to conduct such study on the Indian people and whether the programme was a clinical trial or promotional activity. The Committee took note of the fact that the Enquiry Committee meeting held on September 27, 2010, noted as under (Appendix 20.5):

> "....Besides the factual information about the terms of reference the Committee was greatly concerned with the aspect of commercial interests of manufacturers influencing the Government policy on this expensive vaccine. The committee observed that the study was initiated by PATH on its own …….. without any reference from the National Technical Advisory Group on Immunization (NTAGI), the official body of the GOI on vaccines.....It is not clear whether the State expenses were funded by PATH or came from their own resources. The monetary contributions of ICMR are also not clear. The Committee therefore felt that it would be in the fitness of the inquiry to document the sources and magnitude of funding of the study".

3.9 In this connection, the Committee also noted that one of the roles assigned to ICMR in the MOU signed by the Director General of the ICMR was "advising on plans for results dissemination to support decision making for use of the HPV vaccine".

3.10 **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 approved 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.**

3.11 The Committee noted that there were many gaps and missing links in the whole episode and enquired as to when ICMR came into contact with PATH. First a vaccine should get the approval from the Government and then only it can be used in UIP. Secretary, Department of Health Research/DG, ICMR while responding to the queries, informed that the first discussion with the PATH was held in 2006 followed by signing of agreement in the year 2007. At that time HPV vaccine had not been approved in India and no study was conducted on it. This was all a preparatory exercise.

3.12 The Committee was informed that the trial was on the two vaccines approved by DCGI. It was also stated that these vaccines had been tested abroad and on a limited number of people in India as per rules following which DCGI had given the approval for their marketing in the country, and then a post-marketing surveillance trial.

3.13 The Committee in this connection took note of the fact that before any drug is tested especially on a large population of 25,000- 32,000 children between the age of 10 to 14, then according to the CDSCO guidelines, no such trial can be conducted on children until a similar, prior trial is conducted on adults to determine efficacy and safety.

3.14 The Secretary, Department of Health Research/DG, ICMR while deposing before the Committee in its meeting held on 25th July, 2011, stated that the terms of reference of the Enquiry Committee was to find out any relation between the deaths with the administration of vaccine and any incidents of irregularities in the implementation of the study. He stated that the Enquiry Committee concluded that the deaths reported during trial had no uniform pattern to link them to the administration of vaccines.

3.15 The Committee noted that all the seven deaths were summarily dismissed as unrelated to vaccinations without in-depth investigations. According to Inquiry Committee report, the speculative causes were suicides, accidental drowning in well (why not suicide?), muyalaria, viral infections, sub-arachnoid haemorrhage (without autopsy) etc. The Committee has been given to understand that suicidal ideation is caused by many drugs. Since then one more death due to suicide in case of Gardasil has been reported in addition to 5 deaths reported during 2009-10. Therefore, HPV vaccine as a possible, if not probable, cause of suicidal ideation cannot be ruled out.

3.16 The Secretary of DHR/ DG, ICMR acknowledged that certain irregularities were reported in the implementation of the project. With regard to Informed Consent, he said that though the consent was taken properly in Gujarat, there were gross violations of norms in Andhra Pradesh. He informed the Committee that DCGI, had sought explanation for the incidents of irregularities.

3.17 The Committee took note of Secretary's comments but sought to know as to how ethical it was on the part of ICMR to become a party to a project in the name of Public-Private Partnership (PPP mode). How ICMR, which is mandated to formulate ethical guidelines for researchers, can become a direct party in such a study. The Secretary, Department of Health Research admitted that presence of ICMR in the Project's Advisory Committee-responsible and accountable for various acts of omissions and commissions-clearly indicates Conflict of Interest. Therefore, ICMR owes full moral responsibility for numerous irregularities reportedly committed in the study.

3.18 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.

3.19 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 activities of ICMR functionaries involved in PATH project.

3.20 Secretary of Department of Health Research and DG, ICMR in their defense also claimed that the ICMR had fulfilled the written role entrusted to it but the irregularities that took place during the implementation of the study clearly indicate that there were certain micro (ground) level issues requiring more attention. For instance, it was noticed that States were not even capable of monitoring the adverse effects. He stated that this all was a learning exercise.

3.21 It maybe pertinent to mention here that the safety, efficacy and introduction of vaccines in India is handled by National Technical Advisory Group on Immunization (NTAGI). Thus, at the very outset, ICMR should have either referred PATH to NTAGI or at least taken NTAGI on board.

