REPORT NO.
81

सत्यमेव जयते

PARLIAMENT OF INDIA
RAJYA SABHA

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE

EIGHTY FIRST REPORT

Action Taken by Government on the Recommendations/ Observations contained in the Seventy-second Report on Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by PATH in India

(Ministry of Health and Family Welfare)

(*Presented to the Rajya Sabha on* 23*rd December,* 2014)
(*Laid on the Table of Lok Sabha on* 23*rd December,* 2014)

भारतीय संसद, राज्य सभा
PARLIAMENT OF INDIA, RAJYA SABHA

Rajya Sabha Secretariat, New Delhi
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(2013-14)

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*7. Shri Rasheed Masood
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Shri R.B. Gupta, *Director*
Shrimati Arpana Mendiratta, *Joint Director*
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Shri Pratap Shenoy, *Committee Officer*

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(2014-15)

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Shri Pratap Shenoy, *Committee Officer*

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, hereby present this Eighty-first Report of the Committee on Action Taken by Government on the Recommendations/Observations contained in the Committee's Seventy-second Report on "Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by PATH in India".

2. The Seventy-second Report of the Department-related Parliamentary Standing Committee on Health and Family Welfare was presented to Rajya Sabha and laid on the Table of Lok Sabha on 30th August, 2013. Replies of the Government on the recommendations contained in the Report, received from the Department of Health Research were examined by the previous Committee. However, the previous Committee could not finalise its Report due to dissolution of the 16th Lok Sabha. The replies were further examined by the Committee after its reconstitution on the 1st September, 2014.

3. The Committee considered the Draft Report and adopted the same in its meeting held on the 22nd December, 2014.

SATISH CHANDRA MISRA
Chairman,
Department-related Parliamentary Standing Committee on Health and Family Welfare

NEW DELHI;
22nd *December,* 2014
Pausha 1, 1936 (*Saka*)

ACRONYMS

AIIMS	:	All India Institute of Medical Sciences
AP	:	Andhra Pradesh
AE	:	Adverse Eevents
AEFI	:	Adverse Events Following Immunizations
CDC	:	Center for Disease Control
CDSCO	:	Central Drugs Standard Control Organization
CORT	:	Centre for Operations Research and Training
DCGI	:	Drug Controller General of India
DHR	:	Department of Health Research
FERA	:	Foreign Exchange Regulation Act
FEMA	:	Foreign Exchange Management Act
FCRA	:	Foreign Contribution Regulations Act
GCP	:	Good Clinical Practice
GSR	:	General Statutory Rules
GOI	:	Government of India
GSK	:	Glaxo Smith Kline
HPV	:	Human Papilloma Virus
HMSC	:	Health Ministry Screening Committee
ICMR	:	Indian Council of Medical Research
IND	:	Investigational New Drugs
MHA	:	Ministry of Home affairs
MEA	:	Ministry of external Affairs
MOU	:	Memorandum of Understanding
MoHFW	:	Ministry of Health and Family Welfare
NTAGI	:	National Technical Advisory Group on Immunization
NRHM	:	National Rural Health Mission
NDAC	:	New Drug Advisory Committee
NHRC	:	National Human Rights Commission
NHM	:	National Health Mission
O&G	:	Obstetrics and Gynaecology
PBC	:	Public Benefit Corporation
PATH	:	Programme for Appropriate Technology in Health
PI	:	Principal Investigator
PSURs	:	Periodic Safety Update Reports
PAN	:	Permanent Account Number
RoC	:	Registrar of Company
RBI	:	Reserve Bank of India
SAE	:	Serious adverse events
UIP	:	Universal Immunization Programme

REPORT

The Report of the Committee deals with the action taken by the Department of Health Research (Ministry of Health and Family Welfare) on the recommendations contained in the Seventy-second Report of the Committee on the "Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by PATH in India".

2. Action Taken Notes (ATNs) have been received from the Government in respect of the recommendations contained in the Report. They have been categorized as follows:

(i) Recommendations/Observations in respect of which replies of the Government have been accepted by the Committee: Nil

Total–0 (Chapter-I)

(ii) Recommendations/Observations which the Committee does not desire to pursue in view of the Government's replies: 1.2, 1.7, 1.12, 2.1, 2.2, 2.3, 2.4, 3.6, 3.7, 3.8, 3.22, 4.1, 5.1, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11, 6.18, 6.19, 6.20, 6.21, 6.22, 6.24, 6.29, 6.30, 6.31, 6.32,

Total–31 (Chapter-II)

(iii) Recommendations/Observations in respect of which replies of the Government have not been accepted by the Committee: 3.5, 3.10, 3.18, 3.19, 4.4, 4.5, 4.6, 6.14, 6.15, 6.16, 6.17, 6.25, 6.26, 6.33, 6.34, 6.35, 6.36, 6.37

Total–18 (Chapter-III)

(iv) Recommendations/observations in respect of which final replies of the Government are still awaited: 2.5, 6.12, 6.13, 6.28, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 7.10, 7.11, 7.12, 7.13, 7.14, 7.15

Total–19 (Chapter-IV)

3. The details of the ATNs are discussed in various Chapters in the succeeding pages.

CHAPTER-I

RECOMMENDATIONS/OBSERVATIONS IN RESPECT OF WHICH REPLIES OF THE GOVERNMENT HAVE BEEN ACCEPTED BY THE COMMITTEE

–Nil–

CHAPTER-II

RECOMMENDATIONS/OBSERVATIONS WHICH THE COMMITTEE DOES NOT DESIRE TO PURSUE IN VIEW OF THE GOVERNMENTS REPLIES

I. BACKGROUND

Observation/Recommendation

2.1 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. (Para 1.2)

Reply of the Ministry

2.2 The Ministry of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH.

2.3 The Inquiry Committee was of the view that by whatever name it was called, the project proposal had been carried out as research on human participants. As such, it had to follow all guidelines and statutory requirements applicable on research on human participants. The Committee further reported that the deaths were most probably unrelated to the vaccine under trial, as there was no characteristic and uniform pattern of illness preceding the death, or temporal/spatial clustering. The Committee also observed that in the absence of control group, it was not possible to say whether there were excess deaths in the vaccinated group or not. Based on the data of background deaths from routine mortality reporting system from the same area for the vaccination period as collected by the Committee, it opined that overall death rate during the period of vaccination was not significantly different, supporting the contention that reported deaths are independent of the HPV vaccination. It further stated that internationally as on the 31st January, 2010, 49 deaths were reported in the USA against approximately 28 million doses of Gardasil vaccine distribution. Out of these, 28 deaths have been traced. According to CDC (Center for Disease Control, USA),there was no unusual pattern or clustering to the deaths that would suggest that they were caused by the vaccine. It is further added that these two vaccines are included in the National Immunization Programmes for prevention of cervical cancer in women in many countries, like, USA, Canada, New Zealand, France Germany, Sweden, Australia, Russia, UK, Mexico, etc.

2.4 The Inquiry Committee in its report had, however, identified various deficiencies in the planning and conduct of the study by PATH. The gist of the same is as under:

- Consent forms and the actual implementation of the consent process.
- Method of monitoring the adverse effects and the serious adverse effects and remedial measures for such events
- Inclusion of vulnerable tribal population groups.
- Blurring of distinction between National Immunization Program and PATH study.
- Insurance coverage for the study participants
- Free supply of vaccine by the manufacturer and the statement in the consent forms that "you will not be charged for your daughter to receive the vaccine" that could be considered as covert inducement and indirect coercion.

2.5 The penal provisions regarding the import of drugs are provided under Section 13 of the Drugs and Cosmetics Act while penalty for manufacture, sale, etc., of drugs is provided under Section27 of the Act. There are no specific penalties for violation of the provisions relating to clinical trial under the Act.

2.6 The Drugs and Cosmetics Rules, 1945 made under the said Act, under Part X-A of the Rules have provisions for Import or Manufacture of New Drugs for Clinical trials or Marketing. Under Rule 122 DA, the permissions to conduct clinical trials for new drugs/investigational new drugs are granted by the Licensing Authority as defined in Rule 21(b) *i.e.* Drugs Controller General (India). The Schedule Y to the said Rule provides detailed requirements for the Informed Consent to be obtained from each study subject as well as responsibilities of the sponsor, investigator and Ethics Committee. Rule122 DA empowers the DCG(I) to suspend cancel the permission issued to conduct the clinical trials. In the present case, since the ICMR had already suspended the trial, the DCG(I) issued' warning' as an administrative measure to PATH on 3rd July, 2012 that it should be careful while conducting clinical trial so as to ensure that such discrepancies/violation are not repeated in future. It was further directed to comply with the corrective action taken to ensure strict compliance of Schedule Y and GCP in on-going study and proposed to be started in future research studies.

2.7 In the meantime, the Drugs and Cosmetics Rules, 1945 were amended by Gazette Notification GSR 63(E) dated 1.2.2013, *inter-alia* providing for following activities by DCG(I), in case of non-compliance of provisions of clinical trial:–

(a) Reject or discontinue the study;

(b) Suspend or cancel the clinical trial permission;

(c) Debar the Investigator(s), Sponsor including his representative to conduct any clinical trial in future.

2.8 In light of the recommendations of the Hon'ble Committee, the following actions have been taken by the Ministry:

(i) As regard the use of logo of NHRM in the study, the matter is being enquired into *vide* Annexure A.

(ii) The Ministry of External Affairs *vide* letter dated 8th January 2014 has been requested to ascertain the following facts related to the said studies through usual diplomatic channels for enabling the Ministry of Health and Family Welfare for taking further necessary action in the matter.

(iii) Whether the similar studies were conducted by PATH in those countries?

(iv) If so, the strategy followed by PATH in those countries for conduct of the study, and the outcome of the study.

(v) Whether the HPV vaccine has been introduced or not in the National Health Programmes of these countries based on the study conducted by the PATH. A copy of letter is enclosed at Annexure 8.

(vi) The Department of Legal Affairs *vide* note dated 5.1.2014 has been requested for their considered opinion as to whether any further legal action against PATH is possible in the present case. A copy of the note is enclosed at Annexure C.

(vii) The Ministry of Home Affairs *vide* letter dated 5th January 2014 has been requested to examine the recommendation of the Hon'ble Committee and take appropriate action. The Ministry has also been requested to furnish its response to the Ministry of Health and Family Welfare for taking further necessary action in the matter. A copy of letter is enclosed at Annexure D.

(viii) The National Human Rights Commission, New Delhi *vide* letter dated 5th January 2014 has been apprised of the recommendations of the Hon'ble Committee for appropriate action. The Commission has also been requested to send their comments/views to the Ministry in this regard. A copy of letter is enclosed at Annexure E.

(ix) The Ministry of Women and Child Development *vide* letter dated 8th January, 2014 has been requested to examine the recommendations of Parliamentary Standing Committee and give its response for further necessary action. A copy of letter is enclosed at Annexure F.

(x) The Permanent Mission of India to the UN in Geneva *vide* letter dated 8th January, 2014 has been apprised of recommendations of the Hon'ble Committee. A copy of letter is enclosed at Annexure G.

(xi) The Ministry of External Affairs *vide* letter dated 6th January, 2014 has been requested to examine the recommendations of the Hon'ble Committee and take appropriate action. The Ministry has also been requested to furnish their response. A copy of letter is enclosed at Annexure H.

Observation/Recommendation

2.9 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 b een 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 some what 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 the real facts about the HPV vaccine trial are made known without any further delay and corrective measures not only in the 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". (Para 1.7)

Reply of the Ministry

2.10 The Inquiry Committee was constituted on 15th April, 2010. The Committee submitted their report to Ministry of Health and Family Welfare in February, 2011. Action has been taken on all the recommendations of the Committee.

