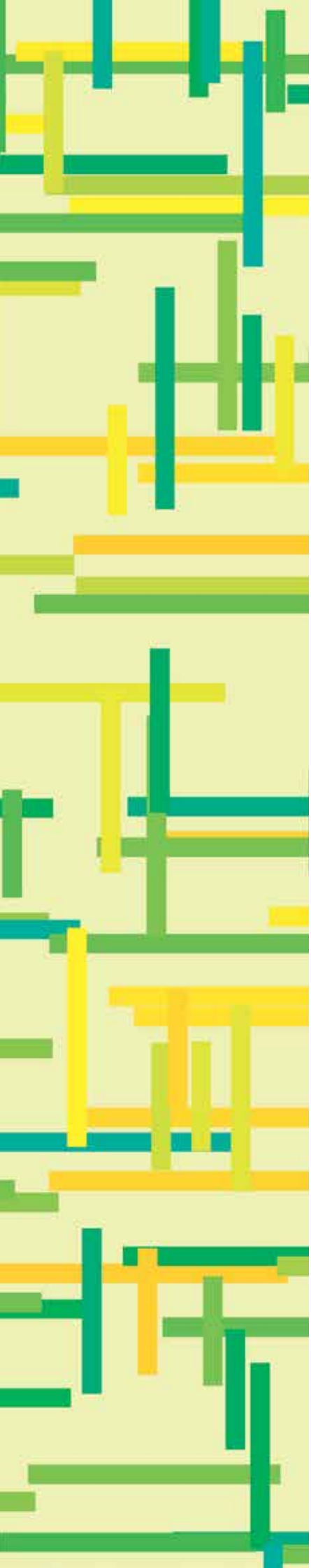

GUIDANCE
FOR INDUSTRY ON
PHARMACOVIGILANCE REQUIREMENTS FOR BIOLOGICAL PRODUCTS

File No. DCGI/PvPI-Guidance/2017 (I)
Central Drugs Standard Control Organization
Office of Drugs Controller General (India)

FDA Bhawan, Kotla Road
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ORDER

Subject: The Guidance for Industry on Pharmacovigilance Requirements for Biological Products

As per provisions under Schedule Y of Drugs and Cosmetics Act 1940 and Drugs and Cosmetics Rules, 1945, subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed and marketing authorization holder shall submit the periodic safety update reports on regular interval.

The Guidance for Industry, Pharmacovigilance activities for vaccines as a part of post licensure procedures involves the Pharmacovigilance Programme of India (PvPI) at the National Coordinating Centre in IPC Ghaziabad, Adverse Events Following Immunization (AEFI) Division, Ministry of Health and Family Welfare, submission of Periodic Safety Update Reports and Post Marketing Surveillance Studies to Central Drugs Standard Control Organization (CDSCO) according to conditions of Marketing Authorization as granted by the Licensing Authority. This document has been prepared in line with recommendation of the NRA Assessment 2012 to provide guidance for the Marketing Authorization Holder to perform specific safety study throughout the product life cycle.

The present document provides the roles and responsibilities of all the concerned stakeholders and document has been developed in consultation with all involved in Pharmacovigilance activities of vaccines viz. Immunization Division, Ministry of Health and Family Welfare, PvPI IPC Ghaziabad, Central Drugs Standard Control Organization and vaccines manufacturers/importers.

In this regard, on 01-July-2014, a draft Guidance document was placed in the website of CDSCO for comments of public/stakeholders. After having considered the comments received, the guidance document has been finalised and approved by the competent authority.

The guidance document has been further updated as per the amended regulations and as per current regulatory procedures and sharing of information between CDSCO, PvPI at NCC and Immunization Division, MoHFW.

The final guidance document for Industry on Pharmacovigilance Requirements for Biological Products as approved is enclosed for all concerned.

(Dr. G. N. Singh)
Drugs Controller General (India)

PREFACE

This is in consonance with the objective of the Drugs & Cosmetics Act 1940 and Rules 1945 there under and other functions of CDSCO wherever applicable. These guidelines are intended for the guidance of the Marketing Authorization Holders (MAHs) i.e. manufacturers and importers of biological products. The procedure set out to facilitate the industry to submit the documents as per the requirements of Drugs and Cosmetics Act and Rules. Guidance documents may be amended from time to time as per requirements after obtaining necessary approval from the competent authority.

FOREWORD

The Central Drugs Standard Control Organization (CDSCO), being the apex regulatory authority for approval of drugs in India, is committed to safeguard and enhance the Public Health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices.

India has extensive Pharmacovigilance activities for vaccines as part of post licensure submissions in form of PSURs, PMS studies, AEFI case reports and individual case safety reports (ICSRs) received by PvPI at IPC. The present document is developed to provide the guidance to all the stakeholders including the Marketing Authorization Holders on the coordinated activities of the various departments within the Ministry of Health and Family Welfare to work together and enhance the pharmacovigilance of vaccines.

The guidance document has been prepared in line with the recommendation of the NRA assessment 2012 to provide guidance for the MAH to perform specific safety study throughout the product life cycle and to define the roles and responsibilities of all the stake holders namely CDSCO, PvPI at IPC, Immunization Division, MAH, private and public practitioners and outlines the Risk Minimization Action Plan. This could provide guidance to the manufacturers and importers of vaccines in the country to strengthen their ADR monitoring and pharmacovigilance department to ensure patient safety.

CONTENTS

ABBREVIATIONS:

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization
CDL	Central Drugs Laboratory
CDSCO	Central Drugs Standard Control Organisation
CRF	Case Report Form
DCG(I)	Drugs Controller General (India)
DIO	District Immunization Officer
DOV	Date of Vaccination
EPI	Expanded Programme on Immunization
FCIF	Final Case Investigation Form
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GLP	Good Laboratory Practices
ICSR	Individual Case Safety Reports
IPC	Indian Pharmacopoeia Commission
ITSU	Immunization Technical Supportive Unit
MAH	Marketing Authorization Holder
NCC	National Coordinating Centre
NRA	National Regulatory Authority
PBRER	Periodic Benefit Risk Evaluation Report
PCIF	Preliminary Case Investigation Form
PSUR	Periodic Safety Update Report
PhFI	Public Health Foundation of India
PvPI	Pharmacovigilance Programme of India
SEPIO	State EPI Officer
UIP	Universal Immunization Programme

1. INTRODUCTION:

Over the last three decades, India has become a vibrant hub of vaccine manufacturing units with state-of-the-art facilities at par with the International manufacturing standards. Today every third child in the world is administered with the vaccine of Indian origin. India can now boast of producing safe, effective and affordable vaccine products which safe guard millions of children in domestic and International Market. This responsibility warrants additional effort of constant vigilance of vaccine products moving in the market.

The pre-market mandatory clinical trial has little scope to assess the inherent risks associated with the nature of antigens /excipients formulation or that cropping up due to specific manufacturing process and raw materials used

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, post marketing surveillance which may be passive or stimulating have major role to assess the actual safety aspects of the vaccine product. Safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

This guidance document focuses on pharmacovigilance activities on a vaccine product circulating in the market throughout its life cycle post licensure period. This guidance uses the term pharmacovigilance to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from post marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacological class. It is possible that even a single well documented case report can be viewed as a signal, particularly if the report describes a positive re-challenge and de-challenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

1.1 OBJECTIVE:

This document intends to be an aid to the Marketing Authorization Holders (MAH) and other allied stake holders who play active role in launching, distribution and bringing the vaccine products to its end users.

The main focus of this guideline is to identify the risks, formulate the risk profile of a vaccine and its administration programme, design of appropriate pharmacovigilance plan to mitigate such risks and to explore the missing critical information which did not emerge during pre-market phase-I/II/III trials and therefore safety profile had not been established.

1.2 BACKGROUND

The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of subject characteristics and the number of patients exposed. In particular, during the early post marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a vaccine is marketed, new information might emerge, which may have an impact on the benefits/risks ratio of the product. Evaluation of this information should be a continuing process in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

1.3 RATIONALE

This document rationally place guidance that all Marketing Authorization Holder (MAH) of Human vaccines(importers and manufacturers)should establish an appropriate pharmacovigilance system with adequate number of qualified, trained, experienced manpower to collect, collate all AEFI (minor, severe and serious). This pharmacovigilance system within the company should conduct decisive causality analysis of the collated AEFI cases, after due investigation and prepare case closure report. In a comprehensive PSUR, all such information shall have to be placed as per the norms stipulated in Schedule-Y of Drugs & Cosmetics Act 1940 and Rules 1945 and submitted to the Licencing Authority i.e DCG(I) in CDSCO (HQ) in a timely manner. CDSCO shall convene the meeting of PSUR committee within a reasonable time period and give opportunities to the concerned Marketing Authorization Holder (MAH) to present their case and PSUR in general. Based on the recommendation of the PSUR committee the vaccine Licensing Authority i.e. DCG(I) will take appropriate regulatory action in accordance with Drugs & Cosmetics Act 1940 and Rules 1945, so as to monitor the safety and effectiveness of human vaccine in the market. MAHs must have a system in place that enhances the overall quality of the receipt, processing and reporting of ADE while ensuring that accurate and complete pharmacovigilance information is provided to CDSCO.

1.4 SCOPE

This document has been framed in compliance with the provisions made under schedule-Y of Drugs & Cosmetics Act 1940 and Rules 1945 and Good Clinical Practices (GCP) Guidelines of India to provide Guidance to Marketing Authorization Holders (Importers and Manufacturers of Human Vaccine) India to establish their pharmacovigilance system to collect all AEFI

cases pertaining to their vaccine products across the domestic and export market, after due investigation & causality analysis at their end and collate all such cases in PSUR for periodic reporting to the Licensing Authority i.e. DCG(I) in CDSCO.

This document does not include all other new Drugs and animal vaccine moving in the market.

This document is designed to facilitate compliance by the Industry and to enhance consistency in the implementation of the regulatory requirements regarding Good Pharmacovigilance Practices.

This document would provide adequate information in a systematic manner for reporting serious adverse event or adverse event when the product is in the market and would enable the systematic sharing of information between CDSCO, Pharmacovigilance Programme of India (PvPI) and the Expanded Programme on Immunization (EPI), Ministry of Health and Family Welfare.

The Roles and Responsibilities of the CDSCO are as per the Drugs and Cosmetics Act 1940 and Rules 1945. The Pharmacovigilance Programme of India has the responsibility to collate the data received by them and to share the adverse reaction reported for vaccines to (i) District Immunization Officer (DIO), (ii) State AEFI Committee and (iii) the National AEFI Committee for examination and recommendation. The results of the cases discussed in the Signal Review Panel of the Pharmacovigilance Programme of India (PvPI) will be shared with AEFI Secretariat and CDSCO for regulatory action.

The Licensing Authority may also advise the MAH to conduct Phase IV trial in case of demonstration of product safety, efficacy and dose definitions. 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 product use. They may be of any type but should have valid scientific objectives, for example, epidemiological studies etc.

Similarly the Immunization Division under Ministry of Health and Family Welfare collects information on adverse event related to vaccines on a regular basis. Information on serious adverse events is collected in the Case Report Form (CRF) and details of the investigation of the reported event are collected in the Preliminary Case Investigation Form (PCIF) and Final Case Investigation Form (FCIF) in which the State AEFI Committee assigns the causality. The AEFI Secretariat will share limited linelist in excel format with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited linelist will be in excel format and will have state, age, sex, date of vaccination (DOV), antigens administered, manufacturing details (name, batch number and expiry date) and reason for reporting. CDSCO will share linelist details for vaccines relevant to the particular manufacturer with instructions that these are being shared with the MAH for internal review and not for investigations in the field.