3.22 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.

IV. ROLE OF DRUGS CONTROLLER GENERAL, INDIA (DCGI)

4.1 The Committee noted that as per Rule122-DA and Schedule Y of the Drugs and Cosmetics Rules, 1945 made under the Drugs and Cosmetics Act, 1940, no clinical trial on a drug can be conducted except under, and in accordance with the permission in writing, of the Licensing Authority i.e. DCGI. All vaccines are deemed to be drugs. Clinical trials of pharmaceutical products are conducted on human subjects in the country to determine or verify safety and/or efficacy. Every permission for conducting clinical trials also, inter alia, includes a condition that in event of trial related injury or death, the sponsor will provide complete medical care as well as compensation. Statement to this effect needs to be incorporated in the Informed Consent Form. The details of compensation provided are to be intimated to the office of DCGI.

4.2 The Committee noted from the evidence available that the nature of the PATH project made it Post-marketing Phase IV Clinical Trial under Drugs and Cosmetic Rules. It was on this basis that DCGI approved the clinical trial on 22 April, 2009 and had earlier issued import licenses on 23 December, 2008 though it was incorrect on the part of DCGI to issue import licences on Form 11 under Rule 33 which states:

Import of drugs for examination, test or analysis: Small quantities of drugs the import of which is otherwise prohibited under section 10 of the Act may be imported for the purpose of examination, test or analysis subject to the following conditions:

(a) No drug shall be imported for such purpose except under a licence in Form 11;

(b) the licensee shall use the substances imported under the license exclusively for purposes of examination, test or analysis and shall carry on such examination, test or analysis in the place specified in the license, or in such other places as the licensing authority may from time to time authorize.

4.3 Since both Gardasil and Cervarix had received marketing approval from CDSCO on 4 July, 2008 and 10 September, 2008 respectively, DCGI should have issued Import Licenses on Form 10 which is applicable to import of drugs already approved.

4.4 The so called Demonstration Project of PATH has the objectives as follows:

Primary Outcomes:

- Number & percentage of vaccinated girls.
- Number & percentage of vaccinated girls experiencing Serious Adverse Events (SAEs)
- Number & percentage of vaccinated girls experiencing non-Serious Adverse Events.
- Timeliness of reporting SAEs to local, state and national authorities.
- Timeliness of reporting Non-SAEs to local, state and national authorities.

4.5 Thus it is clear that PATH project had two well defined and specific objectives:

(a) The commercial objective of the project was to generate evidence, data and arguments to support inclusion of HPV vaccines into India's state-funded Universal Immunization Program (UIP), and

(b) The scientific purpose was to collect data on serious and non-serious adverse effects. Given that similar projects were launched in Peru, Uganda and Vietnam, the entire exercise would have collected side effect profiles of HPV vaccines in all the ethnic groups that reside in developing countries. Such data would be invaluable to promote the two branded, patented, single source HPV vaccines as safe all over the world.

4.6 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.

V. MARKETING APPROVAL TO HPV VACCINES IN INDIA

5.1 Before approving any new drug (including new vaccines), under Drugs and Cosmetics Rules, it is mandatory to conduct Phase III clinical trials in India to determine any ethnic differences in the safety and efficacy profiles. As per records made available to the Committee the following clinical trials, albeit, under various names, were conducted:

Gardasil (Merck): Clinical trials were conducted on 108 subjects (girls in the age group of 9-15 years). Several violations took place in the trial: (a) trials should have been conducted in adults first before exposing children to known and unknown side effects, (b) in adolescents and children the trials should

have been conducted from "top to bottom" age groups i.e. first in adolescents (13-15 years) followed by children (9-12 years). This was not done. Vaccines were administered to children irrespective of age at the same time.

Cervarix (GSK): Clinical trials were conducted on 162 subjects (adults in the age group of 18-35 years). Yet permission was given to use the vaccine in children (10-14 years) in violation of rules.

VI. INQUIRY COMMITTEE

(a) Composition and Terms of Reference

6.1 The Committee was informed that because of the concerns raised at different fora, the study was suspended and an Enquiry Committee was constituted by the Govt. of India vide notification No. V.25011/160/2010-HR dated 15th April, 2010, to enquire into "Alleged irregularities" in the conduct of studies using Human Papilloma Virus (HPV) vaccines by PATH in India.