2.11 Various steps have already been taken to strengthen the regulatory framework for approval as well as monitoring of Clinical Trials of New Drugs including Vaccines. Details are as under:

- 12 New Drug Advisory Committees (NDAC) consisting of experts from the government medical colleges, institutes from all over the country were constituted in March, 2011. Applications for approval of clinical trials excluding Investigational New Drugs (INDs) and approval of new drugs are being evaluated by these Committees.
- All investigational New Drugs applications are evaluated by the IND Committees chaired by Secretary, Department of Health Research and DG, ICMR.
- Drugs and Cosmetics Rules have been amended to make provisions for safeguarding the rights, safety and well being of trials subjects and registration ethics Committee for regulating the clinical trials in the country. The following provisions have been incorporate in the said rules.
  - ➢ Amendment *vide* Gazette Notification G.S.R. 53 (E) dated 30.01.2013 specifying procedures to analyze the reports of Serious Adverse Events occurring during clinical trials and procedures for payment of compensation in case of trial related injury or death as per prescribed timelines.
  - ➢ Amendment *vide* Gazette Notification G.S.R. I 63(E) dated 01.02.2013 specifying various conditions for conduct of clinical trials, authority for conducting clinical trial inspections and actions in case of noncompliance.
  - ➢ Amendment *vide* Gazette Notification G.S.R. 72(E) dated 08.02.2013 specifying requirements and guidelines for registration of Ethics Committees.
- Drugs and Cosmetics (Amendment) Bill, 2013 has been introduced in the Parliament on 29th August, 2013. The Bill contains a separate chapter on clinical trials containing penal provisions, provisions for payment of compensation, Ethics Committees etc.
- An Expert Committee has been constituted to examine the reports of deaths in clinical trials. The Committee has prepared a formula for determining the quantum of compensation in case of clinical trial related deaths which is available in CDSCO website.
- The Committee set up under the Chairmanship of Prof. S.S. Agarwal on clinical trial and new drugs has submitted its report. The Ministry of Health and Family Welfare has examined the recommendations and finalized the action to be taken on various recommendations, the details of which have been posted on the CDSCO website.
- In compliance to the Hon'ble Supreme Court's order dated 03.01.2013, a system of supervision of clinical trial has been put in place by constituting an Apex Committee under Chairmanship of Secretary, Health and Family Welfare and a Technical Committee under Chairmanship of DGHS.
- The present procedure followed for review of Clinical trial applications is a three tier review process. As per the process applications are evaluated by the New Drugs Advisory Committees (NDACs)/lnvestigational New Drugs (IND) Committee. The

recommendations of these committees are finally reviewed by the Technical Committee and then approved by the Apex Committee on the basis of recommendations of the Technical Committee.

- Further, in compliance with the order of Hon'ble Supreme Court dated 26.07.2013, consultations have been made with the Principal Health Secretaries of the States/ UTs, NHRC, Civil Societies and other stakeholders who have submitted their suggestions which are under consideration for further strengthening of regulations on clinical trials.
- DCG (I) through an administrative order dated 30.08.2013 has made it mandatory for the sponsor or his representatives to furnish the details of the contract entered by the Sponsor with Investigator/institutions with regard to financial support, fees, honorarium, payments in kind etc., to be paid to the Investigator.
- In light of the order of Hon'ble Supreme Court dated 21.10.2013, it has been decided that in all clinical trials, in addition to the requirement of obtaining 'Mitten informed consent, audio-visual recording of the informed consent process of each trial subject, including the procedure of providing information to the subject and his/her understanding on such consent is required to be done while adhering to the principles of confidentiality. Such audio-visual recording and related documentation would be preserved. All the Sponsors/Investigators/Institutes/Organizations and other stakeholders involved in conduct of clinical trials in the country are required to adhere to the above requirement of audio-visual recording of informed consent process of trial subjects with effect from 30.11.2013.

Observation/Recommendation

2.12 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. (Para1.12)

Reply of the Ministry

2.13 It is submitted that the role of the ICMR was limited only to the extent of giving advice on preparing the protocol and providing guidance on monitoring the same. ICMR did not lend its platform to PATH in any improper and unlawful manner and it did not attempt to sway the decision making process of the State Governments of Andhra Pradesh and Gujarat in any manner. Being a scientific organization concerned with health problems of public health importance it scientifically facilitated the process of operational research by providing guidance on design and protocol/ procedures pertaining to these vaccines which had the potential of preventing cervical cancer. Benefit from human health perspective and costs would have been or will be to people and Government of India and not to any individual in ICMR. It may be pointed out that no such irregularities, have been pointed by the Inquiry Committee appointed by Ministry of Health and Family Welfare. The recommendations of Parliamentary Standing Committee made in its 41st and 48th reports to stop the ongoing studies and put in place safeguards about ethics, proper consent, monitoring of serious adverse events, compensation etc have all been implemented by ICMR during review process and by DCGI as a regulator when giving approvals. It is requested that Parliamentary Standing Committee may kindly reconsider their interpretation.

II. NATURE OF PROJECT

Observation/Recommendation

2.14 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". (Para 2.1)

2.15 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**.** (Para 2.2)

Reply of the Ministry

2.16 As per Schedule Y, Post Marketing Trials (Phase IV) are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), *e.g.* mortality/ morbidity studies, epidemiological studies etc.

The objective of the PATH study was:

(i) To demonstrate suitable vaccine delivery strategy for HPV to 10-14 years old adolescent girls.

(ii) To raise community awareness on HPV, cancer of the cervix and its prevention.

(iii) To gain experience in HPV vaccination and to build the evidence based of vaccine delivery strategies for future introduction of HPV vaccines into Universal immunization programs.

The primary outcome measures included:

1. Number and percent of eligible girls fully vaccinated, partially vaccinated or not vaccinated at all according to the vaccine delivery strategy.

2. Number and percent of vaccinated girls experiencing serious adverse events, as reported spontaneously through routine mechanisms of the UIP program;

3. Number and percent of vaccinated girls experiencing non-serious adverse events, as reported spontaneously through routine mechanisms of the UIP program;

4. Timeliness of reporting serious adverse events to local, state and national authorities, as per the usual UIP protocol; and

5. Timeliness of reporting non-serious adverse events to local, state and national authorities, as per the usual UIP protocol.

Thus, the PATH study falls under the category of Post Marketing Trial (Phase IV) as per Schedule Y.

Observation/Recommendation

2.17 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". (Para 2.3)

2.18 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 out as research on human participants, it had to follow all the guidelines and statutory requirements applicable for research on human participants. (Para 2.4)

Reply of the Ministry

2.19 The Inquiry Committee under the chairmanship of Prof SS Agarwal was of the opinion that by whatever name it is called, the project proposal had been carried out as research on human participants. As such, it had to follow all guidelines and statutory requirements applicable to research on human participants.

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

Observation/Recommendation

2.20 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. (Para 3.6)

Reply of Ministry

2.21 The protocol submitted by PATH for the said study was approved by DCG (I) in consultation with the ICMR. It is accepted that protocol was not perfect and method of recording SAEs including maintaining diary should have clearly stated. As all experts including official(s) from ICMR are equally responsible, this is a collective failure. It is assured that due care will be taken in future including responsibility to one/more officials for approval and monitoring compliance.

Observation/Recommendation

2.22 Moreover, much before the trials started, many expected side effects including anaphylaxis (severe allergic reaction), syncope, convulsions, asthma, central demyelinating diseases, acute disseminated encephalomyelitis, diopathic 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. (Para 3.7)

Reply of the Ministry

2.23 One of the major deficiencies identified by the Inquiry Committee was total reliance on the State AEFI program to measure four of the five primary outcomes of the study without an independent verification. This has led to delay in reporting of SAE and deaths and their inadequate investigation which precipitated the crisis in the execution of the study. The Committee had opined that monitoring and management of Adverse Event (AE)/Serious Adverse Event (SAE) should have been more vigorously pursued.

Observation/Recommendation

2.24 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 study". **(Para 3.8)**

Reply of the Ministry

2.25 Same as mentioned against Para 2.1*

Observation/Recommendation

2.26 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 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 approval for its marketing in the Country be inquired into by a premier investigating agency and appropriate action be taken there after by the Government in the matter .The Committee expect the Government not to procrastinate in this matter any further. **(Para 3.22)**

Reply of the Ministry

2.27 Response against the observations to **Para 3.18 is reiterated. It is submitted that deficiencies pointed out by the Inquiry Committee on which Parliamentary Standing Committee

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* refer to para 2.16 of Chapter II

** refer to para 3.7 to 3.11 of Chapter III

has based its conclusions do not indicate willful negligence or these were fully anticipatable. In hindsight, these deficiencies should be undertaken as a learning experience. The Inquiry Committee recommended that lessons be incorporated both in the ongoing , proposed to be started and future research studies in general and new vaccines in particular so that public trust in the Vital National Immunization Programme is restored and enhanced. It is submitted that the role of ICMR may be considered in positive light in view of its public health goals. Parliamentary Standing Committee is assured that ICMR will ensure that it will conduct itself in a manner that will not any doubts about its intention and will be within its mandate and role assigned by Government of India.

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

Observation/Recommendation

2.28 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, andaccordance 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. (Para 4.1)

Reply of the Ministry

2.29 Earlier, there were no specific provisions under the Drugs and Cosmetics Rules regarding payment of compensation in case of injury or death occurring during clinical trials.

2.30 However, GCP guidelines required that subjects who suffer physical injury as a result of their participation in clinical trial were entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability subject to confirmation from Ethics Committee.

2.31 From 2011 till the amendment made on 30th January, 2013, every clinical trial permission included a condition that in the 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.

2.32 The Drugs and Cosmetics Rules have since been amended incorporating specific provisions in this regard which are as under:

- Amendment *vide* Gazette Notification G.S.R. 53(E) dated 30.01.2013 specifying procedures to analyze the reports of Serious Adverse Events occurring during clinical trials and procedures for payment of compensation in case of trial related injury or death as per prescribed timelines.
- Amendment *vide* Gazette Notification G.S.R. 63(E) dated 01.02.2013 specifying various conditions for conduct of clinical trial, including reporting of SAE and requirement for payment of compensation in case of trial related injury or death, authority for conducting clinical trial inspections and actions in case of non compliance.

V. MARKETING APPROVAL TO HPV VACCINES IN INDIA

Observation/Recommendation

2.33 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. (Para 5.1)

Reply of the Ministry

2.34 As already mentioned in *Para 1.4 above, the Phase III clinical trials were permitted to be conducted in India as per the provision of Drugs and Cosmetics Rules.

2.35 The Inquiry Committee, in this regard, has also opined that not only the requirement of assessing the safety and efficacy of the vaccine in adult prior to use in children has been fulfilled, the data on adolescent girls has also been acquired. As such, there was no violation of any laid down guidelines for use of New drugs/Vaccine in the pediatric age groups.

VI. INQUIRY COMMITTEE

(b) Conflict of Interest

Observation/Recommendation

2.36 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." (Para 6.4)

2.37 In order to verify the Ministry's claim, the Committee pick adjust one member *i.e.* Professor and HoD of the Department of Obstetrics and Gynecology (O&G) of All Indian 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, serious conflict of interest of this member of the Inquiry Committee. (Para 6.5)

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* refer to Annexure K

Reply of the Ministry

2.38 The Ministry of Health and family Welfare had constituted this Enquiry committee under the Chairmanship of Dr. S.S. Agarwal *vide* order no. V.25011/160/2010-HR dated 15th April, 2010, to enquire into alleged irregularities in the conduct of studies using HPV vaccine by PATH in India.

2.39 While connection between one of members of Enquiry Committee having availed hospitality earlier from the sponsors has been pointed out, Parliament Standing Committee is requested to consider that this Enquiry Committee and the subcommittee appointed by it have objectively analyzed the situation/events in detail and all the shortcomings about consent (procedures and actual implementation); recording of adverse events; inappropriate/inadequate procedures for monitoring and response to adverse events; PI and Advisory Committees not doing proper job to implement the study; lack of insurance cover etc have all been brought out by this Enquiry Committee. These have been endorsed by Parliament Standing Committee.

2.40 While the lapse on the part of Ministry in not specifically asking the question about such possible conflict of interest directly and clearly is acceptable, it will not be fair to question the integrity of all senior members of medical fraternity and have served the nation with distinction in their career. Parliament Standing Committee is requested to reconsider its conclusion that entire process is vitiated. In future, this clarification about conflict of interest/having availed hospitality will be specifically asked.