AEFI Secretariat of the immunization division conducts a quarterly review of completely investigated AEFI cases which are reviewed and classified by the National AEFI Committee (through the causality assessment sub-committee) to the Immunization Division of Ministry of Health and Family Welfare. These assessment reports are shared with CDSCO and based on the causality assessment report detailed inspection related to GMP, product quality assessment etc. and further regulatory action are initiated by the NRA, in case the quality of the implicated vaccines are indicated to be responsible for the adverse events in the causality assessment report.

2. ROLES AND RESPONSIBILITIES OF AUTHORITIES:

2.1 CENTRAL DRUGS STANDARD CONTROL ORGANIZATION:

The Central Drugs Standard Control Organization (CDSCO) under DGHS in Ministry of Health and family welfare (Govt. of India) acts as the nodal agency (NRA) for regulation of "Drugs" as defined in section 3

(b) (i-iv) in Drugs & Cosmetics Act 1940 to ensure the Quality, safety, efficacy of all human vaccines (defined as Drugs). CDSCO is empowered under Drugs & Cosmetics Act 1940 to grant permission, licenses for marketing within the country and foreign country as well. CDSCO is also mandated by Ministry of Health and Family Welfare, Govt. of India, to conduct a nation-wide pharmacovigilance programme in coordination with the Indian Pharmacopoeia Commission (IPC) located at Ghaziabad which is the National Coordinating Centre (NCC) of many ADR monitoring centers established in various medical colleges across the country.

The Roles and Responsibilities of CDSCO are as per the Drugs and Cosmetics Act and Rules. CDSCO is responsible to take appropriate regulatory decision and actions on the basis of recommendations of NCC-PvPI at IPC Ghaziabad and AEFI programme of Immunization division of Ministry of Health and Family Welfare, New Delhi.

CDSCO is also responsible to take regulatory decision on the basis of analysis of the PMS, PSUR, AEFI data done by expert committee of CDSCO (HQ).

The Pharmacovigilance Programme of India has the responsibility to collate the data received by them from the various Adverse Drug Reactions monitoring centers and share the Adverse Reaction reported for vaccines to (i) District Immunization Officer (DIO), (ii) State AEFI Committee and (iii) the National AEFI Committee for examination and recommendation. The PvPI at IPC has established a Signal Review Panel signal identification/review from the committed individual case safety reports to World Health Organization–Uppsala Monitoring Centre (WHO-UMC). The results of the cases discussed in the Signal Review Panel of the Pharmacovigilance Programme of India (PvPI) will be shared with AEFI Secretariat and CDSCO. These results will be used as additional evidence during causality assessment by the CA sub-committee and finalised by the National AEFI Committee. As a part of the condition of the Marketing Authorization, the MAH is also required to submit PMS/PSUR after licensure of the product. The PSURs is to be submitted every six months for first two years of the approval and for subsequent two years annually. The Licensing Authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health.

The Licensing Authority may also advise the MAH to conduct Phase IV trials which go beyond the prior demonstration of product safety, efficacy and dose definitions. These trials may not be considered necessary at the time of new vaccine approval but may be required by the Licensing Authority for optimizing the vaccine's use. They may be of any type but should have valid scientific objectives.

2.2 PHARMACOVIGILANCE PROGRAMME OF INDIA AT IPC:

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Indian Pharmacopoeia commission, Ghaziabad has

initiated a nation-wide Pharmacovigilance programme for protecting the health of the patients by assuring drug safety. The programme is coordinated by the Indian Pharmacopoeia commission, Ghaziabad as a National Coordinating Centre (NCC). The centre operates under the supervision of a Steering Committee. Indian Pharmacopeia commission, Ghaziabad is an autonomous organization under MoHFW, having primary mandate for preparation of standards for all drugs including bulk antigens and vaccine products, publish of Indian Pharmacopoeia (IP) with monographs for all drugs including vaccines, publish of National Formulary (NFI), preservation of reference standards for Drugs, but not the antigens of vaccine which is maintained at NIB (Noida) and CDL (Kasauli). This organization has also been mandated by MoHFW to act as NCC for all ADR centers across the country to collect, collate ADR for all drugs including AEFI cases of Human vaccines, line listing of these ADRs (AEFIs), conduct the meeting of Signal review Panel (SRP) approved by MoHFW, which in turn place their recommendation to the NRA (CDSCO) for appropriate regulatory action on Vaccines licensed in the country for marketing by MAHs.

In case of vaccine related AEFI, the Signal Review Panel place their observations to the National AEFI Causality Analysis Committee at LHMC (New Delhi). After due deliberation, the committee proposes its recommendation on the further course of action, including regulatory action to be undertaken by NRA (CDSCO). These recommendations are finally approved by the National AEFI Committee (Currently chaired by Dr. N.K. Arora, Retd. Prof. HOD of Paediatrics, AIIMS, New Delhi) for appropriate regulatory action by the O/o DCG(I) on the functioning of MAH and/or the vaccine product, which was lincesed in the country by MAH.

Role of PvPI at IPC:
• To monitor Adverse Drug Reactions (ADRs) in Indian population.
• To create awareness amongst health care professionals about the importance of ADR reporting in India.
• To monitor benefit-risk profile of medicines and vaccines
• Generate independent, evidence based recommendations on the safety of medicines.
• Support the CDSCO for formulating safety related regulatory decisions for medicine.
• Communicate findings with all key stakeholders.
• Create a national centre of excellence at par with global drug safety monitoring standards.
• Collaborating with the other international health agencies.
• To share the Adverse reaction reported for vaccines to (i) District Immunization Officer (DIO), (ii) State AEFI Committee and (iii) the National AEFI Committee for examination and recommendation. The results of the cases discussed in the Signal Review Panel of the Pharmacovigilance Programme of India (PvPI) will be shared with AEFI Secretariat and CDSCO. These results will be used as additional evidence during causality assessment by the CA sub-committee and finalised by the National AEFI Committee.

Major roles and responsibilities of PvPI at IPC includes development and implementation of pharmacovigilance system in India, enrolment of all MCI approved medical colleges in the program covering north, south, east and west of India, encouraging healthcare professionals in reporting of adverse reaction to drugs, vaccines, medical devices and biological products and collection of case reports and data in the suspected adverse drug reaction reporting form.

The long term goal of PvPI at IPC includes developing and implementing electronic reporting system (e-reporting), to develop reporting culture amongst healthcare professionals and to make ADR reporting mandatory for healthcare professionals.

The "Guidance document for reporting individual case safety report" drafted by PvPI at IPC to be referred for vaccine adverse reaction reporting in Suspected Adverse Drug Reaction Form.

2.3 AEFI SECRETARIAT, IMMUNIZATION DIVISION OF MINISTRY OF HEALTH AND FAMILY WELFARE:

Immunization is one of the most cost effective public health interventions resulting in reduction of morbidity and mortality of children. Under the Universal Immunization Programme (UIP), Govt. of India is providing vaccination to prevent 7 vaccine preventable diseases (VPDs) namely, Diphtheria, Pertussis, Tetanus, Polio, Measles, Hepatitis B and Tuberculosis and targets 2.6 crore births and 3.0 crores pregnant women annually.

IMMUNIZATION SCHEDULE IN UNIVERSAL IMMUNIZATION PROGRAM

S. No	Vaccine	Protection	Number of Doses	Vaccination Schedule
1	BCG (Bacillus Calmette Guerin)	Tuberculosis	1	At birth (up to 1 year if not given earlier)
2.	OPV (Oral Polio Vaccine)	Polio	5	Birth dose for institutional deliveries, Three primary doses at 6, 10 & 14 week and One booster dose at 16- 24 month of age. Given orally
3.	Hepatitis B	Hepatitis	4	Birth dose for institutional deliveries with 24 hour, Three primary doses at 6, 10 14 week
4.	DPT (Diphtheria, Pertussis and Tetanus Toxoid)	Diphtheria, Pertussis and Tetanus	5	Three primary doses at 6, 10 & 14 weeks and Two booster dose at 16-24 month and 5 years of age
5.	Measles	Measles	2	1 st dose at 9-12 months of age and 2nd dose at 16-24 months

6.	TT (Tetanus Toxoid)	Tetanus	2	- 10 years and 16 years of age, -For pregnant woman, two doses (one dose if previously vaccinated within 3 Year)
7	JE vaccination (in selected 112 high disease burden districts) in 15 states + 62 new districts i.e. total 174 districts in 19 states.	Japanese Encephalitis (Brain disease)	2	2 doses of JE vaccine are given at 9-12 months and 16-24 month of age in endemic districts
8	Hib (given as pentavalent containing Hib+DPT+Hep B)	Haemophilus influenza type B vaccine Hib Pneumonia and Hib meningitis (brain disease)	3	6, 10 & 14 week of age Currently used in 8 states i.e. Kerala, Tamil Nadu, Haryana, Karanataka, Gujarat, Goa, Puducherry and Jammu and Kashmir

IMMUNIZATION DIVISION BRIEF FROM MOHFW

In 2012, AEFI Secretariat was established at Immunization Technical Supportive Unit (ITSU) of Public Health Foundation of India (PHFI) with due approval of MoHFW with mandate of collection, collation, line listing, reporting, sharing with partner organizations (e.g. CDSCO), investigation and causality analysis of AEFI cases.

AEFI surveillance monitors immunization safety, detects and responds adverse events following immunization. Adverse events after immunization can be serious or non serious. Serious AEFIs such as death, hospitalization, disability, and cluster or community concern need to be reported immediately on standard format CRF and investigated timely in the PCIF and FCIF. AEFI surveillance system in the country is currently passive system with immediate direct reporting of serious AEFIs (death, hospitalization, prolongation of hospitalization, persistent or significant disability/ incapacity, or is life threatening, community concern) while the non-serious AEFIs are reported routinely in the Health Management Information System (HMIS). Serious AEFIs are investigated by the District Immunization Officer (DIO) with support of District AEFI committee and reviewed by the State AEFI committee of which the State EPI Officer (SEPIO) is the member secretary.