The inquiry committee consisted of the following:

(1) Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer,

(2) Dr. S.P. Aggarwal, former DGHS, and

(3) Dr. Sunita Mittal, HoD, Obstetrics & Gynaecology, AIIMS

6.2 The terms of reference of the Committee were to enquire into:

(i) Link between the deaths and vaccine, if any, and

(ii) Ethical Issues of subjecting children of marginalized populations to these studies, and investigations in children without appropriate Consent.

6.3 The Committee was assisted by the following experts:

(i) Dr. Rani Kumar, Dean, AIIMS

(ii) Dr. A. K. Dutta, Head of Pediatrics, Kalawati Saran Hospital

(iii) Dr. Y. K. Gupta, Head of Pharmacology, AIIMS

(b) <u>Conflict of Interest</u>

6.4 The Committee sought information from the Ministry of Health and Family Welfare (MoHFW) as to whether members of the Inquiry Committee were asked to file Conflict of Interest declarations. In response the Ministry replied: "No written Conflict of Interest declarations were sought from the core members of the Inquiry Committee as well as experts. It was understood that if there is any conflict, highly learned members will point it out."

6.5 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 speaks of a serious conflict of interest of this member of the Inquiry Committee.

6.6 The Committee also found that the Ministry appointed a senior official of ICMR (described as Resource Person) to assist the Inquiry Committee. The concerned individual was the main link between ICMR and PATH, and had participated actively in all discussions, meetings and helped PATH to carry out the project proactively in every respect right from the beginning in October 2006. As such he had a clear Conflict of Interest and could not be relied upon to give correct information and unbiased opinion. Indeed he should have been summoned as a witness to answer questions and not as an official Resource Person attached to the Enquiry Committee.

(c) Adverse Events Reporting

6.7 The Committee examined the final Report of the Inquiry Committee constituted to enquire into the alleged irregularities in the conduct of studies using HPV vaccines by PATH in India. In its first meeting held on 21-4-2010, the Inquiry Committee sought details on the following core issues:

1. When did PATH approach ICMR for trial runs?
2. With whose permission was MOU signed?
3. Did President of ICMR approve?
4. Whether it had approval of the Screening Committee?
5. Approval of DCGI.
6. Details of reimbursements provided so far by PATH to ICMR
7. Names of beneficiaries.
8. Expenditure incurred by ICMR so far on all items including travel expenses.

6.8 However in its second meeting on 30 April, 2010, no discussion took place on the above crucial issues since the Inquiry Committee wished "to restrict itself to the terms of reference."

6.9 Inexplicably, however, as the records placed before the Committee proved, this decision did not prevent the Inquiry Committee from going into and recommending actions on other matters far beyond the terms of reference.

6.10 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.

6.11 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.

(d) Informed Consent

6.12 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.

6.13 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.

6.14 The Inquiry Committee, while going through the above report, noticed the following irregularities and discrepancies in the study:

(i) The warden/teachers/headmasters were not given written permission by the parents/guardians to sign on behalf of their girls.

(ii) On many forms witness had not signed and of the forms which are signed, it is not clear whether they are signed by full time government employees, as per rules.

(iii) Neither the photograph nor the photo ID card of parents/guardians/wardens is pasted in consent form.

(iv) On many forms investigator has not signed.

(v) On some forms signature of parents/guardians is not matching with their names.

(vi) The date of vaccination is much earlier than the date of signature of parents/guardian in the consent forms. Apparently they were obtained post-facto.

(vii) In some forms, the name is of the father but signature is of probably mother (lady's name).

6.15 Secretary, DHR and DG, ICMR while deposing before the Committee, reiterated that the regulatory approvals given to the project were in proper order and due attention was paid to the guidelines and formats for seeking consent. However, during the implementation of the project certain irregularities took place. He admitted there were cases of discrepancies in A.P. He admitted that many consent forms were filled up by the Principal on behalf of the students. He admitted to gross violation in the recording of SAEs also. He informed the Committee that keeping all these observations in view the DCGI, besides issuing immediate instructions to stop the study, had sought explanations for irregularities committed during the study.

6.16 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.

6.17 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.

6.18 The Committee was informed that the basic aim of the study was to evaluate strategies for introduction and delivery of the vaccines in the public sector. Strangely four of the five primary outcome measures proposed in the study related to evaluation and determination of safety of the vaccines.

