GUIDANCE FOR INDUSTRY ON PHARMACOVIGILANCE REQUIREMENTS FOR HUMAN VACCINES

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ORDER

Subject: The Guidance for Industry on Pharmacovigilance Requirements for Human Vaccine (Version 2.0).

The "Guidance for industry on Pharmacovigilance requirements for Biological Products" earlier prepared and published in 2012, and was revised in 2017. The said document is now further revised in consultation with the AEFI Secretariat and IPC-PVPI as per New Drugs and Clinical Trial Rules, 2019 and introduction of Signal Review Panel for Human Vaccines by AEFI Secretariat, (MoHFW) and online submission of Periodic Safety Update Reports through SUGAM Portal as "**Guidance for Industry on Pharmacovigilance requirements for Human Vaccines, Version 2.0**". A draft was published to solicit suggestions/comments/objections from the stakeholders through CDSCO website on 29.05.2024. Now, the said guidance document is updated after consultation with the AEFI Secretariat and IPC-PVPI and it is published after considering the stakeholder's suggestions/comments/objections.

Dr. Rajeev Singh Raghuvanshi
Drugs Controller General (India)

PREFACE

This is in consonance with the objective of the Drugs & Cosmetics Act 1940 and Rules made thereunder and New Drugs and Clinical Trials Rules 2019 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 Human Vaccines. The procedure set out to facilitate the industry to submit the documents as per the requirements of Drugs and Cosmetics Act 1940 and Rules 1945. 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 including vaccines, 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). The present document is developed to provide the guidance to all the stakeholders including the MAH on the coordinated activities of the various departments within the Ministry of Health & Family Welfare to work together and enhance the pharmacovigilance of vaccines.

The present document is developed to provide the guidance to all the stakeholders including the MAHs about Vaccine Safety Monitoring, Audits and Inspection; Risk Management Plan (RMP) wherever applicable and Periodic submission of Risk Benefit Evaluation Report i.e., PSUR to the Licensing Authority.

The guidance document has been prepared in line with the Drugs & Cosmetics Act 1940 and Rules made thereunder and NDCT Rules, 2019 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 stakeholders 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 AE/AEFI Pharmacovigilance system to ensure patient safety.

List of Abbreviations

Abbreviations	Full Forms
AE	Adverse Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
CAPA	Corrective And Preventive Actions
CDL	Central Drugs Laboratory
CDSCO	Central Drugs Standard Control Organization
CIOMS	Council for International Organizations of Medical Sciences
CoWIN	Covid Vaccine Intelligence Network
CRF	Case Report Form
CLA	Central Licensing Authority
DCG (I)	Drugs Controller General (India)
DIO	District Immunization Officer
DLP	Data Lock Point
DOV	Date of Vaccination
FCIF	Final Case Investigation Form
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professionals
ICSR	Individual Case Safety Reports
IPC	Indian Pharmacopoeia Commission
ITSU	Immunization Technical Support Unit
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MoHFW	Ministry of Health & Family Welfare

NCC	National Coordination Centre
NRA	National Regulatory Authority
NTAGI	National Technical Action Group on Immunization
PIL	Patient Information Leaflet
PBRER	Periodic Benefit Risk Evaluation Report
PCIF	Preliminary Case Investigation Form
PI	Prescribing Information
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVMF	Pharmacovigilance System Master File
PVOIC	Pharmacovigilance Officer-In charge
PvPI	Pharmacovigilance Programme of India
QA	Quality Assurance
SAE	Serious Adverse Events
SEPIO	State EPI Officer
SIO	State Immunization Officer
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPEAC/CEPI	Safety Platform for Emergency Vaccines/ Epidemic Preparedness Innovations
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. India can now boast of producing safe, effective and affordable vaccine products which safeguard millions of children at domestic and International level. This responsibility warrants additional efforts 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 in formulations 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, understanding and prevention of adverse events. As per WHO, Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization. The primary goal of vaccine pharmacovigilance is early detection, assessment, timely response to adverse events, signal management and continuous benefit risk assessment. In this guidance document, safety signal refers to a concern about a new risk or a new aspect of an already known risk or excess of adverse events compared to what would be expected to be associated with a product's use.

Signals can be identified from post marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacological class.