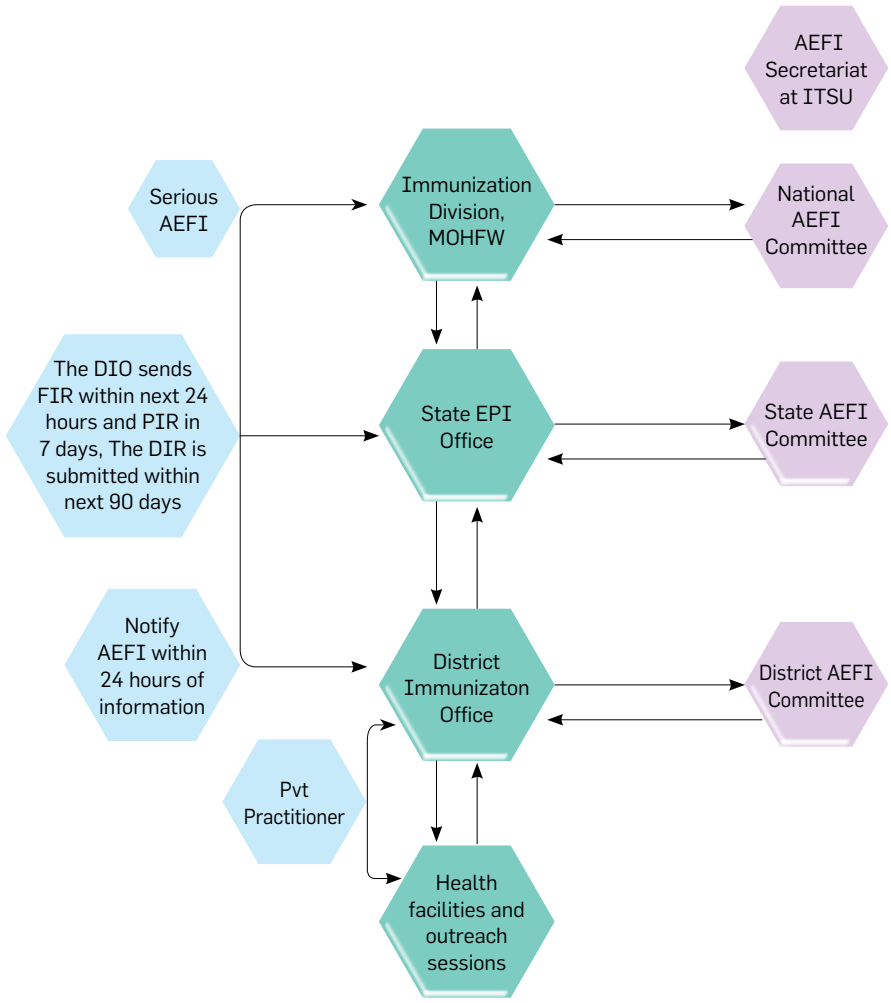
The state AEFI committee conducts a causality assessment to the report and sends to the National level in specified formats (CRF, PCIF and FCIF) within pre-defined timelines. These are then collated and are put up to the National AEFI Committee for review and assessment. The role of the AEFI Committees at different administrative levels is to strengthen AEFI reporting, conduct thorough investigation, reduce program error and timely detection of signals. An AEFI report can be sent to the email address aefi.cdsco@gmail.com

The reporting can occur from any level of government or private sector including the private practitioner in the CRF form. To obtain detail about completing CRF,

PCIF & FCIF, AEFI- Surveillance and Response Operational Guidelines of Ministry of Health & Family Welfare, Govt. of India has to be referred.

Each serious event (s) should be followed up to determine the cause for its occurrence (causality assessment). The causality assessment is done by the state AEFI committee/ National AEFI committee depending on the urgency of the situation.

AEFI ORGANIZATIONAL STRUCTURE



The AEFI Secretariat will share limited linelist in excel format with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited linelist will be in excel format and will have state, age, sex, DOV, antigens administered, manufacturing details (name, batch number and expiry date) and reason for reporting. Based on the causality assessment report detailed inspection related to GMP, product etc. and further regulatory action are initiated by CDSCO in case the quality of the implicated vaccines are indicated to be responsible for the adverse events in the causality assessment report.

Also as mentioned in the AEFI operational guidelines, in case of urgent situation, the state AEFI committee along with the state drug control authorities should

immediately inform to CDSCO/National AEFI committee, Govt. of India to take the following steps together.

- Report the findings of the investigation of the state government & Govt. of India.
- The details of the implicated vaccine or product should be submitted to Govt. of India immediately so that a decision could be made on the temporary suspension of its use & await further instruction from Govt. of India.
- CDSCO along with CDL & Immunization division will co-ordinate a re-evaluation of the quality of the vaccine & communicate to the manufacturer (by CDSCO), if necessary.

2.4 PHARMACOVIGILANCE DIVISION (HUMAN VACCINE) AT CDSCO

Pharmacovigilance Division (Human vaccine) is a part of Biological Division and monitors all post licensure activities of vaccine related AEFI, PSUR and any other data on adverse reactions.

Pharmacovigilance Division (Human vaccine) shall be responsible for (i) the coordination with NCC-PvPI (IPC-Gzb.) and Immunization Division, Ministry of Health and Family Welfare for the various AEFI reported in the field (ii) to attend various meeting with the stake holders for coordination purpose or whenever situation arises (iii) collecting all the adverse events/ SAE reported by the immunization division and IPC, which shall be reviewed by the expert committee constituted for this purpose for taking further regulatory action.

PMS/PSUR being conditions for Market Authorization and Licensing and therefore in order to ensure the regulatory conformance and proper design of post marketing studies, this division shall work within the licensing division. This division is responsible for collecting, compiling and collating the data received from the MAH as per the requirements of Schedule Y. The compiled PMS/ PSUR data will then be reviewed by the advisory committee constituted by the Drugs Controller General of India in consultation with Ministry of Health and Family Welfare. Based on the analysis of the advisory expert committee, regulatory decision will be taken by CDSCO for further generation of safety and efficacy data not limiting to the initial pre licensure study, if necessary. The design of the study will be suggested by the advisory expert committee and the committee may also review the need for further submission of PMS/PSUR data beyond 4 years as per Drugs and Cosmetics Act and Rules.

Further, all cases involving serious unexpected adverse reactions must be reported to the Licensing Authority within 15 days of initial receipt of the information by the Industry. The same will be reviewed by advisory committee and a regulatory decision for marketing shall be taken. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

Sharing of AEFI with Marketing Authorization Holder:

The AEFI Secretariat will share limited linelist in excel format with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited linelist will be in excel format and will have state, age, sex, DOV, antigens administered, manufacturing details (name, batch number and expiry date) and reason for reporting. CDSCO will share linelist details for vaccines relevant to the particular manufacturer with instructions that these are being shared with the MAH for internal review and not for investigations in the field.

3. PHARMACOVIGILANCE PLAN

The MAH will develop a comprehensive pharmacovigilance plan as outlined below.

3.1 PHARMACOVIGILANCE METHODS

The best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, the MAH should employ the most appropriate design.

Following are the key methods used in pharmacovigilance.

3.1.1 Individual Case Safety Report:

After obtaining either manufacturing licence and/or Import registration and /or import licence from the office of DCG (I) at CDSCO (HQ), all MAHs shall place the vaccine products in the market and simultaneously initiate collection, collation and monitoring of all major and minor AEFI cases across the country by choosing an appropriate method of vigilance activities as follows::

A) Passive Surveillance

- **Spontaneous Reports**

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a MAH, regulatory authority that describes one or more adverse drug reactions in a patient who was given one or more biological products and that does not derive from a study or any organized data collection scheme.

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a MAH can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.

B) Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early post-marketing phase, MAH might actively provide health professionals with safety information and at the same time encourage cautious use

of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by MAH representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early post-marketing phase can lead MAH to notify healthcare professionals of new therapies and provide safety information early in use by the general population. This should be regarded as a form of spontaneous event reporting, and thus data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

C) Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact In general; it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

All the SAE during the period of PMS/PSUR shall be reported within 15 days to the Licensing Authority in the prescribed format (VAERS) Vaccine Adverse Events Reporting System.

3.1.2 Periodic Safety Update Report:

PSUR are important pharmacovigilance documents. They provide an opportunity for MAHs to review the safety profile of their products and ensure that the SmPC and Package Leaflet within reasonable tme frame. Periodic Safety Update Reports (PSUR) present the world-wide safety experience of a medicinal product/vaccines at defined times post-authorization, in order to report all the relevant new safety information from appropriate sources; relate these data to patient exposure; summarize the market authorization status in different countries and any significant variations related to safety; create periodically the opportunity for an overall safety re-evaluation; indicate whether changes should be made to product information in order to optimize the use of the product

As per the Drugs and Cosmetics Rules, the applicants shall furnish Periodic Safety Update Reports (PSURs) in order to-

(a) Report all the relevant new information from appropriate sources;
(b) Relate these data to patient exposure;
(c) Summarize the market authorization status in different countries and any significant variations related to safety; and
(d) Indicate whether changes should be made to product information in order to optimize the use of the product.
    (i) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR separate presentations of data for different dosage forms, indications or separate population need to be given.
    (ii) All relevant clinical and non-clinical safety data should cover only the

period of the report (interval data). The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the PSURs need to be submitted annually. Licensing Authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.

However, all cases involving serious unexpected adverse reactions must be reported to the Licensing Authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

A PSUR should be structured as follows:

(a) Title Page:
The title page of PSUR should capture the name of Medicinal product(s); reporting interval; approved Indication of Medicinal Products; date of approval of new drug; date of marketing of new drug; MAH(s) name(s) and address(es).

(b) Introduction:
This section of PSUR should capture the reporting interval; medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s); a brief description of the approved indication(s) and population(s).

(c) Current Worldwide Marketing Authorization Status:
This section of PSUR should capture the brief narrative overview including details of country where the product is currently approved along with date of first approval, date of marketing and if product was withdrawn in any of the countries with reasons thereof.

(d) Actions Taken in Reporting Interval for Safety Reasons:
This section of PSUR should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsor of a clinical trial(s), regulatory authorities, data monitoring committees, or ethics committees.

(e) Changes to Reference Safety Information:
This section of PSUR should capture any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, adverse drug reactions (ADRs), overdose, and interactions; important findings from ongoing and completed clinical trials and significant non-clinical findings (e.g., carcinogenicity studies).

(f) Estimated Patient Exposure:
This section of PSUR should provide the estimates of the size and nature of the population exposed to the medicinal product. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided.

(i) Cumulative and interval subject exposure in Clinical Trials
(ii) Cumulative and interval patient exposure from Marketing Experience from India
(iii) Cumulative and interval patient exposure from Marketing Experience from rest of the world

(g) Presentation of Individual Case Histories:
This section of PSUR should provide the individual case information potentially available to a MAH provide brief case narrative, concomitant medications, medical history indication treated with suspect drug(s), re-challenge & de-challenge, causality assessment. Provide following information:

(i) Reference Prescribing Information for causality assessment
(ii) Individual Cases received from India
(iii) Individual cases received from rest of the world
(iv) Cumulative and Interval Summary Tabulations of Serious Adverse Events from Clinical Trials
(v) Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

(h) Studies:
This section of PSUR should capture the brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the MAH's sponsored clinical trials and published safety studies that became available during the reporting interval of the report which has potential impact on product safety information.

(i) Summaries of Significant Safety Findings from Clinical Trials during the reporting period
(ii) Findings from Non-interventional Studies
(iii) Findings from Non-Clinical Studies
(iv) Findings from Literature

(i) Other Information:
This section of PSUR should include the details about signals and Risk Management Plan in place by MAH (if any).

- Signal and risk evaluation: In this section MAH will provide the details of signal and risk identified during the reporting period and evaluation of signals identified during the reporting period.
- Risk Management Plan: In this section MAH will provide the brief details of safety concern(s) and necessary action taken by him to mitigate these safety concerns.

(j) Overall Safety Evaluation:
This section of PSUR should capture the overall safety evaluation of the medicinal product based upon its risk benefit evaluation for approved indication.

(i) Summary of Safety Concerns
(ii) Benefit Evaluation
(iii) Benefit Risk Analysis Evaluation

(k) Conclusion:
This section of PSUR should provide the details on the safety profile of medicinal product and necessary action taken by the MAH in this regards.

(l) Appendix:
The appendix includes the copy of marketing authorization in India, copy of prescribing information, line listings of Individual Case Safety
Reports (ICSR), SOP's for data collections & review etc.

It is recommended that the MAH can submit the PSUR data either in Schedule Y format or in conformity with Periodic Benefit-Risk Evaluation Report (PBRER) as per ICH E2C (R2) according to the current practices of the developed countries and developing countries and continue to monitor the safety of the vaccines throughout the lifecycle of the product and produce the report as and when required by the licensing authority.

3.1.3 Post marketing trials (Phase-IV):

Post Marketing trials 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 new drug's (vaccine'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.

(4) ROLES AND RESPONSIBILITIES OF THE DESIGNATED PERSON

(a) within the company of MAH:

In accordance with the Govt. GazetteNotification No. GSR 287 (E) dated March, 2016, for the purpose of Post Market Surveillance, the MAH shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the Licensing Authorities for information on adverse event following immunization (AEFI) emerging from the use of the vaccine manufactured and marketed by the MAH in the country. The system shall be managed by qualified and trained personnel and officer-in-charge of collection and processing of data shall be a Medical officer or a pharmacist trained in collection and analysis of ADR.