6.19 One of the experts has stated that there was lack of rigour in the design regarding reporting and dealing with serious adverse events. He has pointed out absence of preparedness in the event of any such occurrence that would put children at grave risk. The side effects mentioned by the manufacturers themselves were revised several times and now include serious health issues. Since there were contra-indications to the use of the vaccines, the reasons for not ascertaining contra-indications before the girls were vaccinated is clearly an act of willful negligence.. The design of the project neither took the possibility of Serious Adverse Event (SAE) seriously nor was there any attention paid to the need for an independent monitoring agency. Consequently action on investigations into the causes of deaths took an unacceptably long time. A number of discrepancies and gaps in the investigations of the deaths have also been pointed out. There was no diary card based reporting of adverse events for recording minor or major adverse events in the study protocol in such a large study. This resulted in gross under reporting of the adverse events.

6.20 Another expert, while analyzing deaths and Adverse Events Following Immunizations (AEFI) has observed after reviewing all seven deaths (five deaths from AP in the Gardasil group and two deaths in Gujarat from Cervarix group), that there was no common pattern to the deaths that would suggest that these were caused by the vaccine. However, the reporting system as per Government of India surveillance of vaccine preventable disease guidelines notification was not done within time limit in two cases in AP and both the cases in Gujarat. There was no uniformity in the reporting system of AEFI in both the States. The primary end point of the study was to find out the number of girls having serious and non serious adverse events following vaccination through routine UIP system. He has opined that in

this regard first of all routine system of reporting should have been verified in both States.

6.21 Another expert has stated that the reporting of non-serious AEs was grossly under reported and hence the accuracy of SAEs is doubtful as well. It has been observed that delay in reporting and investigations of deaths could have been due to sole dependence on routine UIP protocol. It was a significant lapse in the protocol and execution of the study. While reporting on safety aspects in the study, it has been pointed out that there was absence of preparedness to handle Serious Adverse Events (SAE) like anaphylaxis, cardiac arrest, seizures, etc. occurring at the sites of vaccine administration. Though such serious adverse events might be rare but it was advisable to be well prepared for such an eventuality through adequate training of health workers. Assessment of the immune status of the participants by the ANM, ASHA or the health workers was virtually non-existent. These issues needed to be addressed as prescribing information of the HPV vaccines specifically contra-indicates administration in immune-compromised subjects (such as HIV/AIDS etc.).

6.22 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.

(e) Role of Ethics Committees

6.23 While examining the role of the Ethics Committees in both the States, one of the experts pointed out that Ethics Committees were supposed to meet periodically to evaluate and monitor the progress of the project and review SAE reports. No such meetings were held by the Committees. Only after reports of deaths appeared in the media, the meetings of these Committees were held.

6.24 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.

(f) Use of Official Machinery

6.25 The Committee has noted that the information/publicity material displayed/distributed at trial sites implied that the Government had started a vaccination programme. Thus, the credibility of the Universal Immunization Programme (UIP) was used to promote private, foreign interests. It has been found that the funds meant for the NRHM were used, without authorization for monitoring and transportation of the vaccines to the fields for use in the project.

6.26 **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 UIP 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.

6.27 Besides, the Committee notes that no information had been provided to Indian authorities about funding of the project except that it was reportedly funded by Bill and Melinda Gates Foundation and that the vaccines had been donated by the manufacturers. The information regarding financial investments of ICMR and State Governments in the project was not provided, though the States clearly provided cold chain and manpower for immunization. **The Committee, accordingly, observes that it might have been more prudent if the National Technical Advisory group on Immunization (NTAGI) had been brought into the picture right in the beginning to review and give its views on the study prior to its approval and implementation.**

6.28 No information is available on the total outlay on the project spent by PATH, ICMR, state governments of Andhra Pradesh and Gujarat (immunization staff, cold chain system, equipment, transportation etc.). According to the documents submitted by PATH to ICMR/Health Ministry Screening Committee, the total outlay by PATH for expenses in India was Rs. 29,76,000. However Centre for Operations Research and Training (CORT), a sub-contractor of PATH had quoted US$ 83,889 (first year) and US$ 96,472 (second year), which is not included in the figure submitted to ICMR/HMSC.

6.29 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.