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 for the MAHs and for other allied stakeholders who play active role in launching, introduction, distribution and bringing the vaccine products to end users, to implement an effective PV System for ensuring patient safety. 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 vaccine 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 vaccine 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 risks/benefits ratio of the product. Evaluation of this information should be a continuous process in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all vaccine products to ensure their safe use. The risk-benefit balance can be improved by reducing risks to patients through effective pharmacovigilance system that can enable information feedback to the users of medicines in a timely manner.

1.3 RATIONALE

This document rationally places guidance that all MAHs of Human vaccines (importers and manufacturers) should establish and implement an appropriate effective pharmacovigilance system with adequate number of qualified, trained, experienced manpower to collect, collate and analyze all AEFI (minor, severe and serious) as per Fifth Schedule of New Drugs and Clinical Trials Rules, 2019. This Pharmacovigilance system within the company should conduct decisive causality assessment (AEFI Surveillance and Response — Operational Guidelines 2024) 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 Fifth Schedule of New Drugs and Clinical Trials Rules, 2019 and submitted to the Licensing Authority i.e. DCG (I) in CDSCO (HQ) within the stipulated time period. After review of the submitted PSUR, CDSCO shall convene the meeting of PSUR committee within a reasonable time period and give opportunities to the concerned MAHs 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 made thereunder, so as to monitor the safety and effectiveness of human vaccine in the market so as to safeguard the public health. MAHs must have a Pharmacovigilance system in place that enhances the overall quality of the receipt, processing and reporting of AE/ AEFI while ensuring that accurate and complete information with respect to patient safety is provided to CDSCO.

1.4 SCOPE

This document has been framed in compliance with the provisions made under Fifth Schedule of New Drugs and Clinical Trials Rules 2019, Schedule M of Drugs & Cosmetics Act 1940 and Good Clinical Practices (GCP) Guidelines of India, AEFI Surveillance and response operational Guidelines to provide guidance to MAHs (Importers and Manufacturers of Human Vaccine) of India to establish their Pharmacovigilance System for collection,detection, assessment, monitoring, and prevention all AE/ AEFI cases pertaining to vaccine products across the domestic and export market, after due investigation & causality assessment 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 provides adequate information in a systematic manner for reporting serious adverse event or adverse event following immunization when the product is in the market and would enable the systematic sharing of information between CDSCO, Pharmacovigilance Programme of India (PvPI) and the Universal Immunization Program (UIP), Ministry of Health and Family Welfare.

The roles and responsibilities of the CDSCO are as per the Drugs and Cosmetics Act, 1940 and Rules made thereunder.

In case, the Pharmacovigilance Programme of India receives AEFI information the same shall be shared with the AEFI Secretariat under the Immunization Division (MoHFW). The AEFI Secretariat will process the AEFI cases for causality assessment and signal detection and management and present the data to the National AEFI Committee (for approval of results of causality assessment) and the Signal Review Panel (for signal assessment) and further recommendations to CDSCO for regulatory actions. 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.

The Immunization Division under Ministry of Health and Family Welfare collects information on adverse event related to Universal Immunization Program (UIP) vaccines on a regular basis through the AEFI surveillance system. Information on serious adverse events is collected in the Case Reporting Form (CRF) and details of the investigation of the reported event are collected in the Case Investigation Form (CIF) by the DIO with all supporting documents such hospital records, post mortem reports, etc. These are then shared with the SIO who presents it to the state AEFI committee which assigns the causality. In addition to the state AEFI committee, causality assessments are also done at the national level by AEFI

Secretariat. The causality assessment results in the form of a linelist are shared with the CDSCO for further analysis and necessary regulatory actions.

The AEFI Secretariat will share line-listing in excel (.xls) format with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited line list 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.

In tandem is the process of signal management for vaccines being done at the AEFI Secretariat. A Signal Review Panel for vaccines assesses and reviews the detailed signal assessments at regular interval and the recommendations are then forwarded through the proper channel to CDSCO for further dissemination to MAHs. A detailed process is outlined in further sections.

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. 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 Coordination 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 1940 and Rules made thereunder. 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 decisions on the basis of recommendations shared by Signal Review Panel of Vaccines where-in a detailed analysis of the PMS, PSUR, AEFI data is done by expert committee. CDSCO (HQ) then reviews the recommendations and shares them with MAHs for necessary actions.