Hence, the Marketing Authorization Holder (MAH) should establish an appropriate pharmacovigilance system by assuming the responsibilities and liabilities for its vaccine product(s) circulating in the market and should ensure that appropriate action may be taken whenever safety concerns arise after due investigation and scientific evaluation. The Marketing Authorization Holder (MAH) should appoint as per the norms laid down in schedule-Y under Drugs & Cosmetics Act 1940 and Rules 1945, a qualified and trained personnel with duly given responsibilities for continuously monitoring of the vaccine products at his disposal

(b) Adverse Drug Reaction Reporting:

4.1. Procedures and Processes

4.1.1 The MAH shall have a pharmacovigilance system in place for collecting, processing and forwarding the report to the licensing authority for information on adverse drug reactions emerging from the use of the drug manufactured or marketed by the applicant in the country. The system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports.

The procedure should include but not be limited to the following:

4.1.1.1 Provisions for timely and thorough review to determine whether the complaint represents an ADR;

4.1.1.2 Personnel responsible to receive the incoming correspondence (phone calls, letter, email, etc.) relating to potential ADRs through product complaints;

4.1.1.3 How an unique identifier is assigned to each case; and

4.1.1.4 Clear and defined processes on ADR/complaint, evaluation and follow-up.

4.2 Manufacturers and importers should have in place systems and procedures for the receipt, handling, evaluation and reporting of ADRs that are adequate to effectively sustain ADR reporting within 15 days of receipt to CDSCO of domestic serious expected and unexpected ADRs, foreign serious unexpected ADRs, as well as any follow-up information for initial case reports. This should be read in conformity

with para 4, under heading Post Marketing Surveillance sub para (iii) of Schedule Y of Drugs and Cosmetics Rules.

For importer, India specific PSUR should be compiled and submitted in a separate section within the PSUR data. All the SAE shall be reported within 15 days.

In case of manufacturer, distributing countries specific PSUR should be compiled and submitted in a separate section within the PSUR data. All the SAE reported in the distributing countries shall be reported within 15 days.

4.3 MAHs should have in place adequate procedures for ADR receipt, handling, evaluation and reporting and should include but not be limited to the following.

4.3.1 Requirement to report to CDSCO within 15 days of receipt by the MAH, reports of serious ADRs occurring within India, and serious unexpected ADRs occurring outside of India and any unusual failure in efficacy for new drugs occurring within India, if applicable;

4.3.2 Address all the specific Indian regulatory requirements, such as when notification is required, definition of serious and non-serious adverse reactions, definition of unusual failure in efficacy of new drugs, if applicable, retention of all records associated with ADR, etc.;

4.3.3 Requirement to have a qualified health care professional to evaluate and assess ADR reports, including the process to review ADRs.

4.3.4 Identifying the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse reaction) for submitting a case;

4.3.5 Identifying key personnel who are responsible for forwarding the ADR reports to the Licensing Authority;

4.3.6 Procedure on how complaints and ADRs are tracked/logged in;

4.3.7 Procedure on how the MAH is to be notified of foreign serious unexpected drug reactions;

4.3.8 The decision-making process to assess report ability of ADRs;

4.3.9 The responsibilities for the final approval of ADR evaluation and appropriate follow-up;

4.3.10 Requirement to conduct a critical analysis of ADR reports received and preparation of a summary report on an annual basis, or at the request of the Licensing Authority (CDSCO). As per Drugs and

Cosmetics Rules, Schedule M para 28 under heading “Complaints and Adverse Reaction”, sub-para 28.2 reports of serious adverse drug reaction resulting from the use of a drug along with comments and documents shall be forthwith reported to concerned Licensing Authority. The Licensing Authority in this case shall be both CDSCO and State Licensing Authorities.

4.4 Importers should have in place adequate procedures for ADRs receipt, handling, evaluation (for determination of complaints or ADR) and forwarding ADRs to the MAH and should include but not be limited to the following

4.4.1 Procedure on how complaints and ADRs are tracked/logged in;

4.4.2 Procedure on how complaints are assessed in order to determine if it is an ADR;

4.4.3 Identifying key personnel who are responsible for forwarding the ADRs reports to the MAH;

4.4.4 Requirement to report ADRs to the MAH within an appropriate timeframe to allow for expedited reporting (if required); and all SAEs to be reported within15 days of receipt of information to CDSCO This should be read in conformity with para 4,

under heading Post Marketing Surveillance sub para iii of Schedule Y of Drugs and Cosmetics Rules.

4.4.5 Requirement to follow up with the MAH to ensure that ADRs have been assessed and sent to Drugs Controller General (India), if required;

4.4.6 Requirement to maintain records of all ADRs received and ADRs sent to the MAHs and subsequent correspondence; and ensure that as per Drugs and cosmetics Rules, Schedule M para 28 under heading complaints and adverse reaction, sub-para 28.2 reports of serious adverse drug reaction resulting from the use of a drug along with comments and documents are forthwith reported to concerned Licensing Authority (CDSCO).

4.5 Procedures should be written, reviewed and approved by qualified personnel.

4.6 Procedures should be made available to all relevant personnel involved in pharmacovigilance activities before the procedures are effective.

4.7 Procedures should be reviewed on a periodic basis to ensure that they accurately reflect current practice.

4.8 Changes to procedures should be tracked and documented.

4.9 Deviations from procedures relating to pharmacovigilance activities should be documented

4.10 When part or all pharmacovigilance activities are performed by a third party, MAH and importers should review procedures to ensure that procedures are adequate and compliant with applicable requirements stated in the Drugs and Cosmetics Act and Rules. Copies of the procedures should be readily available to the inspector/ regulator.

4.11 MAHs

4.11.1 The ADR evaluation, including but not limited to, seriousness and expectedness assessment should be completed in a manner which would ensure expedited reporting timelines are met. For both domestic and foreign reports, the expectedness should be determined from the relevant labeling such as the product monograph, labeling standards, information approved for market authorization, or the product label.

4.11.2 Mechanisms should be in place to determine whether an ADR qualifies for 15 day expedited reporting. When a case is found not reportable, justification is provided and documented.

4.11.3 For ADR reports that qualify for expedited reporting, the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse reaction) for submitting a case are met.

4.11.4 Process should be in place for determining if a solicited report is to be submitted to Licensing Authority in an expedited fashion (within 15 days).

4.11.5 A qualified health care professional evaluates and assesses ADRs to determine whether the ADR qualifies for expedited 15-day reporting.

4.12 Reports of ADR cases from 2 or more sources

4.12.1 A mechanism should be in place to identify ADR data that were reported to the MAH more than once.

4.12.2 When similar reports are found, verifications should take place to determine if they are duplicate reports.

4.12.3 Multiple copies of the same ADR reports should be nullified within the

pharmacovigilance system and the record of nullification should be maintained, allowing for auditing of the nullified record in the future.

4.12.4 Documented procedure and process should be in place describing when ADR reports may be nullified.

4.12.5 Documentation related to nullified cases should be retained.

4.12.6 Additional information received for previously submitted ADR reports

4.12.7 Upon receipt of follow-up information, ADR reports should be re-evaluated.

4.12.8 Follow-up information received for previously submitted ADR reports must be sent to Licensing Authority within the prescribed timelines. Reference should be made to the initial report by including the MAH number specific to the report either in the follow-up report or on the fax cover sheet.

4.12.9 All reportable ADRs that have been upgraded to serious upon receipt of follow-up information are to be sent to Licensing Authority within the prescribed timelines

4.12.10 Rationale for changing the seriousness of an ADR report should be documented.

4.12.11 Process for seeking follow-up information and submitting it to Licensing Authority should be in place. All attempts to obtain follow-up information should be documented.

4.13 Reporting of ADR data

4.13.1 MAHs

4.13.2 All ADRs shall be reported to Licensing Authority (CDSCO) in accordance with Drugs and Cosmetics Rule.

4.14 Importers

4.14.1 All suspected ADRs received should be sent to the MAH within an appropriate time frame to allow for expedited reporting (if required), and should therefore be reported to Licensing Authority by the MAH in accordance with the requirements of the Drugs and Cosmetics Rule, if required.

4.14.2 Importers should follow-up with the MAH to ensure that ADRs have been assessed and submitted, if required.

4.15 Literature Search

4.15.1 MAHs

4.15.1 The process, including but not limited to how the search is done, the database(s) used, and the periodicity of those searches describing the search in the literature should be written in a procedure.

4.15.2 ADRs found during literature searches should be classified according to their seriousness and expectedness. These assessments

should be retained and be well documented.

4.15.1.3 ADR reports from the scientific and medical literature must be reported to Licensing Authority in accordance with the Drugs and Cosmetics Rule.

4.15.1.4 Results of the literature searches should be documented.

4.15.1.5 When literature search is performed by a third party, contractual agreements describing each party's responsibilities should exist.

Periodic Self-inspections

4.16 MAHs and Importers

4.16.1 A self-inspection program that covers all departments that may receive ADR reports or that are involved in pharmacovigilance activities may help to ensure

compliance with the appropriate sections of the Drugs and Cosmetics Rule applicable to adverse drug reaction reporting. Self-inspection programs should be in place and should include but not be limited to the following;

4.16.1.1 A comprehensive written procedure that describes the functions of the self-inspection program.

4.16.1.2 Periodic self-inspections that are carried out at defined frequencies, which are documented. If no ADRs have been received, the periodic self-inspections should include a simulation exercise.

4.16.1.3 Reports on the findings of the self-inspections and on corrective actions. These reports should be reviewed by appropriate senior MAH management. Corrective actions should be implemented in a timely manner.

4.17 Periodic self-inspections should be conducted by personnel independent from the pharmacovigilance department and that are suitably qualified to perform and evaluate the inspections.

Personnel and Training

4.18 MAHs and Importers

4.18.1 The individual in charge of the pharmacovigilance department should be qualified by pertinent training and experience relevant to their assigned responsibilities

4.18.2 The qualified health care professional;

4.18.2.1 Should have knowledge of all applicable sections of the Food and Drug Regulations related to the ADR reporting requirements, and of key pharmacovigilance activities performed as part of the MAH's pharmacovigilance system.

4.18.2.2 Should be responsible for establishing and managing/maintaining a system which ensures that information concerning all suspected ADRs that are reported to the personnel of the MAH and to medical representatives is collected and evaluated.

4.18.2.3 All personnel involved in pharmacovigilance activities, which may include customer service, sales representatives and receptionists, should have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities.

4.18.2.4 All personnel involved in pharmacovigilance activities should be aware of the principles of pharmacovigilance that affect them, and all personnel should receive relevant training. 4.18.2.5 When responsible personnel are absent, qualified personnel should be appointed to carry out their duties and functions.

4.18.2.6 A qualified health care professional with adequate experience and training, should be available to evaluate information in respect of a potential ADRs, assesses the seriousness, expectedness, and report ability of ADRs, and determine if the ADR report qualifies for expedited reporting (within 15 days) and if the report is to be included in the annual summary

4.18.2.7 Training should be provided prior to implementation of new or revised procedures. Records of training should be maintained.

4.18.2.8 Consultants and contractors should have the necessary qualifications, training, and experience to fulfill their responsibilities.