(g) Action taken on the Inquiry Committee Report

6.30 With a view to find out the action taken by the Government on the findings of the Inquiry Committee, the Committee again heard the Secretary, Department of Health Research/DG, ICMR along with DCGI at its meeting held on 24th May, 2013. The Secretary informed the Committee that after the submission of Report by the Inquiry Committee, they were formally called to give explanation in the year 2011. In addition, clarifications were also sought from them in between which were formally answered to. The Committee in the said meeting desired to know whether criminal inquiry, if any, has been initiated against PATH on account of the following irregularities in the conduct of trial as pointed out by the Inquiry Committee:

(i) Irregularities in obtaining consent forms and actual implementation of the consent process;

(ii) Lack of monitoring and preparedness to deal with serious adverse events;

(iii) Inclusion of vulnerable and tribal population groups;

(iv) Blurring of distinction between Universal Immunization Programme and PATH study;

(v) Absence of insurance coverage for the study participants; and

(vi) Inclusion of the statement in the consent form that "you will not be charged for your daughter to receive the vaccine" that could be construed as covert inducement.

6.31 The Committee also sought to know as to whether any compensation was awarded to the families of children for suppression of material information before administering vaccines.

6.32 The Committee also took note of the Action Taken Note submitted by Department of Health Research wherein it was informed that subsequent to findings of the Inquiry Committee following action was taken:

(i) PATH was informed about suggestions made by the Committee;

(ii) Principal Investigators of other suspended studies on HPV vaccines were informed to get their studies re-examined from respective Ethics Committees after addressing the concerns raised by the Inquiry Committee;

(iii) DCG(I) was informed of the suggestions of the Committee for necessary action; and

(iv) Suggestions were forwarded to the relevant authority for inclusion in the Draft bill on Biomedical Research on Human Subjects.

6.33 DCG(I) informed the Committee that subsequent to findings of the Inquiry Committee; the following action was taken:

(i) Both the manufacturers of HPV vaccines have been asked to submit additional data for 4 years on PSURs (Periodic Safety Update Reports), every 6 months for first 2 years, and annually during the subsequent 2 years, and to submit protocol for approval for conducting post marketing surveillance study;

(ii) Proposal to amend the definition of "New Drug" under rule 122-E would be taken up for consideration; and,

(iii) In future the following steps would be ensured before approving a clinical trial by DCG(I): (a) every clinical trial is to be registered at ICMR's clinical trial registry of India; (b) every approval would include a condition for provision of complete medical care in case of study related injury/death & the statement to this effect is to be included in the informed consent: (c) DCG(I) should be informed about death/ injury: (d) Schedule 'Y' would be amended to expand the responsibilities of sponsors, investigators & Ethics Committees; and (e) the consent forms are to be amended to

include details of address and occupations of subject giving socio-economic background.

6.34 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.

6.35 The Committee observes that the Department has nothing fresh to offer in the status note as the same information was furnished by it in December, 2012 vide its updated note on Action Taken after availability of Report of nquiry Committee.

6.36 **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.**

6.37 **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.**

VII. PROGRAMME FOR APPROPRIATE TECHNOLOGY IN HEALTH (PATH)

7.1 The Committee during the course of its present examination sought information from the Government about PATH in order have a better understanding of its legal status and its *locus standi* in carrying out various activities on the Indian soil including the project in question where apparently several laws of India and possibly of its country of origin had been violated.

7.2 The information furnished to the Committee reveals that PATH describes itself as an "International nonprofit, non-government organization based in the United States." Legally, it is a Public Benefit Corporation (PBC) registered (number 600588751 dated 28th August 1981) by the Corporation and Charities Division in the State of Washington. For all practical purposes its legal status in US is equivalent to a Registered Society in the Indian context. It is certainly not a commercial company and hence would not be subject to the jurisdiction of Company Law Board or Registrar of Companies in India. Incidentally, Ford Foundation is also a PBC (Registration number 768093 dated 15th January 1936). Under American laws organizations such as Trusts, Fraternal Societies, Savings & Loan Associations, Municipal Utility Services etc. are all registered as PBCs.