The regulatory recommendations are disseminated to MAHs through proper channel by CDSCO. 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/ Marketing and annually for subsequent years, till the product is categorized as 'New Drug'. The Licensing Authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSUR furnished by the Importers/Manufacturers of vaccines holding marketing authorization is deliberated in PSUR Expert Committee Meetings conducted by CDSCO. The PSUR data is also considered while reviewing the UIP vaccine safety database for signals by the AEFI Secretariat.

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 (PvPI), Indian Pharmacopoeia Commission (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 has initiated a nation-wide Pharmacovigilance programme for protecting the health of the patients by assuring drug safety. Later the MoHFW recasted these programmes on 15th April 2011 vide an order number X.11035/7/2011-DFQC shifting the National Coordination Centre from AIIMS, New Delhi to IPC, Ghaziabad. The programme is coordinated by the Indian Pharmacopoeia Commission, Ghaziabad as the National Coordination Centre (NCC). The center operates under the supervision of a Steering Committee. Indian Pharmacopeia Commission, Ghaziabad is an autonomous organization under the MoHFW, having mandate for preparation of standards for all drugs including bulk antigens and vaccine products, publication of Indian Pharmacopoeia (IP) with monographs for all drugs including vaccines, publication of National Formulary of India (NFI), preservation of reference standards for Drugs, however, the vaccine reference standards on behalf of IPC are maintained by CDL (Kasauli). IPC is also the National Coordination Centre for all ADR Monitoring Centers across the country to collect, collate AE/ADRs for all drugs, including vaccines.

Major roles and responsibilities of PvPI at IPC includes development and implementation of pharmacovigilance system in India, enrolment of all hospitals/medical colleges in the program covering north, south, east and west of India, encouraging HCPs in reporting of adverse reaction to drugs, vaccines, medical devices and biological products along with 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 HCPs. The adverse events following vaccinations, which are reported from the AMCs, are shared with the AEFI Secretariat, for examination and after validation for signal assessments. The AEFI Secretariat has established a Signal Review Panel for vaccines which share the recommendations and updates to the National AEFI Committee and CDSCO for regulatory actions.

2.2.1 Role of PvPI at IPC

- To monitor Adverse Drug Reactions (ADRs) in Indian population.
- To create awareness amongst health care professionals about theimportance of ADR reporting in India.
- To monitor benefit-risk profile of medicines
- 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.
- To share the Adverse Reactions reported for UIP vaccines to AEFI Secretariat through CDSCO for data analysis and discussion in the Signal Review Panel of vaccines (MoHFW) for appropriate action.

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 eleven vaccine preventable diseases (VPDs) namely, Diphtheria, Pertussis, Tetanus, Polio, Measles, Hepatitis B and Tuberculosis.

IMMUNIZATION SCHEDULE IN UNIVERSAL IMMUNIZATION PROGRAM

Vaccine	VPD	Due Age	Max age
BCG	Tuberculosis	At birth	till one year of age
Hepatitis B - Birth dose	Hepatitis B	At birth	within 24 hours

OPV-0	Polio	At birth	within the first 15 days
OPV 1, 2 & 3		At 6 weeks, 10 weeks & 14 weeks	till 5 years of age
Pentavalent 1, 2 & 3** (Diphtheria+ Pertussis + Tetanus + Hepatitis B +Hib)	Diphtheria, Pertussis , Tetanus , Hepatitis B , Haemophilus Influenzae B	At 6 weeks, 10 weeks & 14 weeks**	1 year of age
Fractional IPV (Inactivated Polio Vaccine)	Polio	At 6 ,14 weeks and 9 month	1 year of age
Rotavirus	Rotavirus	At 6 weeks,10 weeks & 14 weeks	1 year of age
Pneumococcal Conjugate Vaccine (PCV)	Pneumococcal Disease	At 6 weeks & 14 weeks At 9 completed months - booster	1 year of age
Measles/ Rubella 1st dose ##	Measles , Rubella	At 9 completed months-12 months.	5 years of age
Japanese Encephalitis – 1 (Where applicable)	Japanese Encephalitis	At 9 months-12 months	15 years of age
Vitamin A (1st dose)		At 9 months	5 years of age (1 lakh IU)
DPT Booster-1	Diphtheria, Pertussis , Tetanus	16-24 months	7 years of age
Measles/ Rubella 2nd dose ##	Measles , Rubella	16-24 months	5 years of age
OPV Booster	Polio	16-24 months	5 Years
Japanese Encephalitis – 2 (Where applicable)	Japanese Encephalitis	16-24 months	till 15 years of age
Vitamin A (2nd to 9th dose)		At 16 months. Then, one dose every 6 months.	up to the age of 5 years
DPT Booster-2	Diphtheria, Pertussis Tetanus	5-6 years	7 Years of age
Td	Tetanus	10 years & 16 years	16 Years
Td-1	Tetanus	Early in pregnancy	Give as early as possible in pregnancy
Td-2*	Tetanus	4 weeks after TT-1*	
Td- Booster	Tetanus	If received 2 TT doses in a pregnancy within the last 3 years*	