Contractual Agreements

4.19 MAHs and Importer

4.19.1 Contractual agreement should exist with every party that conducts pharmacovigilance activities, including third- party private label or other MAH whose name is included in the product information or appears on the label and should

include; 4.19.1.1 who is responsible for determining if a complaint is a potential ADR,
4.19.1.2 Who is responsible to report ADR,
4.19.1.3 Who is responsible for preparing the ASR, including the critical analysis of the annual summary reports, and what process is utilized to conduct the critical analysis,
4.19.1.4 Who is responsible for conducting literature searches?
4.19.1.5 Processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place between the MAH and its partners (including, but not limited to, consultants and contractors).
4.19.1.6 To notify other party if changes to procedures are made.
4.19.2 In the case of foreign MAHs, the contractual agreement should specify to send known ADRs to the local MAH in a timely manner so as to promote compliance with regulatory reporting obligations.
4.19.3 In the case where the importer is responsible for the pharmacovigilance activities, the contractual agreement should specify that the foreign MAH is to send the ADR data to the importer in a timely manner.
4.19.4 All records (including, but not limited to, contractual agreements and safety data/ADR data) should be available on the premises of the MAH and the importer for auditing purposes
4.19.5 When there is a transfer of market authorization/mergers, contractual agreement should exist between the previous MAH and the new one outlining each party responsibility.
4.19.6 Contractual agreement should be shared and signed off by each party.
4.19.7 Contractual agreement should be reviewed periodically in order to reflect current regulations and practices.

Validation of Computerized Systems
4.20. MAHs, Importer, and all parties involved in pharmacovigilance activities who use an electronic system.
4.20.1 Data of the validation of system(s) used for recording, evaluating, and tracking complaints and ADRs should be available.
4.20.2 Computerized systems should be validated and systems are periodically and suitably backed up at predefined intervals.

5. DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS

The MAH shall develop, implement and evaluate risk minimization action plan which shall include (1) Initiating and designing plans called risk minimization action plans or Risk MAPs to minimize identified product risks, (2) selecting and developing tools to minimize those risks, (3) evaluating Risk MAPs and monitoring tools. The goal of risk minimization is to minimize a product's risks while preserving its benefits. The statutory standard for NRA approval of a product is that the product is safe and effective for its labeled indications under its labeled conditions of use. Rather, a product is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has an appropriate benefit-risk balance for the intended population and use. Benefit and risk information emerges continually throughout a product's lifecycle (i.e., during the investigational and marketing phases) and can reflect the results of both labeled and off-label uses. Assessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of societal, healthcare, and individualized patient factors. To help ensure safe and effective use of their products, sponsors have always sought to maximize benefits and minimize risks. Routine risk minimization measures such as labeling practices describing the conditions in which the drug can be used safely and effectively, updated from time to time to incorporate information from post marketing surveillance or studies revealing new benefits (e.g., new indications or formulations) or risk concerns. Communication of risks and benefits through product labeling is the corner stone of risk management efforts for prescription drugs. Risk Maps should be used judiciously to minimize risks without Encumbering drug availability or other wise interfering with the delivery of product benefits to patients. To help ensure safe and effective use of their products, MAH has always sought to maximize benefits and minimize risks. Routine risk minimization measures such as labeling practices describing the conditions in which the drug can be used safely and effectively, updated from time to time to incorporate information from post marketing surveillance or studies revealing new benefits (e.g., new indications or formulations) or risk concerns. Risk MAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. A Risk MAP targets one or more safety zrelated health outcomes or goals and uses one or more tools to achieve those goals. A Risk MAP could also be considered as a selectively used type of Safety Action Plan. A risk warranting the consideration of a Risk MAP could emerge during premarketing or post marketing risk assessment. The appropriate information for consideration in making such a determination should include, as applicable,

(1) data from the clinical development program, post marketing surveillance, and phase 4 studies, and
(2) the product's intended population and use.

Although it is expected and hoped that MA holders will determine when a Risk MAP would be appropriate, It may be recommended for a Risk

MAP based on the authority's own interpretation of risk information. Decisions to develop, submit, or implement a Risk MAP are always made on a case-by-case basis, but several considerations are common to most determinations of whether development of a Risk MAP may be desirable:

5.1. NATURE AND RATE OF KNOWN RISKS VERSUS BENEFITS:

Comparing the characteristics of the product's adverse effects and benefits may help clarify whether a Risk MAP could improve the product's benefit-risk balance. The characteristics to be weighed might include the

1. types, magnitude, and frequency of risks and benefits;
2. populations at greatest risk and/or those likely to derive the most benefit;
3. existence of treatment alternatives and their risks and benefits; and
4. reversibility of adverse events observed.

Preventability of adverse effects:

Serious adverse effects that can be minimized or avoided by preventive measures around drug prescribing are the preferred candidates for Risk MAPs.

Probability of benefit: If factors are identified that can predict effectiveness, a Risk MAP could help encourage appropriate use to increase benefits relative to known risks.

A risk minimization tool is a process or system intended to minimize known risks. Tools can communicate particular information regarding optimal product use and can also provide guidance on prescribing, dispensing, and/or using a product in the most appropriate situations or patient populations. A number of tools are available and may be used as required. A variety of tools are currently used in risk minimization plans. These fall within three categories:

(1) targeted education and outreach,
(2) reminder systems, and
(3) performance linked access systems.

5.2. TARGETED EDUCATION AND OUTREACH

It is recommended that MA holders consider tools in the targeted education and outreach category.

(i) When routine risk minimization is known or likely to be insufficient to minimize product risks or
(ii) As a component of Risk MAPs using reminder or performance-linked access systems.

Sponsors are encouraged to continue using tools, such as education and outreach, as an extension of their routine risk minimization efforts even without a Risk MAP.

Tools which may be used as routine risk minimization efforts even without a Risk MAP may be:

- Training programs for healthcare practitioners or patients
- Continuing education for healthcare practitioners such as product-focused programs developed by sponsors and/or sponsor-supported accredited CE programs
- Prominent professional or public notifications
- Patient labeling such as Medication Guides and patient package inserts

Promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks

- Patient-sponsor interaction and education systems such as disease management and Patient access programs
- Healthcare practitioner letters

In addition to informing healthcare practitioners and patients about conditions of use contributing to product risk, educational tools can inform them of conditions of use that are important to achieve the product's benefits.

On the other hand, deviations from the labeled dose, frequency of dosing, storage conditions, or other labeled conditions of use might compromise the benefit achieved, yet still expose the patient to product related risks. Risks and benefits can have different dose-response relationships. Risks can persist and even exceed benefits when products are used in ways that minimize effectiveness. Therefore, educational tools can be used to explain how to use products in ways that both maximize benefits and minimize risks.

It is recommended that tools in the reminder systems category be used in addition to tools in the targeted education and outreach category when targeted education and outreach tools are known or likely to be insufficient to minimize identified risks.

Tools in the reminder system include systems that prompt, remind, double-check or otherwise guide healthcare practitioners and/or patients in prescribing, dispensing, receiving, or using a product in ways that minimize risk. Examples of tools in this category are as follows:

- Patient education that includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are sometimes called consent forms.
- Healthcare provider training programs that include testing or some other documentation of physicians' knowledge and understanding.
- Enrolment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.
- Limited number of doses in any single prescription or limitations on refills of the product.
- Specialized product packaging to enhance safe use of the product.
- Specialized systems or records that are used to attest that safety measures have been satisfied (e.g. Prescription stickers, physician attestation of capabilities).

5.3. PERFORMANCE-LINKED ACCESS SYSTEMS

Performance-linked access systems include systems that link product access to laboratory testing results or other documentation. Tools in this category, because they are very burdensome and can disrupt usual patient care, should be considered only when

(1) Products have significant or otherwise unique benefits in a particular patient group or condition, but unusual risks also exist, such as irreversible disability or death, and

(2) Routine risk minimization measures, targeted education and outreach tools, and reminder systems are known or likely to be insufficient to minimize those risks.

In choosing tools for a Risk MAP, it is recommended that sponsors:

- Maintain the widest possible access to the product with the least burden to the healthcare system that is compatible with adequate risk minimization (e.g., a reminder system tool should not be used if targeted education and outreach would likely be sufficient).

- Identify the key stakeholders who have the capacity to minimize the product's risks (such as physicians, pharmacists, pharmacies, nurses, patients, and third party payers) and define the anticipated role of each group.
- Seek input from the key stakeholders on the feasibility of implementing and accepting the tool in usual healthcare practices, disease conditions, or lifestyles, if possible. Examples of considerations could include (but would not be limited to) patient and healthcare practitioner autonomy, time effectiveness, economic issues, and technological feasibility.
- Acknowledge the importance of using tools with the least burdensome effect on Healthcare practitioner- patient, pharmacist-patient, and/or other healthcare relationships.

It is recommended that MA holders periodically evaluate each Risk MAP tool to ensure it is materially contributing to the achievement of Risk MAP objectives or goals.

6. DEFINITIONS

A. Adverse Event (AE):
Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given. Also see Serious Adverse Event.

B. Adverse Event Following Immunization (AEFI):
This is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavourable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

C. Adverse Drug Reaction (ADR):

(a) In case of approved pharmaceutical products: A noxious and unintended response at doses normally used or tested in humans

(b) In case of new unregistered pharmaceutical products (or those products which are not yet approved for the medical condition where they are being tested): A noxious and unintended response at any dose(s).

The phrase ADR differs from AE, in case of an ADR there appears to be a reasonable possibility that the adverse event is related with the medicinal product being studied.

Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic). Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are, therefore, readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

D. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)
An AE or ADR that is associated with death, inpatient hospitalization, prolongation of

hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

This is to be read along with the definition as mentioned in Drugs & Cosmetics Act 1940 and Rules 1945 there under as- A Serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

E. Suspected Serious Adverse Reaction (SSAR):
An adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out.

- In the case of a licensed product, in the summary of product characteristics (SmPC) for that product.
- In the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.

F. Suspected Unexpected Serious Adverse Reaction (SUSAR):
An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out.

- In the case of a licensed product, in the summary of product characteristics (SmPC) for that product.
- In the case of any other investigational medicinal product, in the IB relating to the trial in question.

G. Third Party:
For the purpose of this guidance documents means that the entity who is nor the manufacturer neither the importer.

H. Market Authorization Holder (MAH):
For the purpose of this guidance document means the manufacturer or the importer of the drug, who has valid manufacturing or import license.

I. Cluster:
Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered.

7. REFERENCES

- ICH Guideline. E2E: Pharmacovigilance Planning
- Drugs and Cosmetics Act 1940 & Rules 1945– Schedule Y
- Guidance for Industry – Development and Use of Risk Minimization Action Plans – US FDA

Annexure 1

AEFI CASE REPORTING FORM (CRF)

AEFI reporting ID: IND (AEFI) /__ST_/DIS_/_YR _/_NUM_ (to be allotted by DIO)

Section A (To be submitted by MO within 24 hours of case notification to DIO)

State	**District**
Block/ward	**Village/urban area**

Name of reporting MO (person filling this form):	Today's date:
Posted at: Designation:	Time of preparing this form: a.m./p.m.
Contact phone number: email:	Date case visited and examined/interviewed: __ __/__ __/__ __ __ __
Notified by (name): Date notified to MO: __ __/__ __/__ __ __ __	Designation (please circle): health worker/government doctor/private practitioner/community/media/others (specify) _____ _____

Patient's name																				

Date of birth DD/MM/YYYY	**Age** (in months): _____ months	**Sex**	Male / Female

Mother's name																				
Father's name																				

Complete address of the case with landmarks *(street name, house number, village, block, tehsil, pin no., telephone no.)*

P	i	n	-							P	h	o	n	e	-											

Date of vaccination: __ __/__ __/__ __ __ __ Time of vaccination: __ __: __ __a.m./p.m.	Address of session site:
Session: Routine (including SIW)* **Campaign** (SIA)-IPPI/MR/JE/others (specify):_____ Other _____	**Place of vaccination:** govt health facility/outreach/private health facility/others ____

Names of vaccines received (write vaccine & diluent details in separate rows)	Dose no. (zero/first/second/etc. as applicable)	Name of manufacturer	Batch/lot No.	Expiry date	Date of opening of vial	Time of opening the vial (for reconstituted vaccine)	No. of OTHER beneficiaries who received vaccine from the SAME vial in this session

Date of first symptom	D	D	M	M	Y	Y	Y	Y	Time of first symptom	H	H	M	M	a.m.	p.m.
Hospitalization: No/yes – (Date)	D	D	M	M	Y	Y	Y	Y	Time of hospitalization	H	H	M	M	a.m.	p.m.