Observation/Recommendation

2.41 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. (Para 6.6)

Reply of the Ministry

2.42 It is submitted that the official from ICMR was appointed as resource person to provide the documents as he fully knew about records/happenings but was not associated with the proceedings at any stage. Report does not exonerate ICMR/the concerned official from not doing the job of giving proper advice in design, protocol, implementation and monitoring. To avoid any such misgivings/impression, due care will be exercised in future.

(c) Adverse Events Reporting

Observation/Recommendation

2.43 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: (Para 6.7)

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 reimbursement provided so far by PATH to ICMR

7. Names of beneficiaries

8. Expenditure incurred by ICMR so far on all items including travel expenses.

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

2.45 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**.** (Para 6.9)

2.46 The Committee notes that once this matter was taken up by it, the Government appointed an Inquiry Committee on 15th 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. (Para 6.10)

2.47 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 21st 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 unravelling the truth but also the country would have known the exact details as to what transpire red in this sordid incident. (Para 6.11)

Reply of the Ministry

2.48 Parliament Standing Committee is requested to consider the fact that Inquiry Committee and the Subcommittee appointed by it have objectively analyzed the situation/events in detail and all the shortcomings about consent (procedures and actual implementation); recording of adverse events; in appropriate/inadequate procedures for monitoring and response to adverse events; Pl and Advisory Committees not doing proper job to implement the study: lack of insurance cover etc have all been brought out by this Inquiry Committee. These have been endorsed by Parliament Standing Committee. Even though it chose not to address these additional points subsequently, it fulfilled its objectives in a comprehensive manner based on which reforms in review, approval and monitoring process have been undertaken by Government of India pertaining to clinical research.

Observation/Recommendation

2.49 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 majors proposed in the study related to evaluation and determination of safety of the vaccines**.** (Para 6.18)

2.50 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 wilful 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. (Para 6.19)

2.51 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 no 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. (Para 6.20)

2.52 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 tr at 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 nonexistent. These issues needed to be addressed as prescribing information of the HPV vaccines specifically contra-ind1cates administration in immune-compromised subjects (such as HIV/AIDS etc.). (Para 6.21)

2.53 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. (Para 6.22)

Reply of the Ministry

2.54 One of the major deficiencies identified by the inquiry committee was total reliance on the State AEFI Programme to measure four of the five primary outcomes of the studies without an

independent verification. This has led to delay in reporting of SAE and deaths and their inadequate Investigation which precipitated the crisis in the execution of the study. The committee had opined that monitoring and management of AE/SAE should have been more vigorously pursued.

2.55 As already mentioned in *Para 4.6, the Inquiry Committee has observed that such deficiencies do not appear to be wilfully or fully anticipatable. In hindsight these deficiencies should be undertaken as a learning experience. The committee recommends that these lessons be incorporated both in the ongoing, proposed to be started and future research studies in general and new vaccines in particular that public trust in the vital national immunization programme is restored and enhanced.

2.56 Ministry agrees with the observations of Parliament Standing Committee about safeguards, consent taking monitoring of trials/intervention studies, compensation/insurance, blurring of distinction between this study and UIP; use of NHRM machinery and making Ethical Committees accountable. The Inquiry Committee had also made similar conclusions. MoHFW (Department of Health Research – ICMR and Department of Health and family Welfare – DCGI and NHM) will ensure that such lapses do not occur.

(e) Role of Ethics Committees

Observation/Recommendation

2.57 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 Ethic Committees should strictly follow them. The functioning of Ethics Committees should be regularly monitored. **(Para 6.24)**

Action Taken

2.58 As already mentioned in *Para 4.6, the Inquiry Committee has observed that such deficiencies do not appear to be willfully or fully anticipatable. In hindsight these deficiencies should be undertaken as a learning experience. The Committee recommends that these lessons be incorporated both in the ongoing, proposed to be started and future research studies in general and new vaccines in particular so that public trust in the Vital National Immunization Programme is restored and enhanced.

2.59 In the meantime, the rules have been amended and the registration of Ethics Committee has been made mandatory. As per new regulations, the functioning of Ethical Committees will be closely monitored and strict compliance to clearly defined procedures will be ensured.

Observation/Recommendation

2.60 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

* please refer to para 3.18 to 3.22 of Chapter III
* please refer to para 3.18 to 3.22 of Chapter III

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. **(Para 6.29)**

Reply of the Ministry

2.61 As mentioned in the response to *Para 4.6, the Inquiry Committee has concluded that such deficiencies do not appear to be wilfully or fully anticipatable. In hindsight these is deficiencies should be undertaken as a learning experience. The Committee recommends that these lessons be incorporated both in the ongoing, proposed to be started and future research studies in general and new vaccines in particular so that public trust in the vital national Ministry assures that such lapses or acts of omission/commission do not occur in future.

(g) Action taken on the Inquiry Committee Report

Observation/Recommendation

2.62 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: (Para 6.30)

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

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

2.64 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 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 Suggestions were forwarded to the relevant authority for inclusion in the Draft bill on Biomedical Research on Human Subjects. (Para 6.32)

* please refer to para 3.18 to 3.22 of Chapter III

Reply of the Ministry

2.65 The Inquiry Committee was constituted on 1st April, 2010. The Committee submitted their reports to Ministry of Health and Family Welfare in February, 2011. Based on the discrepancies outlined in the enquiry committee report and its observations/recommendations, a warning letter was issued to M/s PATH, on 03.07.2012, to ensure that such discrepancies/violation are not repeated in future. It was also directed to comply with the corrective action taken to ensure strict compliance of Schedule Y and GCP in ongoing study and proposed to be started in future research studies.

2.66 Further various steps have been taken to strengthen the regulatory framework for approval as well as monitoring of Clinical Trials of New Drugs including Vaccines. Details have been mentioned in *Para 1.7.

* refer to para 2.10 & 2.11 of Chapter II

CHAPTER-III

RECOMMENDATIONS/OBSERVATIONS IN RESPECT OF WHICH REPLIES OF THE GOVERNMENT HAVE NOT BEEN ACCEPTED BY THE COMMITTEE

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

Observation/Recommendation

3.1 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 Ministry. The Memorandum of Understanding (MoU) was signed by PATH and ICMR on 20th 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. (Para 3.5)

Reply of the Ministry

3.2 It is a fact that main objective of Global Project of PATH was to generate evidence for considering the introduction of HPV vaccines into public health programmes of these countries including where cervical cancer was/is still important from public health point of view. Company would have clearly benefited but this is linked to benefit to human health. All the facts mentioned above by Parliamentary Standing Committee are matter of record. It is true that association of ICMR in this study as partner creates doubts and raises the issues of conflict of interest of appearing as promoter of introduction of introduction these vaccines, giving advice on ethics and at the same, not being in a position to ensure monitoring. As the state systems showed some laxity in the manner of authorization and taking proper consent and also monitoring serious adverse effects, there is concern about the entire process. ICMR had associated with this project with the objective of generating information that could have been potentially useful to programme if NTAGI had required such information to consider introduction of any of such vaccines in the programme. It is reiterated that ICMR had associated with post-marketing surveillance cum operational research project purely for scientific purposes. Procedure followed for clinical trials were also followed in this case, however, these were not found to be adequate at the end but these are collective failure

of a system (different Committees) to foresee that such things can happen and thus it is requested that these may not be concluded as responsibility of one official or organizations such happenings have raised doubt about the neutrality of important organizations like ICMR, Department of Health Research will ensure that it keeps the observations of Parliament Standing Committee in view and will not allow ICMR headquarters or any of its scientists to associate with such projects in future unless specifically asked by Government for that purpose.

Further Recommendation

3.3 **The Government's admission that the association of ICMR in the Study as partner creates doubt and raises the issue of conflict of interest of appearing as promoter of introduction of these vaccines, giving advice of ethics and at the same time not being in the position to ensure monitoring indicates that ICMR should have been more careful in such trials. In future efforts should be made to ensure that ICMR or any of its scientists do not associate with such projects without prior approval and permission of the Department. The Committee desires to be informed of the actions taken to streamline the system.**

Observation/Recommendation

3.4 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. (Para 3.10)

Reply of the Ministry

3.5 As stated in *para 3.5, this method of functioning even though done with the goal of generating information for decision making by the programme, has raised doubts about the neutrality of important organizations like ICMR, Department of Health Research will ensure that it keeps the observations of Parliament Standing Committee in view and will not allow ICMR headquarters or any of its scientists to associate with such projects in future unless specifically asked by Government for that purpose.

Observation/Recommendation

3.6 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. (Para 3.18)

Reply of the Ministry

3.7 As regards to the fixing responsibility, the Inquiry committee has recommended that it is true that deaths have occurred in the recipients of the HPV Vaccine under the PATH study in Andhra Pradesh and Gujarat, and it is also true that lot of negative *vibe* has been generated against this project due to mishandling of the entire situation. But the committee has not been able to identify a single event, individual or agency which can be held entirely accountable for it. However,

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* refer to para 3.2 above

some deficiencies in the implementation of the project did occur which have been detailed in the report. These deficiencies noted by the Committee should serve " as a lesson for strengthening clinical research in future rather than starting any punitive or disciplinary proceeding.

3.8 The deficiencies do not appear to be willful or fully anticipatable. In hindsight, these deficiencies should fully be undertaken as a learning experience. The Committee recommends that these lessons be incorporated both in the ongoing, proposed to be started and future research studies in general and new vaccines in particular so that public trust in the vital national immunization programme is restored and enhanced.

3.9 The Development of HPV vaccine has provided a new opportunity for the prevention of cancer of cervix, which is an important health burden for the women of our country.

3.10 HPV vaccination is not to replace the cancer cervix screening programmes, but to supplement it. However, since the vaccine is expensive an element of effectiveness and determination of complete cost health immunization priorities should have been addressed in the study. The fact that the vaccine was provided by the manufacturers free of cost does raise the concern about the undeclared conflict of interest since the results of the study may be used to influence the decision by the Government. Again, since there does not appear to be covert mal-intention, no responsibility can be fixed on one However, any programme focusing on vaccination also be targeting on public education for cancer cervix screening.

3.11 It is assured that due care will be taken in future in all procedural issues so that no doubt about the neutrality of ICMR and its objectivity for working for public purpose only arises.

Observation/Recommendation

3.12 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. (Para 3.19)

Reply of the Ministry

3.13 It is accepted that association of ICMR in this study as partner creates doubts and raises the issues of conflict of interest of appearing as promoter of introduction of these vaccines, giving advice on ethics and at the same not being in a position to ensure monitoring. As the state systems showed some laxity in the manner of authorization and taking proper consent and also monitoring serious adverse effects, there is concern about the entire process. ICMR had associated with this project with the objective of generating information that could have been potentially useful to programme if NTAGI had required such information to consider introduction of any of such vaccines in the programme. It is reiterated that ICMR had associated with post-marketing surveillance cum operational research project purely for scientific purposes. Procedures which were followed for clinical trials were also followed in this case, however, these were not found to be adequate at the end but these are collective failure of a system (different committees) to foresee that such things can happen and thus it is requested that these may not be concluded as responsibility of one official or organization. As such happenings have raised doubt about the neutrality of important organizations like ICMR, Department of Health Research will ensure that it keeps the observations of Parliament Standing Committee in view and will not allow ICMR headquarters or any of its scientists to associate with such projects in future unless specifically asked by Government for that purpose.

Further Recommendation (Paras 3.10, 3.18, 3.19)

3.14 **The plea of the Government that being a scientific organization concerned with health problems of public health importance it (ICMR) scientifically facilitated the process of operational research by providing guidance on design and protocols/procedures pertaining to these vaccines which had the potential of preventing cervical cancer is untenable as it is the DCG(I) and NTAGI who are mandated to perform these tasks and ICMR is the apex organization for medical research in India. The Committee has no doubt at all that but for the involvement of ICMR name, no State Government would have permitted the trial conducted by the foreign private entity.**

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

Observation/Recommendation

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

Primary Outcomes:

- Number and percentage of vaccinated girls.
- Number and percentage of vaccinated girls experiencing Serious Adverse Events (SAEs)
- Number and 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.