2.3.1 Immunization Division brief from MoHFW

In 2012, AEFI Secretariat was established with due approval of MoHFW with mandate of collection, collation, line listing, reporting, sharing with partner organizations (e.g. CDSCO), investigation, causality analysis and signal assessment of AEFIs.

Adverse events following use of vaccine, whether in the Universal Immunization Programme (UIP) or private sector, pediatric vaccines or vaccines used in adults or for international travel, etc. should be reported to the AEFI surveillance system and CDSCO. All cases involving serious unexpected adverse reactions must be reported to the licensing authority within fifteen days of initial receipt of the information by the applicant (MAH).

AEFI Secretariat manages AEFI data (adverse events reported as hospitalizations, deaths, etc. following vaccination), follows up with states for investigations, and facilitates causality assessments of cases at national level. The Secretariat provides strategic vision to improve AEFI surveillance and vaccine safety under overall guidance of the National AEFI Committee and National AEFI Technical Collaborating Centre at Lady Hardinge Medical College (LHMC), New Delhi. Signal management is another core function of the secretariat and regular bimonthly meetings of the signal review panel are conducted to review the signals. It supports MoHFW in taking policy decisions related to AEFI surveillance and vaccine safety. The national AEFI surveillance guidelines are developed and updated by the AEFI Secretariat with support of WHO-India Country Office.

Adverse Events Following Vaccinations can be serious or non-serious. Serious AEFIs such as death, life-threatening, hospitalization, disability, congenital anomaly/ birth defect and cluster or community concern need to be reported immediately through CRF and investigated timely in the CIF. Serious AEFIs are reported on SAFE-VAC directly or through UWIN. Non-Serious AEFIs are reported in UWIN. Numbers of minor and serious AEFI are also reported every month through Health Management Information System (HMIS). For COVID-19 vaccines also AEFIs have been collected routinely from Co-WIN Chapter. A self-reporting Chapter also is functional for reporting AEFIs by the vaccine recipients.

Serious AEFIs are investigated by Drug inspectors deputed by the concerned State Drug Control Department and the concerned CDSCO (zonal) office as

members of the district AEFI committee which investigates AEFIs with the DIO. The drug inspectors are responsible for collecting samples of implicated vaccine vials and other concomitant drugs, diluents, etc. after a decision has been made to do so by the district AEFI committee in consultation with the State Immunization Officer. The collected vaccine samples are sent to CDL, Kasauli for testing and analysis.

The state AEFI committee conducts a causality assessment to the report and sends to the National level 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. The reporting can occur from any level of government or private sector including the private practitioner in the CRF form. Refer to the National AEFI Surveillance and Response Operational Guidelines of Ministry of Health & Family Welfare, Govt. of India for details.