Name and address of hospital (if hospitalized):

Current status (encircle)	Death/still hospitalized/recovered & discharged with sequelae/recovered completely and discharged/left against medical advice (LAMA)/not hospitalized																	
If died, date of death	D	D	M	M	Y	Y	Y	Y	Time of death	H	H	M	M	a.m.	p.m			
Post mortem done? Yes/no/unknown If yes, then write date post mortem done	D	D	M	M	Y	Y	Y	Y	If not done, but planned, write date planned	H	H	M	M	Y	Y	Y	Y	

Describe AEFI (signs and symptoms):

Suspected adverse event(s) (tick at least one):

☐ Severe local reaction
- ○ *>3 days*
- ○ *beyond nearest joint*

☐ Seizures
- ○ *febrile*
- ○ *afebrile*

☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Intussusception

☐ Fever≥39 °C (102 °F) ☐ Hypotonic hyporesponsive episode (HHE) ☐ Acute flaccid paralysis ☐ Sudden unexplained death syndrome

☐ Death due to any reason other than above – specify.....

☐ Hospitalization due to any reason other than above – specify..... ☐ Disability

☐ Cluster – is this case part of a cluster? Yes/no/unknown

If Yes, no of other cases in the cluster _____ (use separate form for each case in a cluster)

Signature and name of reporting medical officer:

Section B: District immunization office to complete and forward to state and national level within 24 hours of receiving the above information

Date case reporting form received at the district: __ __/__ __/__ __ __ __

Proposed date of preliminary investigation: __ __/__ __/__ __ __ __

Remarks:

DIO/district nodal person *(officer forwarding this report)*

Name ..... Date.....Designation.....Mobile No.....

Landline (with STD code)..... Fax No. .....

email id..... Complete office address (with Pin code).....

.....

.....Signature/seal

To be sent to: State Immunization Officer & Deputy Commissioner (UIP),
Immunization Division of Govt of India, MoHFW,
Nirman Bhawan, New Delhi – 110108.
Fax: 011-23062728 **email**: aefiindia@gmail.com

Date report received at state level – __ __/__ __/__ __ __ __

Remarks:

Section C: National level to complete

Date report received at national level – __ __/__ __/__ __ __ __

Remarks:

Annexure 2

PRELIMINARY CASE INVESTIGATION FORM

AEFI reporting ID: IND (AEFI) /__ST_/DIS_/_YR _/_NUM_ (To be allotted by DIO)

Section A Basic details

State	**District**
Block/ward	**Village/urban area**
Place of vaccination: Govt health facility/outreach/private health facility/others (specify) ____	
Session: Routine (including SIW) Campaign (SIA)-IPPI/MR/JE/others (specify):_____ Other _____	
Name of investigator:	Date case visited and investigated: __ __/__ __/__ __ __ __
Posted at: Designation:	Date of preparing this form:__ __/__ __/__ __ __ __ Time of preparing this form: _____ a.m./p.m. This report is ☐ Preliminary ☐ Final
Contact phone number: email:	
Patient's name	
Date of Birth DD/MM/YYYY Age (in months): _____ months	Sex Male Female
Mother's name	
Father's name	
Complete address of the case with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No.)*	
Pin- Phone-	
Date of vaccination: __ __/__ __/__ __ __ __ Time of vaccination: __ __: __ __ a.m./p.m.	Address of session site:
Date first notified to government health system: __ __/__ __/__ __ __ __	Notified by (please circle): Health worker/government doctor/private doctor/community/media/others (specify) _____

Name of vaccines received (write vaccine & diluent details in separate rows)	Dose no. (zero/ first/ second, etc.)	Name of manufacturer	Batch/lot No.	Expiry date	Date of opening of vial	Time of opening the vial (in case of reconstituted vaccines)	No. of OTHER beneficiaries who received vaccine from SAME vial in this session

Date of first symptom	D	D	M	M	Y	Y	Y	Y	Time of first symptom	H	H	M	M	a.m.	p.m.	
Date of key symptom	D	D	M	M	Y	Y	Y	Y	Time of key symptom	H	H	M	M	a.m.	p.m.	
Hospitalization No/Yes – Date	D	D	M	M	Y	Y	Y	Y	Time of hospitalization	H	H	M	M	a.m.	p.m.	
Name and address of hospital (if hospitalized):																
Current status (encircle)	Death/still hospitalized/recovered & discharged with sequelae/ recovered completely and discharged/left against medical advice (LAMA)/not hospitalized															
If died, date of death	D	D	M	M	Y	Y	Y	Y	Time of death	H	H	M	M	a.m.	p.m.	
Post mortem done? Yes/no/unknown If yes, then write date post mortem done	D	D	M	M	Y	Y	Y	Y	If not done, but planned, write date planned	H	H	M	M	Y	Y	Y	Y

Section B Relevant patient information prior to immunization		
Criteria	**Finding**	**Remarks (If "Yes" provide details)**
Past history of similar event	Yes/No/UK	
Adverse event after previous vaccination (s)	Yes/No/UK	
History of vaccine, drug or food allergy	Yes/No/UK	
Pre-existing illness (past 30 days)	Yes/No/UK	
Congenital disorder	Yes/No/UK	
History of hospitalization in past 30 days with reasons (in remarks column)	Yes/No/UK	
Was the patient on any concomitant medication at the time of AEFI? (If yes, name the drug, indication, doses & treatment dates – write in remarks column)	Yes/No/UK	
Family history of any disease (relevant to AEFI) or allergy	Yes/No/UK	
If patient is an adult woman • Currently pregnant? Yes; Weeks _____/No/UK • Currently breastfeeding? Yes/No		
If patient is an infant, birth details		Any birth complication (specify)
1. Birth weight:		
2. Duration of pregnancy ☐ Full term ☐ Premature ☐ Postdated		
3. Place of birth ☐ Home delivery ☐ Institutional		
4. Delivery procedure ☐ Normal ☐ Caesarian ☐ Assisted		

Section C Details of first examination of reported AEFI case**

Source of information (✓ *all that* apply): ☐ Examination by the investigator ☐ Medical case records ☐ Verbal autopsy ☐ Other_____ If from verbal autopsy, please mention relationship with the deceased_____

In case of sudden unexplained death, please also fill SUD verbal autopsy form as per the guidelines)

Name of the person who first examined/treated the patient_____
Name of other persons from whom care was sought _____
Other sources who provided information (specify)_____

Signs and symptoms (in chronological order from the time of vaccination)

Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, lab and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.

- ***If patient has taken medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and post mortem reports, if available) and write only information unavailable in the attached documents below
- ***If patient has not taken medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets as required)

Name of person filling up clinical details given below:	Designation:	Date/time

Consciousness	Alert/Drowsy/Unconscious/Other (specify)_____ Describe:
Vitals	Pulse Temperature Respiratory rate BP Weight
Skin	Rash/Cyanosis/Petechiae/Pallor/Jaundice/Others (specify)_____ Describe:
Eyes	Vision: Normal/impaired Pupil: Normal/Constricted/Dilated/Reacting to light
Hearing, speech	Normal/Impaired: Describe Normal/Abnormal: Describe
Neck	Neck stiffness: Present/Absent
Chest	Auscultation Normal/Crepts/Rhonchi Heart sounds Normal/Murmur (describe)
Respiration	Normal/Cough/Shortness Of Breath/Others (specify)_____ Describe:
GI	Pain abdomen/Vomiting/Diarrhoea/Dysentery/Others (specify)_____ Describe:
Abdomen	Normal/distended/tender Liver: Not palpable/Palpable (If palpable specify size) Spleen: Not palpable/Palpable (If palpable specify size) Describe:
Limbs	Tone • Upper limbs: Normal/Increased /Decreased • Lower limbs: Normal/Increased /Decreased Reflexes

	• Biceps Normal/Increased /Decreased/Absent • Triceps Normal/Increased /Decreased/Absent • Supinator Normal/Increased /Decreased/Absent Plantar Extensor/Flexor
Any other abnormal signs	
Treatment provided	
Provisional diagnosis	

Section D	**Details of vaccines provided on vaccination day at the site linked to AEFI**												
Number immunized for each vaccine at session site. Attach record if available.	Vaccine name												
	No of doses administered												

1.	When was the patient immunized? (✓ the ☐ below and respond to ALL questions)		
	☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown		
2.	In case of multi-dose vials, was the vaccine given – ☐Within the first few doses of the vial administered ☐ Within the last doses of the vial administered ☐Unknown		
3.	**Based on your investigation, is it possible that:** *(Please provide explanation for any "yes" answer in the remark column)*		
A	There was an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes/No/Unable to assess	Remark
B	The vaccine (ingredients) administered could have been unsterile?	Yes/No/Unable to assess	Remark
C	The vaccine's physical condition (colour, turbidity, foreign substances) was abnormal at the time of administration?	Yes/No/Unable to assess	Remark
D	There was an error in vaccine reconstitution/preparation by the vaccinator (wrong product, wrong diluent, improper mixing, improper syringe filling)?	Yes/No/Unable to assess	Remark
E	There was an error in vaccine handling (break in cold chain during transport, storage and/or immunization session)?	Yes/No/Unable to assess	Remark
F	The vaccine was administered incorrectly (wrong dose, site or route of administration, wrong needle size, not following good injection practice)?	Yes/No/Unable to assess	Remark

4. Number immunized from the concerned vaccine vial/ampoule in this session	
5. Number immunized from the concerned vaccine vial/ampoule since vial was opened (in case of open vial policy)	
6. Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations _____	
7. **Is this case a part of a cluster?**	Yes/No/UK
A If yes, how many other cases have been detected in the cluster?	
B Did all the cases in the cluster receive vaccine from the same vial?	Yes/No/UK
C If no, number of vials used in the cluster	

Section E **Immunization practices at the place(s) where concerned vaccine was used** *(fill up this section by asking and/or observing practice)*				
Syringes and needles used:				
• Are AD syringes used for immunization?				Yes/No/UK
If "No", specify the type of syringes used: ☐Glass ☐Disposable ☐Recycled disposable ☐Other _____				
Specific key findings/additional observations and comments:				
Reconstitution: (complete only if applicable, ✓ NA if not applicable)				
• Reconstitution procedure (✓)	Status			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA	
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA	
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA	
Separate reconstitution syringe for each vaccination?	Yes	No	NA	
• Are the vaccines and diluents used the same as recommended by the manufacturer?	Yes	No	NA	
Specific key findings/additional observations and comments:				

Section F **Cold chain and transport** *(fill up this section by asking and/or observing practice)*	
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes/No
○ If, "Yes", has there been any deviation outside of 2–8 °C after the vaccine was placed inside?	Yes/No
○ If, "Yes", provide details of monitoring separately:	
• Is the correct procedure of storing vaccines, diluents and syringes being followed?	Yes/No/UK
• Any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes/No/UK
• Are partially used reconstituted vaccines stored in the refrigerator?	Yes/No/UK
• Unusable vaccines (expired, no label, VVM stage 3 & 4, frozen) in the refrigerator?	Yes/No/UK
• Unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes/No/UK
Specific key findings/additional observations and comments:	
Vaccine transportation:	

• Type of vaccine carrier used	
• Vaccine carrier sent to the site on the same day of vaccination?	Yes/No/UK
• Vaccination carrier returned from the site on the same day of vaccination?	Yes/No/UK
• Conditioned ice pack used?	Yes/No/UK
Specific key findings/additional observations and comments:	

Section G Community investigation (please visit locality and interview parents/others)

Any similar events reported recently in the locality? Yes/No/UK
If "Yes", describe:

If "Yes", how many events/episodes?