(Para 4.4)

3.16 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. (Para 4.5)

3.17 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 rooms must be enforced However, it remained as a silent spectator thereafter, even when its own rules and regulations were being so fagrantly violated. The approval's 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**.** (Para 4.6)

Reply of the Ministry

3.18 As already mentioned in [*]Para 2.1, the PATH study falls under the category of Post Marketing trial (Phase IV) as per Schedule Y.

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[*] refer to para 2.16 of Chapter II

3.19 The Inquiry Committee has recommended that it is true that deaths have occurred in the recipients of the HPV Vaccine under the PATH study in Andhra Pradesh and Gujarat, and it is also true that lot of negative *vibe* has been generated against this project due to mal-handling of the entire situation, but the committee has not been able to identify a single event, individual or agency which can be held entirely accountable for it. However, some deficiencies in the implementation of the project did occur which have been detailed in the report. These deficiencies noted by the Committee should serve as a lesson for strengthening clinical research in future rather than starting any punitive or disciplinary proceedings.

3.20 The deficiencies do not appear to be willfully or fully anticipatable. In hindsight, these deficiencies should be viewed as a learning experience. The Committee recommends that these lessons be incorporated both in the on-going, proposed to be started and future research studies in general and new vaccines in particular so that public trust in the vital national immunization programme restored and enhanced.

3.21 The Development of HPV vaccine has provided a new opportunity for the prevention of cancer of cervix, which is an important health burden for the women of our country. HPV vaccination is not to replace the cervix cancer screening programmes, but to supplement it. However, since the vaccine is expensive, an element of cost effectiveness and determination of complete health immunization priorities should have been addressed in the study. The fact that the vaccine was provided by the manufacturers free of cost does raise the concern about the undeclared conflict of interest since the results of the study may be used to influence the decision by the government. Again since there does not appear to be covert mal- intention, no responsibility can be fixed on one person. However, any programme focusing on vaccination should also be targeting on public education for cancer Cervix screening.

3.22 Based on the discrepancies outlined in the Inquiry Committee report and its observations/ recommendations, a warning letter was issued to PATH, on 3 July, 2012, to ensure that such discrepancies/violation are not repeated in future. It was also directed to comply with the corrective action taken to ensure strict compliance of Schedule Y and GCP in ongoing study and proposed to be started in future research studies.

Further Recommendation (Paras 4.4, 4.5, and 4.6)

3.23 **The Committee had observed that DCGI has played a very questionable role in entire matter by remaining a mute spectator to violations of its own rules and regulations and recommended for enquiring into the role of DCGI. The Committee is disappointed to note that no action in this regard has been taken. The Committee accordingly impresses upon the Department to take all possible measures and adopt abundant safeguards to see that such violations are not replicated in future.**

VI. INQUIRY COMMITTEE

(d) Informed consent

Observation/Recommendation

3.24 The Inquiry Committee, while going through the above report, noticed the following irregularities and discrepancies in the study. (Para 6.14)

(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 postfacto.

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

3.25 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 too 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. (Para 6.15)

3.26 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 were 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. (Para 6.16)

Reply of the Ministry

3.27 Response as mentioned against *Paras 4.6 is reiterated.

Observation/Recommendation

3.28 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

* please refer to para 3.18 to 3.22 of Chapter III

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. (Para 6.17)

Reply of the Ministry

3.29 The Ministry of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Committee in its report identified various deficiencies in the planning and conduct of the study by PATH.

3.30 The Inquiry Committee was of the view that by whatever name it was called, the project proposal had been carried out as research on human participants. As such, it had to follow all guidelines and statutory requirements applicable on research and human participants. The Committee further reported that the deaths were "most probably" unrelated to the vaccine under trial, as there was no characteristic and uniform pattern of illness preceding the death, or temporal/spatial clustering. The Committee also observed that in the absence of control group, it was not possible to say whether there were excess deaths in the vaccinated group or not. Based on the data of background deaths from routine mortality reporting system from the same area for the vaccination period as collected by the Committee, it opined that overall death rate during the period of vaccination was not significantly different, supporting the contention that reported deaths are independent of the HPV vaccination. It further stated that internationally as on the 31st January, 2010, 49 deaths were reported in the USA against approximately 28 million doses of Gardasil vaccine distribution. Out of these, 28 deaths have been traced. According to CDC (Centre for Disease Control, USA), there was no unusual pattern or clustering to the deaths that would suggest that they were caused by the vaccine. It is further added that these two vaccines are included in the National Immunization Programmes for prevention of cervical cancer in women in many countries, like, USA, Canada, New Zealand, France, Germany, Sweden, Australia, Russia, UK, Mexico, etc.

3.31 The Inquiry Committee in its report had, however, identified various deficiencies in the planning and conduct of the study by PATH. The gist of the same is as under:

1. Consent forms and the actual implementation of the consent process.
2. Method of monitoring the adverse effects and the serious adverse effects and remedial measures for such events
3. Inclusion of vulnerable tribal population groups.
4. Blurring of distinction between National Immunization Program and PATH study.
5. Insurance coverage for the study participants
6. Free supply of vaccine by the manufacturer and the statement in the consent forms that "you will not be charged for your daughter to receive the vaccine" that could be considered as covert inducement and indirect coercion.

3.32 The penal provisions regarding the import of drugs are provided under Section 13 of the Drugs and Cosmetics Act while penalty for manufacture, sale, etc., of drugs is provided under Section 27 of the Act. There are no specific penalties for violation of the provisions relating to clinical trial under the Act.

3.33 The Drugs and Cosmetics Rules, 1945 made under the said Act, under Part XA of the Rules have provisions for Import or Manufacture of New Drugs for Clinical trials or Marketing. Under Rule 122DA, the permissions to conduct clinical trials for new drugs/investigational new drugs are granted by the Licensing Authority as defined in Rule 21(b) *i.e.* Drugs Controller General (India). The Schedule Y to the said Rule provides detailed requirements for the Informed Consent to be obtained from each study subject as well as responsibilities of the sponsor, investigator and Ethics Committee. Rule 122DB empowers the DCG(I) to suspend or cancel the permission issued to conduct the clinical trials. In the present case, since the ICMR had already suspended the trial, the DCG(I) issued 'warning' as an administrative measure to PATH on 3rd July, 2012 that it should be careful while conducting clinical trial so as to ensure that such discrepancies/violations are not repeated in future. It was further directed to comply with the corrective action taken to ensure strict compliance of Schedule Y and GCP in ongoing study and proposed to be started in future research studies.

3.34 In the meantime, the Drugs and Cosmetics Rules, 1945 were amended by Gazette Notification GSR 63(E) dated 1.2.2013, inter alia providing for following activities by DCG(I), in case of non-compliance of provisions of clinical trial:–

(a) Reject or discontinue the study;

(b) Suspend or cancel the clinical trial permission;

(c) Debar the investigator(s), Sponsor including his representative to conduct any clinical trial in future.

3.35 In light of the recommendations of the Hon'ble Committee for legal action, the Ministry of Health and Family Welfare *vide* its note dated 6.1.2011 has requested Ministry of Law and Justice for their considered opinion as to whether any further legal action is possible in the present case. A copy of the note is enclosed at Annexure C.

Further Recommendation (Paras 6.14, 6.15, 6.16, 6.17)

3.36 **The Committee may be apprised of the opinion of the Ministry of Law and Justice as solicited by the Ministry and action taken thereon.**

(f) Use of Official Machinery

Observation/Recommendation

3.37 The Committee has noted that the information/publicity material dissolved/distributed at trial sites implied that the Government 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. **(Para 6.25)**

3.38 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. **(Para 6.26)**

Reply of the Ministry

3.39 Same as mentioned against *Para 1.2, the matter pertaining to the wrongful use of NRHM logo by PATH is being enquired into.

Further Recommendation (Paras 6.25 and 6.26)

3.40 **According to the laid down rules, regulations and procedures, the sponsor (PATH) is responsible under Drugs and Cosmetics Rules because NRHM logo was displayed at the site(s) of the trial. The Committee desires that the inquiry should be completed at the earliest. The findings of the inquiry being done in this regard may also be shared with the Committee.**

Observation/Recommendation

3.41 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 22-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 CMR'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 and 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 and Ethics Committees; and (e) the consent forms are to be amended to include details of address and occupations of subject giving socio-economic background. **(Para 6.33)**

Reply of the Ministry

3.42 As regards to the amendment of the definition of New Drugs under Rule 122 E, it may be mentioned that the amendment has been issued *vide* Gazette Notification *vide* G.S.R. No. 724 (E) dated 07.11.2013 omitting the words "or its inclusion in Indian Pharmacopeia, whichever is earlier" in Rule 122 E, in clause C, in the explanation, in item (ii) Thus, as per this amendment, even if a drug including vaccine is listed in Indian Pharmacopeia, the New drug status shall be considered as per Drugs and Cosmetics Rules.

Thus, any Vaccine will always be considered as a New Drug even if it is included in I.P.

3.43 The Informed Consent Forms has been amended to include the details of socio-economic status of the trial participants. As indicated earlier, other measures have been taken to strengthen the regulatory framework of clinical trials.

Observation/Recommendation

3.44 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

* refer to para 2.2 to 2.8 of Chapter II

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 DCG(I). (Para 6.34)

Reply of the Ministry

3.45 Same as mentioned in [**]Para 1.7

Observation/Recommendation

3.46 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 inquiry Committee. (Para 6.35)

Reply of the Ministry

3.47 Same as mentioned in (Para 1.7)

Observation/Recommendation

3.48 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. (Para 6.36)

Reply of the Ministry

3.49 As mentioned in Para 4.6, the Inquiry Committee has observed that such deficiencies do not appear to be wilful or fully anticipatable. In hindsight these deficiencies should be undertaken as a learning experience. The committee recommends that these lessons be incorporated both in the ongoing, proposed to be started and future research studies in general and new vaccines in particular so that public trust in the vital national immunization programme is restored and enhanced. Details of actions taken are at [*]Para 1.2 and [**]Para 1.7

Observation/Recommendation

3.50 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 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. (Para 6.37)

Reply of the Ministry

3.51 As mentioned in [***]Para 6.33, the amendment has been issued *vide* Gazette Notification *vide* G.S.R. No. 724 (E) dated 07.11.2013 omitting the words "or its inclusion in Indian Pharmacopeia, whichever is earlier" in Rule 122 E, in clause C, in the explanation, in item (ii). Thus, as per this amendment, even if a drug including vaccine is listed in Indian Pharmacopeia, the New drug status

[*] refer to para 2.2 to 2.8 of Chapter II
[**] refer to para 2.10 & 2.11 of Chapter II
[***] refer to para 2.69 to 2.70 of Chapter II

shall be considered as per Drugs and Cosmetics Rules. Thus, any Vaccine will always be considered as a New Drug even if it is included in I.P.

3.52 It is submitted that Inquiry Committee while examining the link between deaths and vaccination had identified these lapses but had inferred that all procedures being followed at that time were followed in this case as well and there was no deliberate act of omission/ commission. As these lapses could not be foreseen by any of the committees which examined and advised on the process/procedures, Parliament Standing Committee is requested to consider the conclusions of Inquiry Committee which did not find any evidence of wilful negligence/ lapse and concluded that these lapses could not be anticipated. As this is learning in hindsight to improve and strengthen our systems, MOHFW has taken necessary steps and may be given opportunity to implement the new improved procedures and guidelines.

Further Recommendation (Paras 6.33, 6.34, 6.35, 6.36, 6.37)

3.53 **The Committee is not convinced with the rationale of the Ministry. The Ministry seems to have conveniently ignored the fact that had the extant rules been followed scrupulously, they would have taken care of the irregularities at the very outset. The Committee would thus observe that the DCG(I) did not make appropriate interventions as are necessary and failed to discharge the responsibilities as a regulator. The Committee hopes that such instances are not repeated in future. The system should be made foolproof and transparent.**

CHAPTER-IV

RECOMMENDATIONS/OBSERVATIONS IN RESPECT OF WHICH FINAL REPLIES OF THE GOVERNMENT ARE STILL AWAITED

II. NATURE OF PROJECT

Observation/Recommendation

4.1 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 programmes 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.