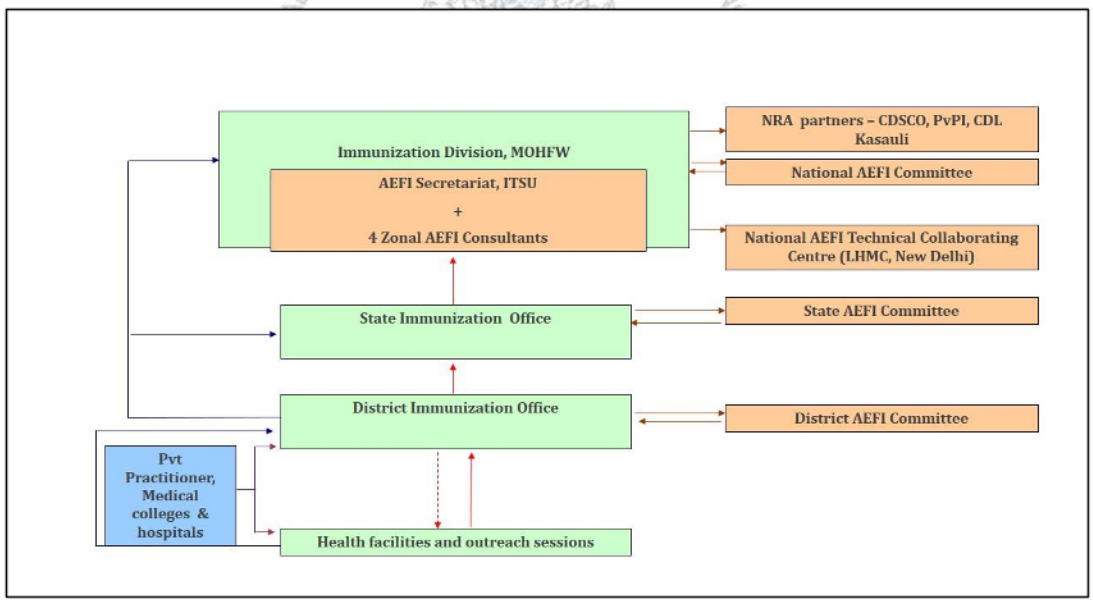

Figure 1: AEFI Secretariat Organogram

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. The AEFI Secretariat shares a linelist in excel format with CDSCO for deaths and clusters on a regular basis and all serious and severe cases on a regular interval. 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 as and whenever required.

Also as mentioned in the AEFI operational guidelines, in case of an urgent situation, the state AEFI committee along with the state drug control authorities should immediately inform AEFI Secretariat, Immunization Division to take the following steps together with the CDSCO.

- 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 regulatory decision could be considered by CDSCO in accordance with D&C Act 1940 and rules made thereunder.
- CDSCO along with CDL, Kasauli & Immunization Division will co-ordinate a re-evaluation of the quality of the vaccine & communicate to the manufacturer (by CDSCO), if necessary.

2.3.2 Signal Detection and Management for Vaccines

A structured approach for spontaneous reporting (Active and Passive Surveillance) of AEFI is an important element of vaccine safety monitoring. The evaluation of safety signals is part of vaccine safety vigilance and is essential to ensure that regulatory authorities and immunization programme have the most up-to-date information on benefits and risks. The benefit-risk balance of many vaccines is dynamic and may change over time, or may appear to change over time, and this may impact pharmacovigilance activities. Council for International Organizations of Medical Sciences 2010 defines Signal as “Information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a vaccine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verification action.” The rapid detection of vaccine safety signals of global importance is complemented by a scientifically sound assessment of the signals through signal management process performed to determine whether there are new risks associated with vaccine or whether known risks have changed, and includes any related recommendations, decisions, communications and tracking. A database is created of all the Adverse Events

(AEs) reported and this database is assessed for trend analysis and safety signals regularly. A trend analysis report on evaluation of AEFIs (minor, serious and severe, causality assessed cases and global updates is prepared to monitor the trends for different vaccines over a period of time in differentage groups on fortnightly basis.

The signal management process includes the following steps: signal detection, validation, confirmation, analysis, prioritization, evaluation, and recommended actions, tracking of follow-up activities, communication, and risk minimization. AEFI database considers Proportional Reporting Ratio (PRR), chi-square ($\chi 2$) statistics, Information Component (IC) and IC025; followed by detailed qualitative assessment of the vaccine-event combinations. A Signal Review Panel which is an independent body at the national level consisting of experienced professionals in the field of clinical pharmacology, medicine, infectious diseases, pediatrics, dermatology, neurology, cardiology, regulatory authority members (CDSCO), (including a Chairperson and a Member Secretary) assesses information on potential signals of possible importance for public health, drug regulation, and science from the data base for both regular UIP and COVID-19 vaccines on a bi-monthly basis. The Panel reports its findings and recommendation to the National AEFI Committee, and the Ministry of Health and Family Welfare (MoHFW). The regulatory recommendations are then forwarded through the proper channel to CDSCO for further dissemination to MAHs.