Of those affected, how many are
- Vaccinated:_____
- Not Vaccinated:_____
- Unknown:_____

Other comments:

Section H Other findings/observations/comments

Section I District AEFI committee review & investigation report

a. Was the case discussed by the district AEFI committee? *If "Yes", then date case discussed by district AEFI committee*	Yes D D M M Y Y Y Y	No
b. *What was the provisional diagnosis of the case concluded by the district AEFI committee?*		
c. Did the district AEFI committee recommend that samples be sent for testing?	Yes	No

Details of vaccine/diluent samples sent to CDL Kasauli

Vaccine/diluent name	Site of collection	Used vial/amp quantity	Batch no, lot no, date of expiry	Date sent	Unused vial/amp quantity	Batch no, lot no, date of expiry	Date sent

Details of syringe/needle samples sent to CDL Kolkata								
Type of syringes	Quantity	Site of collection	Batch no, lot no, date of expiry	Date sent	Type of needles	Quantity	Batch no, lot no, date of expiry	Date sent
a) Any biological product (CSF, blood, urine) sent for testing? *If "Yes", specify details of the lab; attach copy of report if available* *Note: for AEFI resulting within 28 days following JE vaccine, send sample of CSF, serum to nearest NIV lab in Pune or Gorakhpur*							Yes	No
b) Was the local drug inspector involved in collecting additional samples?							Yes	No
c) Specify any other relevant investigation done and attach reports.								

Attached copies of reports/documents with this case investigation report:			
Ser No.	**List of document copies received**	**Availability** *(encircle)*	**Remarks (if any)**
1.	Case reporting form (CRF)	Yes/No	
2.	Post mortem report *(in case of death)*	Yes/No	
3.	Verbal autopsy form (in case of sudden unexplained death)	Yes/No	
4.	**Any pathology/microbiology test report**		
4A	Blood test report	Yes/No	
4B	CSF report	Yes/No	
4C	Urine test report	Yes/No	
5.	Doctor's prescription/treatment record for AEFI	Yes/No	
6.	Doctor's prescription/treatment record for other illness	Yes/No	
7.	Laboratory result of vaccine (if sent for testing)	Yes/No	
8.	Laboratory result of syringes/other drugs (if sent for testing)	Yes/No	
9.	Any other document relevant to case	Yes/No	

District AEFI committee that conducted the investigation			
Name	**Designation**	**Phone #**	**Signature**
1.			
2.			
3.			
4.			

5.			
6.			
7.			

Section J **DIO/district nodal person** ***(Officer forwarding this report)***

Name ..... Designation.....Date of submission to state/national level.....

Mobile No..... Landline (with STD code)..... Fax No. .....

email id..... Complete office address (with Pin code).....

.....

.....Signature and seal..... Date.....

Please ensure that this preliminary investigation form reaches within 10 days of notification to:
1.State Immunization Officer
2. Deputy commissioner, Immunization Division of Govt. of India, MoHFW, Nirman Bhawan, New Delhi–110108.
(Fax: 011 23062728. email: aefiindia@gmail.com)

Annexure 3

FINAL CASE INVESTIGATION FORM

AEFI reporting ID: IND (AEFI) /__ST_/DIS_/_YR _/_NUM_ (To be allotted by DIO)

Section A

State	**District**
Block/ward	**Village/urban area**
Place of vaccination: Govt health facility/outreach/private health facility/other ____	
Session: Routine (including SIW) Campaign (SIA)-IPPI/MR/JE/others (specify):_____ Other _____	
Name of investigator:	Date case visited and investigated: __ __/__ __/__ __ __ __
Posted at: Designation:	Date of preparing this form:__ __/__ __/__ __ __ __ Time of preparing this form: _____ a.m./p.m. This report is ☐ Preliminary ☐ Final
Contact phone number: email:	

Patient's name																											
Date of birth DD/MM/YYYY										Age (in months): _____ months															Sex	Male	Female
Mother's name																											
Father's name																											
Complete address of the case with landmarks *(street name, house number, village, block, tehsil, Pin no., telephone no.)*																											
P	**i**	**n**	**-**							**P**	**h**	**o**	**n**	**e**	**-**												

Attached copies of reports/documents with the final case investigation report:

Sl	List of document copies received	Availability *(encircle)*	Remarks (if any)
1	Case reporting form (CRF)	Yes/No	
2.	Preliminary case investigation form	Yes/No	
3	Any pathology/microbiology test report		
3a	Blood test report	Yes/No	
3b	CSF report	Yes/No	
3c	Urine test report	Yes/No	
4	Doctor's prescription/treatment record for AEFI	Yes/No	
5	Doctor's prescription/treatment record for other illness	Yes/No	
6	Laboratory result of vaccine (if sent for testing)	Yes/No	
7	Verbal autopsy form (in case of reported sudden unexplained death)	Yes/ No	
8	Post mortem report (based on guidelines for autopsy in case of reported unexplained death)	Yes/No	
9	Laboratory result of syringes/other drugs (if sent for testing)	Yes/No	
10	Any other document relevant to case	Yes/No	

Date of Vaccination: __ __/__ __/__ __ __ __ Time of Vaccination: __ __: __ __ a.m./p.m.	Address of session site:
Date first notified to government health system: __ __/__ __/__ __ __ __	Notified by (please circle): Health worker/government doctor/private doctor/community/media/others (specify) _____

Date of first symptom	D	D	M	M	Y	Y	Y	Y	Time of first symptom	H	H	M	M	a.m.	p.m.		
Date of key symptom	D	D	M	M	Y	Y	Y	Y	Time of key symptom	H	H	M	M	a.m.	p.m.		
Hospitalization No/Yes – Date	D	D	M	M	Y	Y	Y	Y	Time of hospitalization	H	H	M	M	a.m.	p.m.		
Name and address of hospital (if hospitalized):																	
Current status (encircle)	Death/still hospitalized/recovered & discharged with sequelae / recovered completely and discharged/left against medical advice (LAMA)/not hospitalized																
If died, date of death	D	D	M	M	Y	Y	Y	Y	Time of death	H	H	M	M	a.m.	p.m.		
Postmortem done? YES/No/Unknown If yes, then give date postmortem done	D	D	M	M	Y	Y	Y	Y	If not done, but planned, give date planned	H	H	M	M	Y	Y	Y	Y

SECTION B: Refer to CRF, PCIF and updated information available for writing the case summary. Remember to include the following points, add additional sheet as necessary

Relevant information prior to immunization:

Status of immunization on the day AEFI reported (completed doses before the event):

Vaccines administered on the day of the event:

Post immunization event:

Examination findings:
Laboratory findings:
Details of community investigation, if conducted:
Any other findings:
Treatment provided:
Post mortem report if available:
Provisional diagnosis:

Add additional pages if needed

SECTION C:

Report of vaccine/diluent samples sent to CDL Kasauli as per details mentioned below

Vaccine/diluent name	Used vial/amp quantity	Batch No, lot No, date of expiry	Date sent	Lab finding	Unused vial/amp quantity	Batch No, lot No, date of expiry	Date sent	Lab finding

Report of syringe/needle samples sent to CDL Kolkata as per details mentioned below

Type of Syringes	Quantity	Batch No, Lot No, date of expiry	Date Sent	Lab finding	Type of needles	Quantity	Batch No, Lot No, date of expiry	Date Sent	Lab finding

Any biological product (CSF, blood, urine) sent for testing? *If yes, specify details of the lab; attach copy of report if available* *Note: For AEFI resulting within 28 days following JE vaccine, send sample of CSF, serum to nearest NIV lab in Pune or Gorakhpur.*	Yes	No	**Lab finding**
Specify any other relevant investigations done and attach reports			

District AEFI committee meeting when case was discussed

Name	Designation	Phone #	Signature
1.			
2.			
3.			
4.			
5.			
6.			
7.			

Section D **DIO/district nodal person** ***(Officer forwarding this report)***

Name ..... Designation.....Date of submission to state/national level.....

Mobile No..... Landline (with STD code)..... Fax No. .....

email id..... Complete office address (with Pin code).....

.....

.....Signature and seal..... Date.....

Please ensure that this investigation form reaches within 70 days of notification to:

1.State Immunization Officer

2. Deputy commissioner, Immunization Division of Govt of India, MoHFW, Nirman Bhawan, New Delhi – 110108.
(Fax: 011 23062728. email: aefiindia@gmail.com)

Annexure 4

AEFI – LABORATORY REQUESITION FORM (LRF)

(To be completed by drug inspector/DIO. LRF should be accompanied with specimens)

AEFI category (encircle): **Death/hospitalized/cluster/disability/others(specify)**____________________

State		**Case ID** **IND (AEFI)/**	*State code /District code /Year /Serial No.*
District			
Block			

Name of drug inspector/DIO:	Date of filling LRF:
Designation:	Mobile No.:
Land line (with STD code):	Fax No.:
Case name	

Date of birth	D	D	M	M	Y	Y	Y	Y	Age (in months)			Sex	Male	Female

Complete address of the case with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*

P	i	n	-					P	h	o	n	e	-

Date of vaccination	D	D	M	M	Y	Y	Y	Y	Date of onset	D	D	M	M	Y	Y	Y	Y
Date of collection of specimen	D	D	M	M	Y	Y	Y	Y	Time of collection of specimen	H	H	M	M	a.m.	p.m.		

1. Precise description of samples:

a) For vaccine/diluents specimens: (to be transported in reverse cold chain)

Mention vaccine/diluent	Quantity sent	Name of manufacturer (in BLOCK Letters)	Batch No.	Manufacturing date	Expiry date

b) For logistics specimens: (AD, reconstitution, disposable syringes)

Mention logistics	Quantity sent	Name of manufacturer (in BLOCK Letters)	Batch No.	Manufacturing date	Expiry date

c) For Biological product specimen: (CSF, blood, urine)

Name of AEFI Case:	**Case ID** **IND (AEFI)/***State Code/District Code/Year/Serial No.*

2. Test requested:
3. Preliminary clinical diagnosis (working hypotheses) of district AEFI committee:

4. Name & complete address of officials to whom laboratory results should be sent:

Send to	Complete address	Phone/fax	Mobile	email ID
State drug controller				
State cold chain officer				
State EPI Officer				
District immunization officer (DIO)				
Others (specify)				

To be completed by lab officials after receiving the specimen

Date of receipt of specimen(s) at laboratory	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*
Name of person receiving specimen(s) at laboratory								
Condition of specimen(s) upon receipt at lab (*encircle*)	Good*		Poor			Unknown		
Comments by pathologist, virologist or bacteriologist:								
Date specimen(s) results sent from this lab	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*
Name of laboratory professional								
Signature								

Landline No.:	Fax No.:	email ID:

**** Criteria for "good" condition: Samples sent as per AEFI guidelines.***

Annexure 5

CAUSALITY ASSESSMENT REPORT

(Office of State Immunization Officer)

(State AEFI committee to complete causality assessment exercise and forward this report to GoI within 30 days of receipt of final CIF at the state)

SECTION A (Preparation for causality assessment)

Date of receipt of Final CIF from district at state	D	D	M	M	Y	Y	Y	Y

Patient's name*																							
* Use separate form for each case in a cluster																							
Date of birth	D	D	M	M	Y	Y	Y	Y	**Age** (in months)			**Sex**	Male	Female									
Complete residential address of the case with landmarks *(Street name, house number, village, block, Tehsil, PIN No. etc.)*																							
P	**i**	**n**	-								**P**	**h**	**o**	**n**	**e**								

Check list for state EPI officer:

Sl. No.	List of document copies received	Availability *(encircle)*	Remarks (if any)
1.	Case reporting form (CRF)	Yes/No	
2.	Preliminary case investigation form	Yes/No	
3.	Postmortem report *(in case of death)*	Yes/No	
4	Verbal autopsy form (in case of sudden unexplained death)	Yes/No	
5	**Any pathology/microbiology test report**		
5A.	Blood test report	Yes/No	
5B.	CSF report	Yes/No	
5C.	Urine test report	Yes/No	
6.	Doctor's prescription/treatment record for AEFI	Yes/No	
7.	Doctor's prescription/treatment record for other illness	Yes/No	
8.	Laboratory result of vaccine (if sent for testing)	Yes/No	
9.	Laboratory result of syringes/other drugs (if sent for testing)	Yes/No	
10..	Any other document relevant to case	Yes/No	

Step 1 (Eligibility)

Name of the Parient	Name of one or more vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine / vaccination caused _____? (The event for review in step 2)

Has the _____ vaccine / vaccination caused _____?