4.2 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. **(Para 2.5)**

Reply of the Ministry

4.3 The Inquiry Committee identified various deficiencies in the planning and conduct of the study by PATH. The gist of the same is as under:

- Consent forms and the actual implementation of the consent process.
- Method of monitoring the adverse effects and the serious adverse effects and remedial measures for such events.
- Inclusion of vulnerable tribal population groups.
- Blurring of distinction between national Immunization Programme and PATH study.
- Insurance coverage for the study participants
- Free supply of vaccine by the manufacturer and the statement in the consent forms that "you will not be charged for your daughter to receive the vaccine" that could be considered as covert inducement and indirect coercion.

4.4 As per the reports published in the journal of Bull World Health Organ 2011; 89:821-830B, from 2006-2010 PATH collaborated with the Government of India, Peru, Uganda and Vietnam to gather evidence that would support decisions on whether and how to introduce HPV vaccine. From the report, it appears that similar strategy was followed in other countries.

4.5 In the light of the recommendations of the Hon'ble Parliamentary Committee, the Ministry of Health and Family Welfare *vide* its letter dated 8th January, 2014 has requested the Ministry of External Affairs to ascertain the following facts related to the said studies through usual diplomatic channels for taking further necessary action in the matter.

- Whether the similar studies were conducted by PATH in those countries
- If so, the strategy followed by PATH in those countries for conduct of the study, and the outcome of the study.
- Whether the HPV vaccine has been introduced or not in the National health programmes of these countries based on the study conducted by the PATH. A copy of letter is enclosed at Annexure B.

Further Recommendation

4.6 **The Committee desires to be informed of the replies received from Ministry of External Affairs.**

VI. Composition and terms of references

(d) Informed consent

Observation/Recommendation

4.7 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**.** (Para 6.12)

4.8 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. (Para 6.13)

Reply of the Ministry

4.9 Response as mentioned against *Para 4.6 is reiterated. It is accepted that there were deficiencies in the study, including the process of informed consent. Corrective measures have been put in place by DCGI.

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*refer to para 3.18 to 3.22 of chapter III.

Observation/Recommendation

4.10 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 document 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 subcontractor 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. **(Para 6.28)**

Reply of the Ministry

4.11 PATH has been asked to clarify as to why it has given different figures to ICMR/ HMSC (Annexure J).

Further Recommendation

4.12 **The Committee would like to be apprised of the response of PATH and the action taken thereupon by the Government.**

VII. PROGRAMME FOR APPROPRIATE TECHNOLOGY IN HEALTH (PATH)

Observation/Recommendation

4.13 The Committee during the course of its present examination sought information from the Government about PATH in order to 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. (Para 7.1)

4.14 The information furnished to the Committee reveals that PATH describes itself as an "International non-profit, 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 and Loan Associations, Municipal Utility Services etc. are all registered as PBCs. (Para 7.2)

4.15 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 and 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 set up 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. (Para 7.3)

4.16 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. **(Para 7.4)**

4.17 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 29.4.19991 it had already opened its office in India. **(Para 7.5)**

4.18 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." **(Para 7.6)**

4.19 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. **(Para 7.7)**

4.20 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. **(Para 7.8)**

4.21 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". (Para 7.9)

4.22 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 and 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. (Para 7.10)

4.23 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 antinational and/ or unlawful activities. (Para 7.11)

4.24 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. (Para 7.12)

Reply of the Ministry

4.25 The Ministry of Health and Family Welfare *vide* its letter dated 6th January, 2014 has requested the Ministry of Home Affairs to examine the recommendation of the Hon'ble Committee and take appropriate action. The Ministry has also been requested to furnish its response to the Ministry of Health and Family Welfare for taking further necessary action in the matter. A copy of letter is enclosed at Annexure D.

Observation/Recommendation

4.26 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. **(Para 7.13)**

Reply of the Ministry

4.27 Details of action taken/being taken against PATH have been mentioned in the *Para 6.17.

4.28 As desired by the Hon'ble Committee, the Ministry of Health and Family Welfare *vide* its letter dated 6th January, 2014 has apprised the recommendations of the Hon'ble Committee to the National Human Rights Commission, New Delhi for appropriate action. The Commission has also been requested to send their comments/views to the Ministry in this regards. A copy of letter is enclosed at Annexure E.

4.29 As recommended by the Hon'ble Committee, the Ministry, *vide* its letter dated 8th January, 2014 has also has been requested the Ministry of Women and Child Development to examine the recommendations of Parliamentary Standing Committee and give its response for further necessary action. A copy of letter is enclosed at Annexure F.

Observation/Recommendation

4.30 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. **(Para 7.14)**

Reply of the Ministry

4.31 As recommended by the Hon'ble Committee, the Ministry of Health and Family Welfare vide its letter dated 8th January, 2014 has apprised the Permanent Mission of India to the UN in Geneva accordingly. A copy of letter is enclosed at Annexure G.

Observation/Recommendation

4.32 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. **(Para 7.15)**

Reply of the Ministry

4.33 As recommended by the Hon'ble Committee, the Ministry of Health and Family Welfare *vide* its letter dated 5th January, 2014 has requested the Ministry of External Affairs to examine the recommendations of the Hon'ble Committee and take appropriate action. The Ministry has also been requested to furnish their response. A copy of letter is enclosed at Annexure-H.

Further Recommendation

4.34 **The Committee feels that the magnitude of the issue has not been appropriately addressed in the communications. The Committee, however, desires that the matter may be pursued for early reply.**

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* refer to para 3.29 to 3.35 of Chapter III

RECOMMENDATIONS/OBSERVATIONS — AT A GLANCE

The Government's admission that the association of ICMR in the Study as partner creates doubt and raises the issue of conflict of interest of appearing as promoter of introduction of these vaccines, giving advice of ethics and at the same time not being in the position to ensure monitoring indicates that ICMR should have been more careful in such trials. In future efforts should be made to ensure that ICMR or any of its scientists do not associate with such projects without prior approval and permission of the Department. The Committee desires to be informed of the action taken to streamline the system. (Para 3.3)

The plea of the Government that being a scientific organization concerned with health problems of public health importance it (ICMR) scientifically facilitated the process of operational research by providing guidance on design and protocols/procedures pertaining to these vaccines which had the potential of preventing cervical cancer is untenable as it is the DCG(I) and NTAGI who are mandated to perform these tasks and ICMR is the apex organization for medical research in India. The Committee has no doubt at all that but for the involvement of ICMR name, no State Government would have permitted the trial conducted by the foreign private entity. (Para 3.14)

The Committee had observed that DCG(I) has played a very questionable role in the entire matter by remaining a mute spectator to violations of its own rules and regulations and recommended for enquiring into the role of DCG(I). The Committee is disappointed to note that no action in this regard has been taken. The Committee accordingly impresses upon the Department to take all possible measures and adopt abundant safeguards to see that such violations are not replicated in future. (Para 3.23)

The Committee may be apprised of the opinion of the Ministry of Law and Justice as solicited by the Ministry and action taken thereon. (Para 3.36)

According to the laid down rules, regulations and procedures, the sponsor (PATH) is responsible under Drugs and Cosmetics Rules because NRHM logo was displayed at the site(s) of the trial. The Committee desires that the Inquiry should be completed at the earliest. The findings of the Inquiry being done in this regard may also be shared with the Committee. (Para 3.40)

The Committee is not convinced with the rationale of the Ministry. The Ministry seems to have conveniently ignored the fact that had the extant rules been followed scrupulously, they would have taken care of the irregularities at the very outset. The Committee would thus observe that the DCG (I) did not make appropriate interventions as are necessary and failed to discharge the responsibilities as a regulator. The Committee hopes that such instances are not repeated in future. The system should be made foolproof and transparent. (Para 3.51)

The Committee desires to be informed of the replies received from Ministry of External Affairs. (Para 4.6)

The Committee would like to be apprised of the response of PATH and the action taken thereupon by the Government. (Para 4.12)

The Committee feels that the magnitude of the issue has not been appropriately addressed in the communication. The Committee, however, desires that the matter may be pursued for early reply. (Para 4.34)

MINUTES

VIII
EIGHTH MEETING

The Committee met at 10.00 A.M. on Tuesday, the 22nd December, 2014 in Room No. '67', First Floor, Parliament House, New Delhi.

MEMBERS PRESENT

1. Shri Satish Chandra Misra — *Chairman*

RAJYA SABHA

2. Shrimati Kahkashan Perween
3. Shri Jairam Ramesh
4. Chaudhary Munvvar Saleem
5. Dr. T.N. Seema

LOK SABHA

6. Shri Thangso Baite
7. Dr. Subhash Bhamre
8. Dr. Ratna De (Nag)
9. Dr. Heena Vijaykumar Gavit
10. Dr. Sanjay Jaiswal
11. Dr. K. Kamaraj
12. Shri J.J.T. Natterjee
13. Shri Chirag Paswan
14. Shri M.K. Raghavan
15. Dr. Manoj Rajoriya
16. Dr. Shrikant Eknath Shinde
17. Shrimati Rita Tarai
18. Shri Akshay Yadav

SECRETARIAT

Shri P.P.K. Ramacharyulu, *Joint Secretary*
Shri R.B. Gupta, *Director*
Shrimati Arpana Mendiratta, *Joint Director*
Shri Dinesh Singh, *Deputy Director*

I. **Opening Remarks**

2. The Chairman, at the outset, welcomed the Members of the Committee and apprised them of the agenda of the meeting *i.e.*, to consider and adopt draft (i) draft 81st Report on Action Taken by Government on Recommendations/Observations contained in the Committee's Seventy-second

Report on “Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by PATH in India”; and (ii) * * *

II.	*	*	*
3.	*	*	*
4.	*	*	*
5.	*	*	*

6. Thereafter, the Committee took up the consideration and adoption of its 81st Report. * * *. The Committee authorized its Chairman and in his absence Shri Jairam Ramesh and Dr. T. N. Seema, Member, Rajya Sabha to present the 81st Report in Rajya Sabha on the 23rd December and Dr. Manoj Rajoriya and in his absence Dr. Subhash Bhamre, Member, Lok Sabha to lay the Report in Lok Sabha on the 23rd December, 2014.

7. The Committee then adjourned at 10.45 A.M.

*** Relate to other matters.

ANNEXURES

ANNEXURE-A

R.K. JAIN, IAS
Additional Secretary & D.G.(CGHS)
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E-mail : asdgcghs-mohfw@nic.in

सत्यमेव जयते

D.O. No. X-11026/242/11-BD
भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

9th January, 2014

Dear Anuradha,

The office of Drugs Controller General (India) [DCG(I)] had granted permission to M/s PATH (Programme for Appropriate Technology in Health) for carrying out the Post licensure observational study of HPV vaccination in Gujarat and Andhra Pradesh on 9th January, 2009 under the Drugs and Cosmetics Rules, 1945. This clinical trial was to be undertaken in 16,000 adolescent girls of age 10-14 years each in Andhra Pradesh and Gujarat with Immunization schedule of 0,1 and 6 months. This project was undertaken by PATH in collaboration with ICMR (Indian Council of Medical Research) and the State. Governments of Gujarat and Andhra Pradesh

2. The Department-Related Parliamentary Standing Committee of the Ministry of Health and Family Welfare in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India has observed that the wrongfu1 use of 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 NRHM programme. A copy of the report is enclosed at Annexure A.

3. In view of the above, the NRHM Division may clarify as to whether the use of NRHM logo in the project implementation by PATH in Gujarat and Andhra Pradesh was allowed by the Division. If so, the same may please be communicated to this division for preparing the Action Taken Report on the recommendations of the Committee.

With regards.

Yours sincerely,

Sd/-
(R.K. Jain)

Shrimati Anuradha Gupta,
Additional Secretary & MD (NRHM),
Ministry of Health and Family Welfare,
Nirman Bhavan,
New Delhi.