7.3 Under Indian rules, foreign non-commercial organizations such as PATH wanting to set up an office in India are required to obtain (a) permission from the Ministry of External Affairs (MEA) from "political angle" (**annexure A**) and (b) permission from Ministry of Home Affairs (MHA) from "security angle" (**Annexure B**). In the latter case, application needs to be forwarded through proper channel such as Ministry of Health & Family Welfare for health-related activities, Ministry of Human Resources for education related activities, Ministry of Labour for trade union or workers related activities etc. Once such an approval is accorded, then an office can be setup which should naturally abide by all other laws of the land such as income tax, shop & establishment act, municipal and other applicable laws, just to mention a few.

7.4 The Committee asked the Department to direct PATH to provide details of various mandatory permissions required by foreign agencies, including charities, for and in connection with opening office in India and the date of opening of its office in

India. Unbelievably, the exact date of opening the office is not even known to its functionaries in New Delhi. To begin with vide its letter dated 5-3-2012, PATH claimed that "it has a Liaison Office status under Income Tax Rules." Since no such provision exists, after prolonged correspondence it settled for 19th April 1999 as the date of opening office based on the fact that its PAN card (number AAFCP2249G) is dated 19th April 1999. The Committee was intrigued because PAN card is issued just for income tax purposes and nothing else. Income Tax Department does not go about permitting foreign entities to open offices in India. In any case PAN card is not a replacement for Ministry of External Affairs and Ministry of Home Affairs approvals. Besides, the application for issuance of PAN card must have been made much before 19th April 1999 there being no online system of obtaining PAN card instantaneously. It can be safely assumed that the date of opening office has to be much earlier than 19th April 1999.

7.5 PATH also produced copy of a letter dated 16-3-1999 from PATH office in US to the Exchange Control Department of the Reserve Bank of India along with reply dated 19-4-1999 received by PATH in US on 29-4-1999. It merely stated that since PATH is "not engaged in any commercial, trading or industrial activity," it does not need "RBI permission from foreign exchange angle. *However you may seek necessary approval from the Government of India or other statutory/regulatory bodies as applicable."* Apparently PATH paid no attention to RBI's sane advice. Even before the letter reached PATH office in the United States on 29-4-1999, it had already opened its office in India.

7.6 The Foreign Exchange Regulation Act (FERA) was replaced with Foreign Exchange Management Act (FEMA) on 1-6-2000. PATH produced post-facto permission from the Reserve Bank of India dated 25-5-2009 which clearly stated:

> *"RBI permission (is) granted from the foreign exchange angle….and should not be construed to convey the approval of any other statutory authority or Government under any other laws/regulations."* Moreover, the Liaison Office is permitted to undertake "solely liaison work for the head office" as mentioned below:
>
> 1. Representing in India the parent company/group companies

2. Promoting export, import from/to India.
3. Promoting technical/financial collaborations between parent/group companies and companies in India.
4. Acting as a communication channel between the parent company and Indian companies.

"The office in India will not render any consultancy or any other services directly/indirectly with or without any consideration."

In addition *"Permission granted by RBI is limited to and for the purpose of the provisions of FEMA-2000 and shall not be construed in any way as regularizing, condoning or in any manner validating any irregularities, contraventions and other lapses, if any, under the provisions of any other law."*

7.7 It is clear that the back dated permission obtained after 10 years of having opened its office in India was merely and exclusively from foreign exchange angle and not a substitute for approval from MEA and MHA.

7.8 Finally and belatedly PATH produced a certificate from the Registrar of Companies (RoC) dated 23-9-2009 stating that PATH, a company originally incorporated in US, had filed documents on 10-09-2009 notifying establishment of place of business in India w.e.f 19-4-1999. The Certificate was apparently issued in violation of its own rules that states that documents must be submitted within 30 days of the establishment of "place of business." In any case such a certificate cannot and does not obviate the need to obtain baseline, mandatory permission from MEA and MHA. Moreover RoC deals with commercial companies, not foreign trusts, foundations and charities.

7.9 PATH also claimed that it had received "permission" from the Ministry of Health and Family Welfare to set up an office in India. The post-facto letter dated 27-4-2001 (two years after PATH admits having opened the office in India) is not a permission at all but a vague, non-specific statement to say that PATH was "engaged in health care related activities".

7.10 According to the published Annual Report of PATH for the year 2008, it received funding in "excess of US $ 1,000" from many governmental sources including the Ministry of Health & Family Welfare, Government of India. However, in response to Rajya Sabha Question Number 952 on 3-8-2010, the Health Minister denied any Ministry funding to PATH.

7.11 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.

7.12 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.

7.13 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.

7.14 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.

7.15 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.