Examples of causality questions

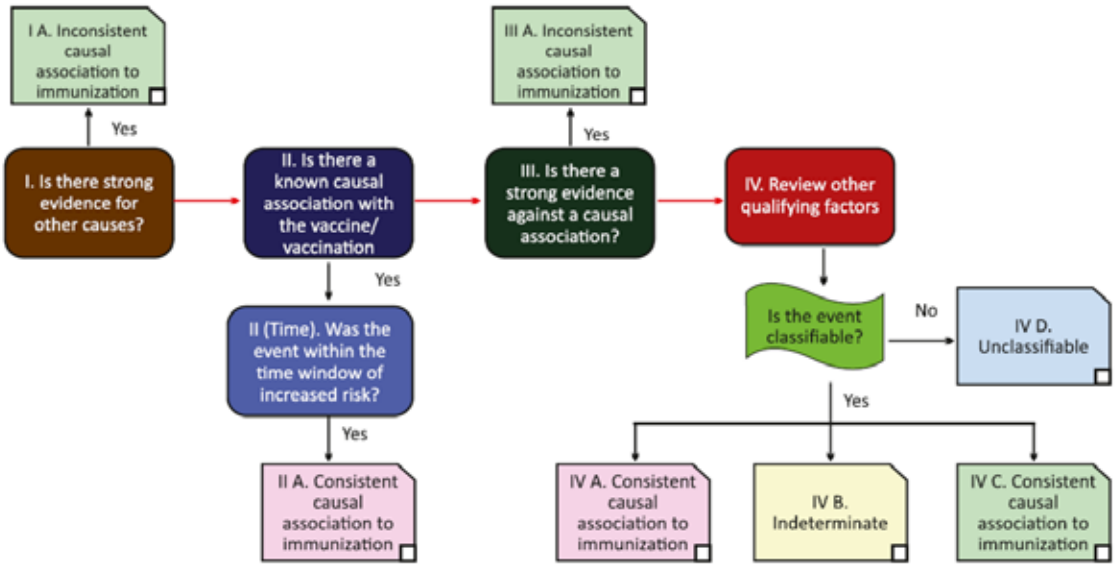
- "Has the vaccine A caused hepatomegaly?" (Anexample of an unfavorable or unintendedor unintended sign)
- "Has the vaccine B caused thrombocytopenia?" (An example of a laboratory finding)
- "Has the patient complained that the vaccine C caused itching and redness?" (An example of a symptom)
- "Has the vaccine D caused meningitis?" (An example of a disease).
- Imp: 'Death' is not a valid diagnosis. The pre-existing conditions or the circumstances leading to death should ne mentioned as a valid diagnosis

Step 2 (Event checklist)

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable

I. Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	☐	☐	☐	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐	☐	☐	☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐	☐	☐	☐	
Immunization error					
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (use beyond the expiry date, wrong recipient, etc.)?	☐	☐	☐	☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐	☐	☐	☐	
Was the vaccine's physical condition (colour, turbidity, presence of foreign substances) abnormal at the time of administration?	☐	☐	☐	☐	
Was there an error in vaccine constitution/preparation by the vaccinator (wrong product, wrong diluent, improper mixing, improper syringe filling)?	☐	☐	☐	☐	
Was there an error in vaccine handling (a break in the cold chain during transport, storage and/or immunization session)?	☐	☐	☐	☐	
Was the vaccine administered incorrectly (wrong dose, site or route of administration; wrong needle size)?	☐	☐	☐	☐	
Immunization anxiety					
Could the event have been caused by anxiety about the immunization (vasovagal, hyperventilation or stress-related disorder)?	☐	☐	☐	☐	
II (time). If "Yes" to any question in II, was the event within the time window of increased risk?					
Did the event occur within an appropriate time window after vaccine administration?	☐	☐	☐	☐	
III. Is there strong evidence against a causal association?					
Is there strong evidence against a causal association?	☐	☐	☐	☐	
IV. Other qualifying factors for classification					
Could the event occur independently of vaccination (background rate)?	☐	☐	☐	☐	
Could the event be a manifestation of another health condition?	☐	☐	☐	☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐	☐	☐	☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐	☐	☐	☐	
Was there acute illness prior to the event?	☐	☐	☐	☐	
Did the event occur in the past independently of vaccination?	☐	☐	☐	☐	
Was the patient taking any medication prior to vaccination?	☐	☐	☐	☐	
Is there a biological plausibility that the vaccine could cause the event?	☐	☐	☐	☐	

Step 3 (Algorithm) Review all steps and (✓) in all appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply

Check ✓ all boxes that apply

Adequate information availble

A. Consistent causal association to immunization

- ☐ A1. Vaccine product-related reaction (As per published literature)
- ☐ A2. Vaccine quality defect-related reaction
- ☐ A3. Immunization error-related reaction
- ☐ A4. Immunization anxiety-related reaction

B. Indeterminate

- ☐ B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (May be new vaccine-linked event)
- ☐ B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent causal association to immunization

- ☐ C. Coincidental

  Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

Adequate information not availble

☐ **Unclassifiable**

Specify the additional information required for classification

* *B1: This is a potential signal and maybe considered for investigation

Summarize the classification logic:
With available evidence, we could conclude that the classification is _____ because:

Details of state AEFI committee members who conducted the causality assessment			
Name	*Designation*	*Phone #*	*Signature*
1.			
2.			
3.			
4.			
5.			
6.			
7.			

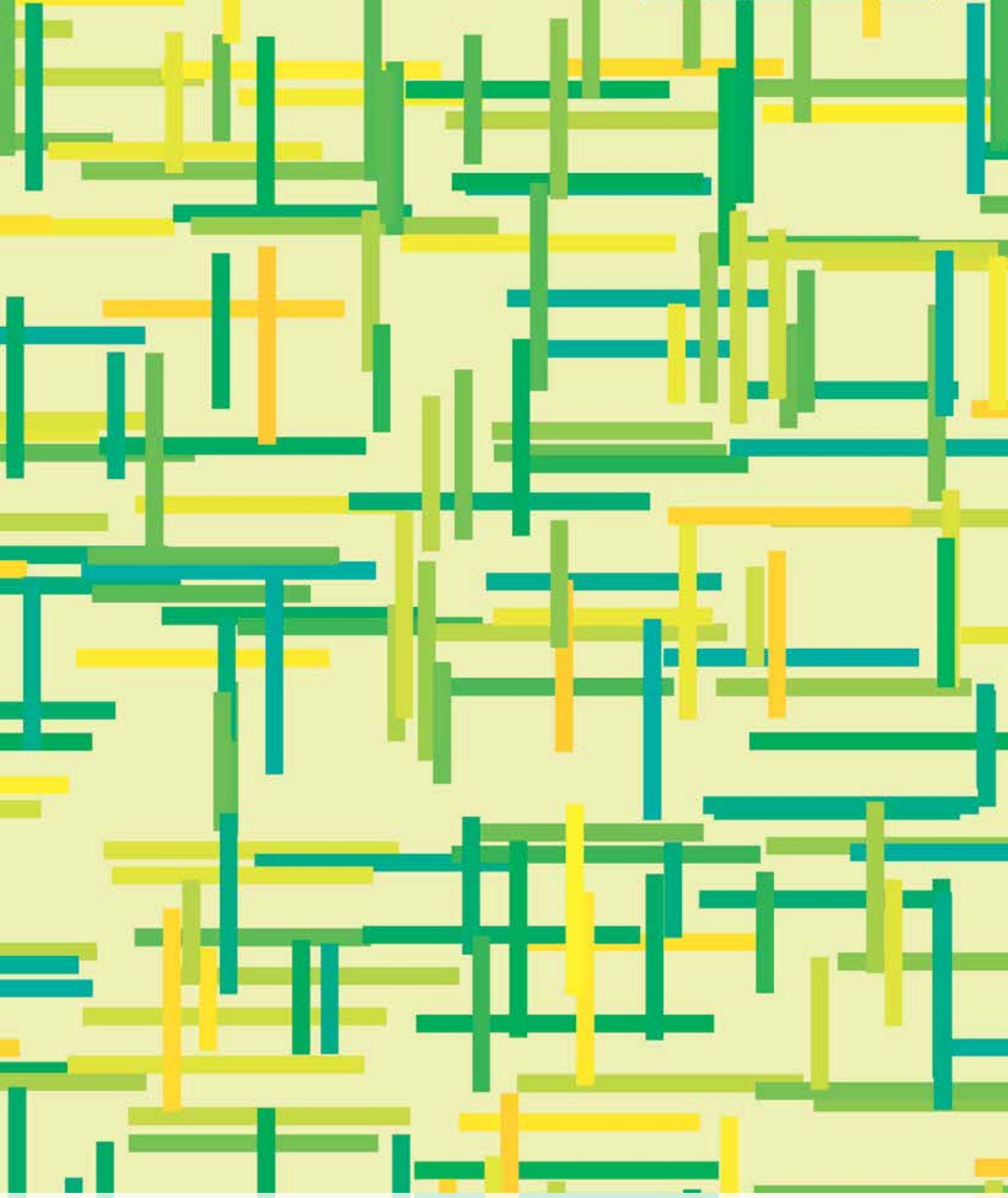
Date of review of this case	D	D	M	M	Y	Y	Y	Y	Date of submission of report to GoI								

State nodal person (officer forwarding this report)
Name ..... Designation.....Date of submission to national level.....
Mobile No..... Landline (with STD code)..... Fax No. .....
Email id..... Complete Office address (with Pin code).....
.....
.....
Signature/seal.....Date.....

Please ensure that this causality assessment report reaches:

Deputy Commissioner,
Immunization Division of Govt of India, MoHFW, Nirman Bhawan,
New Delhi – 110108.
(Fax: 011 23062728 email: aefiindia@gmail.com)

Section B	*For use at national level (Office of Deputy Commissioner- UIP)*							
Date of receipt of final CIF from district at national level	D	D	M	M	Y	Y	Y	Y
Date of receipt of causality assessment report from state	D	D	M	M	Y	Y	Y	Y



CENTRAL DRUGS STANDARD CONTROL ORGANISATION
Directorate General of Health Services
Ministry of Health and Family Welfare, Government of India
FDA Bhawan, Kotla Road, New Delhi -110002