Signal Management Process for Vaccines: At National Level

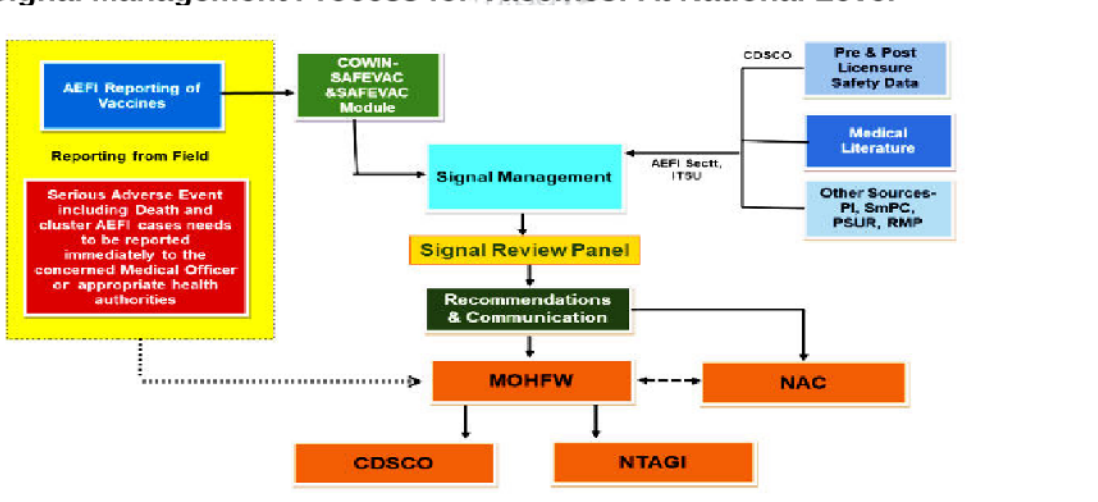

Figure 2: Signal Management Process for Vaccines: At National Level (MOHFW: Ministry of Health and Family Welfare (Immunization Division); AEFI Sect, ITSU: Adverse Events Following Immunization Secretariat, Immunization Technical Support Unit, Immunization Division, MOHFW; NAC: National AEFI Committee; CDSCO: Central Drugs Standard Control Organization (DCGI office); NTAGI: National Technical Advisory Group on Immunization; PI: Prescribing Information; SmPC: Summary of Product Characteristics; RMP: Risk Management Plan; PSUR: Periodic Safety Update Report)

The Signal review Panel and National AEFI Committee may recommend any or combination of the following:

1) No need for further evaluation or action at this point of time, other than routine pharmacovigilance.
2) Seek additional information such as:
    a) Manufacturer will submit additional data regarding the signal available with it;
    b) Manufacturer will report specifically regarding this signal at the time of submission of regular PSUR or submit an ad-hoc PSUR to CDSCO;
    c) Manufacturer will conduct a post-authorization safety study and submit its final results to CDSCO
3) Ask manufacturer to
    a) Update product information, PSURs and/or Risk Management Plan (RMP) with specific recommended changes.
    b) Implement additional risk minimization measures such as the preparation of educational materials, etc.

The regulatory recommendations from the signal review panel are shared with CDSCO to be shared with MAHs for further action which includes inclusion of recommended adverse events in the Summary of Product Characteristics for the said vaccine. Considerations of risk-benefit with regards to the impact on patients' or public health are kept in mind throughout the decision-making process.

2.3.4 Strengthening Safety Surveillance for New Vaccine Introduction or Pandemic Preparedness

New vaccines may be introduced by following the due regulatory and programmatic processes (in the case of routine vaccines) or through emergency use authorization (as for COVID-19 vaccinations). Preparations are required for both situations to enable improved monitoring of vaccine safety. One of the major challenges faced when a new vaccine is introduced is the non-availability of a complete safety profile of the vaccine. Safety data available at the time of introduction is usually limited to clinical trial data.

The regulators determine that the potential benefits outweigh the potential risks of the vaccine and a final analysis will include all safety data accumulated from

phase I, II and III studies. After approval of a vaccine, stringent follow-up is essential to monitor vaccine safety in routine use through phase IV (Post Marketing Trial), Post Marketing Surveillance or observational or non-interventional study for active surveillance, Post Marketing Surveillance including assessment of Adverse Events Following Immunization (AEFI) and Adverse Events of Special Interest (AESI).