ANNEXURE-B

Keshav Desiraju
Secretary
Tel.: 25061865, Fax: 23061252
E-mail : secy.hfw@nic.in
k.desiraju@nic.in

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Deaprtment of Health and Family Welfare
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

D.O. No. X.11026/242/11-BD
8th January, 2014

Dear Smt. Singh,

PATH (Programme for Appropriate Technology in Health), an international NGO, Conducted a post-license trail of Human Papilloma Virus (HPV) vaccine for prevention of cervical Cancer during 2009-2010. The study was carried out in the districts of Khammam of Andhra Pradesh (AP) and Vadodara of Gujarat in India. It was implemented in collaboration with the Indian Council of Medical Research and State Governments of AP and Gujarat. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project. The project was funded by a grant from Bill and Melinda Gates Foundation and donation of HPV vaccine by manufacture, *viz.* GSK and MSD. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the national health authorities for inclusion of the HPV vaccine in the National Programme.

Reports on the deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. The issue was also considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare which took a serious view of the matter. In view of this, the Department of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed at Annexure A.

Based on the discrepancies pointed out, the office of the Drugs Controller General of India issued a warning to M/s PATH on 03 July, 2012, to ensure that such discrepancies/violations are not repeated in future. It was also directed to ensure strict compliance of Schedule Y and GCP Guidelines in ongoing study and in future research studies. The trial was also suspended.

The issue has been raised by the Department-Related Parliamentary Standing Committee in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India. A copy of the report can also be seen at http://164.100.47.5/

newcomittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf. The Committee has made the following observations in respect of the study conducted in different parts of the world:

> "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."

Since we are required to make an appropriate response to the Parliamentary Standing Committee I would be grateful if we could, through usual diplomatic channels, ascertain the following facts related to the said studies.

1. Whether the similar study was conducted by PATH in those countries?
2. If so, the strategy followed by PATH in those countries for conduct of the study, and the outcome of the study.
3. Whether the HPV vaccine has been introduced or not in the national health programmes of these countries based on the study conducted by the PATH.

The information may be collected and communicated on priority for preparing the Action Taken Report on the specific recommendation of the Parliamentary Standing Committee.

Warm regards.

Yours sincerely,

Sd/-
(Keshav Desiraju)

Encls: As above

Ms. Sujatha Singh
Foreign Secretary
Ministry of External Affairs
Government of India
South Block, New Delhi.

ANNEXURE-C

No. X.11026/242/11-BD
Ministry of Health and Family Welfare
Department of Health and Family Welfare

Subject: 72nd Report of the Department-Related Parliamentary Standing Committee of the Ministry of Health and Family Welfare on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India – reference to the Ministry of Law and Justice for taking further action against PATH – regarding.

The office of Drugs Controller General (India) [DCG(I)] in consultation with ICMR (Indian Council of Medical Research) had granted permission to M/s PATH (Programme for Appropriate Technology in Health) for carrying out the Post licensure observational study of HPV vaccination in Gujarat and Andhra Pradesh on 9th January, 2009 under the Drugs and Cosmetics Rules, 1945. This clinical trial was to be undertaken in 16,000 adolescent girls of age 10-14 years each in Andhra Pradesh and Gujarat with immunization schedule of 0, 1 and 6 months. This project was undertaken by PATH in collaboration with ICMR (Indian Council of Medical Research) and the State Governments of Gujarat and Andhra Pradesh. A copy of the permission letter granted to the firm is placed at **Annexure A.**

The project was funded by a grant from Bill and Melinda Gates Foundation and had a donation of HPV vaccine by the manufacturers, *viz.* GSK and MSD to PATH. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the National Health Authorities for inclusion of the HPV vaccine in the National Progamme. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project.

Reports on the deaths of some girls who had received the HPV vaccine under the PATH project were published in the local newspapers. It drew the attention of the human rights activists and National Leaders. The issue was also considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare and it took a serious view of the reports. The Ministry of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed at **Annexure B.**

The inquiry Committee was of the view that by whatever name it was called, the project proposal had been carried out as research on human participants. As such, it had to follow all guidelines and statutory requirements applicable on research and human participants. The Committee further reported that the deaths were most probably unrelated to the vaccine under trial, as there was no characteristic and uniform pattern of illness preceding the death, or temporal/ spatial clustering. The Committee also observed that in the absence of control group, it was not possible to say whether thee were excess deaths in the vaccinated group or not. Based on the data of background deaths from routine mortality reporting system from the same area for the vaccination period as collected by the Committee, it opined that overall death rate during the period

of vaccination was not significantly different, supporting the contention that reported deaths are independent of the HPV vaccination. It further stated that internationally as on the 31st January, 2010, 49 deaths were reported in the USA against approximately 28 million doses of Gardasil vaccine distribution. Out of these, 28 deaths have been traced. According to CDC (Center for Disease Control, USA), there was no unusual pattern or clustering to the deaths that would suggest that they were caused by the vaccine. It is further added that these two vaccines are included in the National Immunization Programmes for prevention of cervical cancer in women in many countries, like, USA, Canada, New Zealand, France Germany, Sweden, Australia, Russia, UK, Mexico, etc.

The inquiry Committee in its report had, however, identified various deficiencies in the planning and conduct of the study by PATH. The gist of the same is as under:

1. Consent forms and the actual implementation of the consent process.
2. Method of monitoring the adverse effects and the serious adverse effects and remedial measures for such events.
3. Inclusion of vulnerable tribal population groups.
4. Blurring of distinction between National Immunization Programme and PATH study.
5. Insurance coverage for the study participants.
6. Free supply of vaccine by the manufacturer and the statement in the consent forms that "you will not be charged for your daughter to receive the vaccine" that could be considered as covert inducement and indirect coercion.

The Department-Related Parliamentary Standing Committee of the Ministry of Health and Family Welfare in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India has raised concern in respect of obtaining Informed Consent from study subjects, and has desired that the 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. A copy of the report is enclosed at **Annexure C.**

The Drugs and Cosmetics Act, 1940 is an Act to regulate the import, manufacture and distribution and sale of drugs and cosmetics in the country. The penal provisions regarding the import of drugs are provided under Section 13 of the Act while penalty for manufacture, sale, etc., of drugs is provided under Section 27 of the Act. There are no specific penalties for violation of the provisions relating to clinical trial under the Act.

The Drugs and Cosmetics Rules, 1945 made under the said Act, under Part X-A of the Rules have provisions for Import or Manufacture of New Drugs for Clinical trials or Marketing. Under Rule 122DA, the permissions to conduct clinical trials for new drugs/investigational new drugs are granted by the Licensing Authority as defined in Rule, 21(b) *i.e.* Drugs Controller General (India). The Schedule Y to the said Rule provides detailed requirements for the informed Consent to be obtained from each study subject as well as responsibilities of the sponsor, investigator and Ethics Committee. Rule 122DB empowers the DCG(I) to suspend or cancel the permission issued to conduct the clinical trials. In the present case, since the ICMR had already suspended the trial, the DCG(I) issued 'warning' as an administrative measure to PATH on 3rd July, 2012 that it should be careful while conducting clinical trial so as to ensure that such discrepancies/violation are not repeated in future. It was further directed to comply with the corrective action taken to ensure strict compliance of Schedule Y and GCP in ongoing study and proposed to be started in future research studies. A copy of the letter is enclosed at **Annexure D.**

In the meantime, the Drugs and Cosmetics Rules, 1945 were amended by Gazette Notification GSR 63(E) dated 1.2.2013, *inter alia* providing for following activities by DCG(I), in cause of non-compliance of provisions of clinical trial:–

(a) Reject or discontinue the study;

(b) Suspend or cancel the clinical trial permission;

(c) Debar the Investigator(s), Sponsor including his representative to conduct any clinical trial in future.

In view of the recommendations of the Parliamentary Standing Committee for legal action, the Ministry of Health and Family Welfare considers it necessary to take the considered opinion of the Ministry of Law and Justice as to whether any further legal action is possible in the present case.

(Arun Kumar Panda)
Joint Secretary
06.1.2011

Secretary
Department of Legal Affairs,
Ministry of Law and Justice
Shastri Bhavan, New Delhi.

ANNEXURE-D

Arun Kumar Panda
Joint Secretary
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सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

D.O. No. X-11026/242/11-BD
Dated 6th January, 2014

Dear Mr. Vumlunmang,

PATH (Programme for Appropriate Technology Health), an international NGO, conducted a post-license trial of Human Papilloma Virus (HPV) vaccine for prevention of cervical Cancer during 2009-2010. The study was carried out in the districts of Khammam of Andhra Pradesh (AP) and Vadodra of Gujarat in India. It was implemented in collaboration with the Indian Council of Medical Research and State Governments of AP and Gujarat. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project. The project was funded by a grant from Bill and Melinda Gates Foundation and donation of HPV vaccine by the manufacturers, *viz.* GSK and MSD. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the National Health Authorities for inclusion of the HPV vaccine in the National Programme.

Reports on the death of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. The issue was considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare and it took a serious view of the matter. In view of this, the Ministry of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed at **Annexue A.**

Based on the discrepancies pointed out the office of the Drugs Controller General of India issued a warning to M/s PATH on 03 July, 2012, to ensure that such discrepancies/violations are not repeated in future. It was also directed to ensure strict compliance of Schedule Y and GCP Guidelines in ongoing study and in future research studies. The trial was also suspended.

The issue has been raised by the Department-Related Parliamentary Standing Committee in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India. A specific concern has been raised 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 has stated that 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 least 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. The Committee has strongly recommended that 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 Government should set up one such umbrella agency which should be linked to all the agencies that are involved in the processing of such requests. A copy of the report is enclosed at **Annexure B.**

The Ministry of Home Affairs may, therefore, examine the recommendations of the Parliamentary Standing Committee and take appropriate action. It may also furnish its response for preparing the Action Taken Report on the specific recommendation.

This may kindly be treated on priority.

Regards,

Yours Sincerely

Sd/-
(Arun Kumar Panda)

Shri V. Vumlunmang
Joint Secretary (Foreigners)
Ministry of Home Affairs
North Block, New Delhi

ANNEXURE-E

Arun Kumar Panda
Joint Secretary
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सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

D.O. No. X-11026/242/11-BD
Dated 6th January, 2014

Dear Madam,

The office of Drugs Controller General (India) [DCG(I)] in consultation with ICMR (Indian Council of Medical Research) had granted permission to M/s PATH (Programme for Appropriate Technology in Health) for carrying out the Post licensure observational study of HPV vaccination in Gujarat and Andhra Pradesh on 9th January, 2009 under the Drugs and Cosmetics Rules, 1945. This clinical trial was to be undertaken in 16,000 adolescent girls of age 10-14 years each in Andhra Pradesh and Gujarat with immunization schedule of 0, 1 and 6 months. This project was undertaken by PATH in collaboration with ICMR (Indian Council of Medical Research) and the State Governments of Gujarat and Andhra Pradesh.

The project was funded by a grant from Bill and Melinda Gates Foundation and had a donation of HPV vaccine by the manufacturers, *viz.* GSK and MSD. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the National Health Authorities for inclusion of the HPV vaccine in the National Programme. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project.

Reports on the deaths of some girls who had received the HPV vaccine under the PATH project were published in the local newspapers. The issue was also considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare and it took a serious view of the reports. The Ministry of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Center for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of the studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed **Annexure A.**

The inquiry Committee was of the view that by whatever name it is called, the project proposal had been carried out as research on human participants. As such, it had to follow all guidelines and statutory requirements applicable on research and human participants. The Committee further reported that the deaths were most probably unrelated to the vaccine under trial, as there was no characteristic and uniform pattern of illness preceding the death, or temporal/ spatial clustering. The Committee also observed that in the absence of control group, it was not possible to say whether there were excess deaths in the vaccinated group or not. Based on the

data of background deaths from routine mortality reporting system from the same area for the vaccination period as collected by the Committee, it opined that overall death rate during the period of vaccination was not significantly different, supporting the contention that reported deaths are independent of the HPV vaccination. It further stated that internationally as on January 31st 2010, 49 deaths were reported in the US against approximately 28 million doses of Gardasil vaccine distribution. Out of these, 28 deaths have been traced. According to CDC (Centre for Disease Control, USA), there was no unusual pattern or clustering to the deaths that would suggest that they were caused by the vaccine. It is further added that these two vaccines are included in the National Immunization Programmes for prevention of cervical cancer in women in many countries, like, USA, Canada, New Zealand, France Germany, Sweden, Australia, Russia, UK, Mexico, etc.

The inquiry Committee in its report had, however, identified various deficiencies in the planning and conduct of the study by PATH. The gist of the same is as under:

1. Consent forms and the actual implementation of the consent process.
2. Method of monitoring the adverse effects and the serious adverse effects and remedial measures for such events.
3. Inclusion of vulnerable tribal population groups.
4. Blurring of distinction between national Immunization Programme and PATH study.
5. Insurance coverage for the study participants.
6. Free supply of vaccine by the manufacturer and the statement in the consent forms that "you will not be charged for your daughter to receive the vaccine" that could be considered as covert inducement and indirect coercion.

The Department-Related Parliamentary Standing Committee of the Ministry of Health and Family welfare in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India has raised concern in respect of obtaining inform Consent from study subjects, and has desired that the 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. The Committee also desired that the National Human Rights Commission and National Commission for Protection of Child Rights may take up the matter from the point of view of violation of human rights and child abuse. A copy of the report is enclosed at **Annexure B.**

The National Human Rights Commission may, therefore, consider taking note of the recommendations of the Parliamentary Standing Committee for appropriate action. It may consider sending its comments/views to the Ministry, if any, in this regard.

Regards,

Yours Sincerely

Sd/-
(Arun Kumar Panda)

Shrimati Parvinder Sohi Behuria
Secretary General
National Human Rights Commission
Manav Adhikar Bhavan, Block C
GPO Complex, INA, New Delhi-110023

ANNEXURE-F

Keshav Desiraju
Secretary
Tel.: 23061863, Fax: 23061252
E-mail : secy.hfw@nic.in
k.desiraju@nic.in

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Deaprtment of Health and Family Welfare
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

D.O. No. X.11026/242/11-BD
8th January, 2014

Dear Shri Jain,

PATH (Programme for Appropriate Technology in Health), an international NGO, conducted a post-license trail of Human Papilloma Virus (HPV) vaccine for prevention of cervical Cancer during 2009-2010. The study was carried out by the districts of Khammam of Andhra Pradesh (AP) and Vadodara of Gujarat in India. It was implemented in collaboration with the Indian Council of Medical Research and State Governments of AP and Gujarat. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project. The project was funded by a grant from Bill and Melinda Gates Foundation and donation of HPV vaccine by manufacture, *viz.* GSK and MSD. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the national health authorities for inclusion of the HPV vaccine in the National Programme.

Reports on the deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. The issue was also considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare which took a serious view of the matter. In view of this, the Department of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed at **Annexure A.**

Based on the discrepancies pointed out, the office of the Drugs Controller General of India issued a warning to M/s PATH on 03 July, 2012, to ensure that such discrepancies/violations are not repeated in future. It was also directed to ensure strict compliance of Schedule Y and GCP Guidelines in ongoing study and in future research studies. The trial was also suspended.

The Department-Related Parliamentary Standing Committee of the Ministry of Health and Family Welfare in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India has raised concern in respect of obtaining

Informed Consent from study subjects, and has desired that the 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. The Committee raised concerns in respect of the violations in the conduct of the clinical trial, causing harm to the life and safety of the girls who were vaccinated. A copy of the report is enclosed at **Annexure B.**

The Committee has recommended in its report that the National Commission for Women and National Commission for Protection of Child Rights may take up the matter from the point of view of violation of human rights and child abuse. The Committee also desired that the Ministry of Health and Family Welfare should report the violations indulged in by PATH to international bodies like UNICEF so as to ensure that appropriate remedial action is initiated by these agencies worldwide.

The Ministry of Women and Child Development may, therefore, examine the recommendations of the Parliamentary Standing Committee and give its response for making suitable reply for preparing the Action Taken Report on the specific recommendation.

Regards

Yours sincerely,

Sd/-
(Keshav Desiraju)

Encls: As above.

Shri A.K. Jain
Secretary
Ministry of Women and Child Development
Shastri Bhavan, New Delhi

ANNEXURE-G

Keshav Desiraju
Secretary
Tel.: 23061863, Fax: 23061252
E-mail : secy.hfw@nic.in
k.desiraju@nic.in

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Deaprtment of Health and Family Welfare
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

D.O. No. X.11026/242/11-BD
8th January, 2014

Dear Dilip,

PATH (Programme for Appropriate Technology in Health), an international NGO, conducted a post-license trail of Human Papilloma Virus (HPV) vaccine for prevention of cervical Cancer during 2009-2010. The study was carried out by the districts of Khammam of Andhra Pradesh (AP) and Vadodara of Gujarat in India. It was implemented in collaboration with the Indian Council of Medical Research and State Governments of AP and Gujarat. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project. The project was funded by a grant from Bill and Melinda Gates Foundation and donation of HPV vaccine by manufacture, *viz.* GSK and MSD. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the national health authorities for inclusion of the HPV vaccine in the National Programme.

Reports on the deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. The issue was also considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare which took a serious view of the matter. In view of this, the Department of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed at **Annexure A.**

Based on the discrepancies pointed out, the office of the Drugs Controller General of India issued a warning to M/s PATH on 03 July, 2012, to ensure that such discrepancies/violations are not repeated in future. It was also directed to ensure strict compliance of Schedule Y and GCP Guidelines in ongoing study and in future research studies. The trial was also suspended.

The issue has been raised by the Department-Related Parliamentary Standing Committee in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India. The Committee in the report has raised concerns in respect of

the violations in the conduct of the clinical trial, causing harm to the life and safety of the girls, who were vaccinated. A copy of the report in enclosed at **Annexure B.**

The Committee has recommended in its report that the Ministry of Health and Family Welfare should 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.

I am not sure what exactly is possible by way of reporting of violations to the WHO. However, you may wish to be apprised of the facts.

Warm regards

Yours sincerely,

Sd/-
(Keshav Desiraju)

Encls: As above

Shri Dilip Sinha
Permanent Mission of India
To the UN in Geneva
9 Rue du Calais
Geneva 1202

ANNEXURE-H

Arun Kumar Panda
Joint Secretary
Tele. : 23063155
Telefax : 23063156
E-mail : arunpanda84@gmail.com

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली–110011
Government of India
Ministry of Health and Family Welfare
Nirman Bhavan, New Delhi-110011

D.O. No. X-11026/242/11-BD
Dated 6th January, 2014

Dear Shri Doraiswami,

PATH (Programme for Appropriate Technology Health), an international NGO, conducted a post-license trial of Human Papilloma Virus (HPV) vaccine for prevention of cervical Cancer during 2009-2010. The study was carried out in the districts of Khammam of Andhra Pradesh (AP) and Vadodra of Gujarat in India. It was implemented in collaboration with the Indian Council of Medical Research and State Governments of AP and Gujarat. Besides India, the project was also carried out in Peru, Uganda and Vietnam as a global project. The project was funded by a grant from Bill and Melinda Gates Foundation and donation of HPV vaccine by the manufacturers, *viz.* GSK and MSD. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. The information derived from the project was expected to be useful to the National Health Authorities for inclusion of the HPV vaccine in the National Programme.

Reports on the deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. The issue was also considered by the Department-Related Parliamentary Standing Committee on Health and Family Welfare and it took a serious view of the matter. In view of this, the Ministry of Health and Family Welfare constituted a Committee under the chairmanship of Dr. S.S. Agarwal, former Director, Advanced Centre for Training, Research, Education on Cancer to enquire into the alleged irregularities in the conduct of studies on Human Papilloma Virus (HPV) vaccine by PATH in India. The Inquiry Committee in its report identified various deficiencies in the planning and conduct of the study by PATH. A copy of the report is enclosed at **Annexue A.**

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The issue has been raised by the Department-Related Parliamentary Standing Committee in its 72nd Report on alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine by PATH in India. The Committee in the report has raised concern in respect of the violations in conduct of the clinical trial resulting in life and safety of the girls, who were vaccinated. A copy of the report is enclosed at **Annexure B.** The relevant extracts of the report are as under:

"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."

"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 the appropriate action is taken against PATH under the laws of its country of origin in case of any violations of laws there."

The Ministry of External Affairs may, therefore, examine the recommendations of the Parliamentary Standing Committee and take appropriate action. It may also furnish its response for preparing the Action Taken Report on the specific recommendation.

Regards,

Yours Sincerely

Sd/-
(Arun Kumar Panda)

Shri Vikram Kumar Doraiswami
Joint Secretary [Americas Division]
Ministry of External Affairs
South Block, New Delhi

ANNEXURE-I

No.HPV/Path/Committee (PSC)/14-NCD-III
Dated 10.1.2014

Office Memorandum

Pursuant to the observations of 72nd Parliamentary Standing Committee Report on effects of HPV Vaccine, Secretary (Department of Health Research) and DG, ICMR has constituted a Committee comprising of following members to examine the global and national data to analyze link, if any, between suicidal ideation and HPV Vaccine administration.

1. Dr. Savita Malhotra, PGIMER, Chandigarh (Chairperson)
2. Dr. Chandra Prabha, NIMHANS, Bangalore
3. Dr. Y.K. Gupta, AIIMS, Delhi
4. Dr. R.M. Pandey, AIIMS, Delhi
5. Dr. S. Khandelwal, AIIMS, Delhi
6. Dr. A.K. Dutta, Kalawati Saran Hospital, Delhi
7. Dr. C.Nath, CDRI, Lucknow
8. Dr. G.N. Singh, DCGI
9. Dr. Tanvir Kaur (ICMR) – Member Secretary

Committee may co-opt any other expert, it may consider necessary and may also examine any material it may consider relevant.

Committee may submit its report by 28th February, 2014.

Sd/-
(D.K. Shukia)
Scientist-F and Head (NCD)

ANNEXURE-J

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फैक्स / PABX : 011-26588662, 011-26589791, 011-26589258

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भारतीय आयुर्विज्ञान अनुसंधान परिषद्
INDIAN COUNCIL OF MEDICAL RESEARCH

स्वास्थ्य अनुसंधान विभाग (स्वास्थ्य एवं परिवार कल्याण मंत्रालय)
वी. रामलिंगस्वामी भवन, अन्सारी नगर, नई दिल्ली–110 029
DEPARTMENT OF HEALTH RESEARCH (MINISTRY OF HEALTH AND FAMILY WELFARE
V.RAMALINGASWAMI BHAWAN, ANSARI NAGAR, NEW DELHI-110 029

No.HPV/Path/Committee (PSC)/14-NCD-RI
Dated: 13.1.2014

Shri Tarun Vij
Country Director,
Programme for Appropriate Technology in Health (PATH)
A-9, US Road, Kutab Institutional Area,
New Delhi – 110 067

Dear

Kindly refer to investigations of Parliamentary Standing Committee regarding the HPV project carried out by PATH in the Khammam district of Andhra Pradesh and Vadodara, Gujarat. The Parliamentary Standing Committee has noted that according to the details submitted by PATH to ICMR/Health Ministry Screening Committee, the total oulay 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.

You are requested to clarify hy there is a disparity between the figures submitted to ICMR/ Health Ministry and your records. This information may be sent at an earliest preferably within 4 weeks so that clarification may be provided to the Parliamentary Standing Committee.

This issues with the approval of Secretary (DHR) and DG, ICMR.

Yours sincerely,

Sd/-
(D.K. Shukia)
Scientist-F and Head (NCD)

Observation/Recommendation

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. **(Para 1.4)**

Reply of the Ministry

As per schedule Y to Drugs and Cosmetics Rules, 3(2), the timing of paediatric studies in the new drug development program depends on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

Before approval of HPV vaccine in India, two Phase III clinical trials were carried out in India. 1) Clinical trial on 330 female subjects between 18-35 years of age for Cerverix vaccine (M/s GSK) and 2) Clinical trial on 108 subjects aged 9-15 years with Gardasil (M/s MSD).

Both the HPV vaccines were already approved and marketed in many countries at the time of granting permissions for the above two studies.

HPV vaccine prevents cervical cancer, when used in female subjects before the sexual activity begins.

In view of above, the permission to conduct the Phase III clinical trial in the age group of 9-15 years was granted as per the provisions of Drugs and Cosmetics Rules.

The Inquiry Committee, in this regard, has also opined that not only the requirement of assessing the safety and efficacy of the vaccine in adult prior to use in children has been fulfilled, the data on adolescent girls has also been acquired. As such, there was no violation of any laid down guidelines for use of New drugs/Vaccine in the paediatric age groups.

LIST OF REPORTS PRESENTED EARLIER

Report No.	Subject
1	2
1.	Demands for Grants 2004-05 of Department of Health (Ministry of Health and Family Welfare)
2.	Demands for Grants 2004-05 of Department of Family Welfare (Ministry of Health and Family Welfare)
3.	Demands for Grants 2004-05 of Department of AYUSH (Ministry of Health and Family Welfare)
4.	Fourth Report of the Committee on Action Taken by the Department of Health on the Recommendations/Observations contained in the First Report of the Committee on Demands-for-Grants (2004-05) of the Department of Health.
5.	Fifth Report of the Committee on Action Taken by the Department of Family Welfare on the Recommendations/Observations contained in the Second Report of the Committee on Demands-for-Grants (2004-05) of the Department of Family Welfare.
6.	Sixth Report on Action Taken by the Department of AYUSH on the Recommendations/ Observations contained in the Third Report of the Committee on Demands-for-Grants (2004-05) of the Department of AYUSH.
7.	Seventh Report on Demands for Grants 2005-06 of Department of Health (Ministry of Health and Family Welfare).
8.	Eighth Report on Demands for Grants 2005-06 of Department of Family Welfare (Ministry of Health and Family Welfare).
9.	Ninth Report on Demands for Grants 2005-06 of Department of AYUSH (Ministry of Health and Family Welfare).
10.	Tenth Report on the Homoeopathy Central Council (Amendment) Bill, 2005
11.	Eleventh Report on the Indian Medicine Central Council (Amendment) Bill, 2005
12.	Twelfth Report on the Drugs and Cosmetics (Amendment) Bill, 2005
13.	Thirteenth Report of the Committee on Action Taken by the Department of Family Welfare on the Recommendations/Observations contained in the Eighth Report of the Committee on Demands-for-Grants (2005-06) of the Department of Family Welfare.
14.	Fourteenth Report of the Committee on Action Taken by the Department of AYUSH on the Recommendations/Observations contained in the Ninth Report of the Committee on Demands-for-Grants (2005-06) of the Department of AYUSH.

1	2
15.	Fifteenth Report of the Committee on Action Taken by the Department of Health on the Recommendations/Observations contained in the First Report of the Committee on Demands-for-Grants (2005-06) of the Department of Health.
16.	Demands for Grants 2006-07 of Department of Health and Family Welfare (Ministry of Health and Family Welfare).
17.	Demands for Grants 2006-07 of Department of AYUSH (Ministry of Health and Family Welfare).
18.	Eighteenth Report on the Indian Medicine and Homoeopathy Pharmacy Bill, 2005
19.	Nineteenth Report on the Indian Medical Council (Amendment) Bill, 2005
20.	Twentieth Report of the Committee on Action Taken by the Department of Health and Family Welfare on the Recommendations/Observations contained in the Sixteenth Report of the Committee on Demands-for-Grants (2006-07) of the Department of Health and Family Welfare.
21.	Twenty-First Report of the Committee on Action Taken by the Department of AYUSH on the Recommendations/observations contained in the Seventeenth Report of the Committee on Demands-for-Grants (2006-07) of the Department of AYUSH.
22.	Demands for Grants 2007-08 of Department of Health and Family Welfare (Ministry of Health and Family Welfare)
23.	Demands for Grants 2007-08 of Department of AYUSH (Ministry of Health and Family Welfare)
24.	Twenty-fourth Report on JIPMER, Puducherry, Bill, 2007
25.	Twentieth-fifth Report of the Committee on Action Taken by the Department of Health and Family Welfare on the Recommendations/Observations contained in the Twenty-second Report of the Committee on Demands-for-Grants (2007-08) of the Department of Health and Family Welfare.
26.	Twenty-sixth Report of the Committee on Action Taken by the Department of AYUSH on the Recommendations/Observations contained in the Twenty-third Report of the Committee on Demands-for-Grants (2007-08) of the Department of AYUSH.
27.	Demands for Grants 2008-09 of Department of Health and Family Welfare (Ministry of Health and Family Welfare).
28.	Demands for Grants 2008-09 of Department of AYUSH (Ministry of Health and Family Welfare).
29.	Demands for Grants 2008-09 of Department of Health Research (Ministry of Health and Family Welfare).
30.	The Drugs and Cosmetics (Amendment) Bill, 2007
31.	The Paramedical and Physiotherapy Central Councils Bill, 2007
32.	The Clinical Establishments (Registration and Regulation) Bill, 2007

1	2
33.	The Post-Graduate Institute of Medical Education and Research, Chandigarh (Amendment) Bill, 2008
34.	The functioning of the three Vaccine Producing PSUs, namely, the Central Research Institute (CRI), Kasauli, the Pasteur Institute of India (PII), Coonoor, and the BCG Vaccine Laboratory (BCGVL), Chennai.
35.	Thirty-fifth Report on Action Taken by Government on the Recommendations/ Observations contained in the Twenty Seventh Report on Demands for Grants 2008-09 of the Department of Health and Family Welfare.
36.	Thirty-sixth Report on Action Taken by Government on the Recommendations/ Observations contained in the Twenty eighth report on Demands for Grants 2008-09 of the Department of AYUSH.
37.	Thirty-seventh Report on Action Taken by Government on the Recommendations/ Observations contained in the Twenty ninth report on Demands for Grants 2008-09 of the Department of Health Research.
38.	Thirty-eighth Report on Major Issues concerning the three vaccine producing PSUs, Namely the Central Research Institute (CRI), Kasauli, the Pasteur Institute of India (PII), Coonoor, and the BCG Vaccine Laboratory (BCGVL), Chennai.
39.	Department-related Parliamentary Standing Committee on Health and Family Welfare Thirty Ninth Report on Demands for Grants (2010-11) pertaining to the Department of Health and Family Welfare.
40.	Department-reated Parliamentary Standing Committee on Health and Family Welfare Fortieth Report on Demand for Grants 2010-11 of Department of AYUSH.
41.	Department-related Parliamentary Standing Committee on Health and Family Welfare Forty First Report on Demands for Grants 2010-11 pertaining to Department of Health Research.
42.	Department-related Parliamentary Standing Committee on Health and Family Welfare Forty Second Report on Demands for Grants 2010-11 pertaining to Department of AIDS Control.
43.	Action Taken by the Department of Health and Family Welfare on the Recommendations/Observations of the Committee contained in its Thirty-Eighth Report on major issues concerning the three vaccine producing PSUs, namely, the Central Research Institute (CRI), Kasauli, the Pasteur Institute of India (PII), Coonoor, and the BCG Vaccine Laboratory (BCGVL), Chennai.
44.	The Transplantation of Human Organs (Amendment) Bill, 2009
45.	Issues Relating to availability of Generic, Generic-branded and Branded Medicines, their Formulation and Therapeutic Efficacy and Effectiveness.
46.	The Indian Medicine Central Council (Amendment) Bill, 2010
47.	The Jawaharlal Institute of Post-Graduate Medical Education and Research, Puducherry (Amendment) Bill, 2010

1	2
48.	Action Taken by Government on the Recommendations/Observations contained in the Forty-First Report on Demands for Grants 2010-11 (Demand No. 48) of the Department of Health Research.
49.	Action Taken by Government on the Recommendations/Observations contained in the Forty-Second Report on Demands for Grants 2010-11 of the Department of AIDS Control.
50.	Action Taken by Government on the Recommendations/Observations contained in the Fortieth Report on Demands for Grants 2010-11 (Demand No. 47) of the Department of AYUSH.
51.	Action Taken by Government on the Recommendations/Observations contained in the Thirty-Ninth Report on Demands for Grants 2010-11 (Demand No. 46) of the Department of Health and Family Welfare.
52.	Action Taken by the Department of Health and Family Welfare on the Recommendations/Observations of the Committee contained in its 43rd Report on Action Taken by the Department of Health and Family Welfare on the Recommendations/Observations of the Committee contained in its 38th Report on major issues concerning the three Vaccine Producing PSUs, namely, the Central Research Institute (CRI), Kasauli, the Pasteur Institute of India (PII), Coonoor, and the BCG Vaccine Laboratory (BCGVL), Chennai.
53.	The National Institute of Mental Health and Neuro-Sciences, Bangalore Bill, 2010
54.	Demand for Grants 2012-13 (Demand No. 46) of the Department of Health and Family Welfare (Ministry of Health and Family Welfare).
55.	Demands for Grants 2012-13 (Demand No. 47) of the Department of AYUSH.
56.	Demands for Grants 2012-13 (Demand No. 48) of the Department of Health Research.
57.	Demand for Grants 2012-13 (Demand No. 49) of the Department of AIDS Control
58.	Action taken by the Government on the Recommendations/Observations contained in the Forty fifth Report on issues relating to availability of Generic, Generic-Branded and Branded Medicines, their formulation and Therapeutic Efficacy and Effectiveness.
59.	The Functioning of the Central Drugs Standard Control Organisation (CDSCO).
60.	The National Commission for Human Resources For Health Bill, 2011
61.	Action Taken by Government on the Recommendations/Observations contained in the Fifty-Fifth Report on Demands for Grants 2012-13 (Demand No. 47) of the Department of AYUSH.
62.	Action Taken by Government on the Recommendations/Observations contained in the Fifty-Seventh Report on Demands for Grants 2012-13 (Demand No. 49) of the Department of AIDS Control.
63.	Report on Action Taken by Government on the Recommendations/Observations contained in the Fifty-Sixth Report on Demands for Grants 2012-13 (Demand No. 48) of the Department of Health Research (Ministry of Health and Family Welfare).

1	2
64.	Action taken by Government on the Recommendations/Observations contained in the Fifty-Fourth report on Demands for Grants 2012-13 (Demand No. 46) of the Department of Health and Family Welfare.
65.	The Proposal to Introduce the Bachelor of Science (Community Health) Course.
66.	Action Taken by the Government on the Recommendations/Observations contained in the Fifty Ninth Report on the functioning of Central Drugs Standards Control Organisation (CDSCO).
67.	Demands for Grants 2013-14 (Demand No. 47) of the Department of Health and Family Welfare.
68.	Demands for Grants 2013-14 (Demand No. 48) of the Department of AYUSH (Ministry of Health and Family Welfare).
69.	Demands for Grants 2013-14 (Demand No. 49) of the Department of Health Research (Ministry of Health and Family Welfare).
70.	Demands for Grants 2013-14 (Demand No. 50) of the Department of AIDS Control (Ministry of Health and Family Welfare).
71.	Functioning of Central Government Health Scheme (CGHS).
72.	Alleged irregularities in the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine by Path in India.
73.	The Indian Medical Council (Amendment) Bill, 2013
74.	The Mental Health Care Bill, 2013
75.	Action Taken by Government on the Recommendations/Observations contained in the Sixty-Eighth Report on Demands for Grants 2013-14 (Demand No. 48) of the Department of AYUSH
76.	Action Taken by Government on the Recommendations/Observations contained in the Seventieth Report on Demands for Grants 2013-14 (Demand No. 50) of the Department of AIDS Control
77.	Action Taken by Government on the Recommendations/Observations contained in the Sixty-Nineth Report on Demands for Grants 2013-14 (Demand No. 49) of the Department of Health Research
78.	Action Taken by Government on the Recommendations/Observations contained in the Sixty-Seventh Report on Demands for Grants 2013-14 (Demand No. 47) of the Department of Health and Family Welfare (Ministry of Health and Family Welfare)
79.	The Drugs and Cosmetics (Amendment) Bill, 2013
80.	The Food Safety and Standards (Amendment) Bill, 2014

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