COVID-19 vaccines were new vaccines, were granted Emergency Use Authorization /approval for restricted use in emergency situations due to the threat of the pandemic. These vaccines underwent modified but rigorous processes of safety assessment prior to their approval. In order to further ensure monitoring of safety and efficacy, the drug regulator directed manufacturers to put in place systems for post-marketing assessment of vaccines in accordance with the general guidelines specified in the Fifth Schedule of the New Drugs and Clinical Trials Rules, 2019. Well-functioning regular passive AEFI surveillance systems can identify rare, serious adverse events following the introduction of new vaccines.

Passive Adverse Events Following Immunization (AEFI) surveillance system captures minor, severe, and serious adverse events and can provide trends and potential signals requiring further studies and assessments. Many new vaccines/COVID-19 vaccines are built using novel platforms or platforms rarely used on a mass scale. Based on the experiences from existing/past vaccines or vaccine platforms on which vaccines are developed, a list of potential AESIs are identified to prioritize enhanced vaccine safety surveillance. For COVID-19 vaccines in India, the Immunization Technical Support Unit (ITSU) under the guidance of a Technical Advisory Group (TAG) has undertaken a multi-centric AESI sentinel surveillance study involving 16 medical colleges across India to understand the risk of occurrence of select AESIs following COVID-19 vaccines. From the list of 23 AESIs shortlisted by SPEAC/CEPI, 10 AESIs were studied. From a public health perspective, timely and effective communication of signal information to relevant stakeholders is the linchpin upon which effective pharmacovigilance practice rests. Understanding the balance between the benefits and risks of vaccination is essential to ensure informed and adequate public health decision-making.

2.4 PSUR/PV/AEFI Division at CDSCO

PSUR/PV/AEFI Division at CDSCO Headquarter monitors all post licensure activities of vaccine related to AEFI surveillance, PSUR review, PV Inspection, Audit and any other data on vaccine safety as and whenever required as per Drugs and Cosmetics Act 1940 and Rules made thereunder.

The PSUR/PV/AEFI Division shall also be responsible for

i) The coordination with NCC-PvPI (IPC, Ghaziabad) and AEFI Secretariat, Immunization Division, Ministry of Health and Family Welfare for the various AEFI reported in the field.

ii) To attend various meeting with the stakeholders for coordination purpose or whenever situation arises.

iii) Collecting all the AE/ SAE reported by the MAHs, various stakeholders, Immunization Division and IPC, which shall be reviewed by the PSUR Expert Committee constituted for this purpose for taking further regulatory action.

PMS/ PSUR being conditions for Market Authorization and Licensing and therefore to ensure the regulatory conformance and proper design of post-marketing studies, this division shall work with coordination of the licensing division. This division is responsible for collecting, compiling and collating the data received from the MAH as per the requirements of Fifth Schedule of New Drugs and Clinical Trials Rules 2019. The compiled PMS/ PSUR data will then be reviewed by the advisory committee constituted by the DCG (I). Based on the analysis of the PSUR Expert Committee, regulatory decision will be taken by CDSCO.

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 regulatory decision shall be taken in accordance with Drug & Cosmetics Act 1940 and Rules made thereunder. If marketing of the new drug is delayed by the applicant after obtaining approvalto market, such data will have to be provided on a deferred basis beginning from the time the new drug is marketed.

2.4.1 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 such data after assessment has to be part of PSUR. The source of reports received may be mentioned accordingly to avoid duplication.

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 a manufacturing license and/or Import registration and /or import license 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 serious & severe 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 HCPs or consumers to a MAH, regulatory authority that describes one or more adverse events 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/ vaccine 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 events. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs/vaccines. 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/vaccine.

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 online 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 HCPs 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/vaccine through a risk management program. Patients who fill a prescription for this drug/vaccine 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 shall be reported within 15 days to the Licensing Authority.

3.2 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 time 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. The MAH shall submit the PSUR report as per fifth schedule of New Drugs and Clinical Trial Rules 2019. A detailed description of PSURs is presented in chapter 4.3.

3.3 Post Marketing Trial (Phase-IV)

Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population. In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines. In such study, the study drug/vaccine may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug/ vaccine free of cost, to the satisfaction of the Central Licencing Authority and the Ethics Committee.

4. PHARMACOVIGILANCE CHAPTERS

4.1 Pharmacovigilance System Master File

4.1.1 Introduction

The Pharmacovigilance System Master File (PVMF) provides a description of the pharmacovigilance system used by the MAH with respect to vaccine products marketed by them. The PVMF is not a part of the marketing authorization dossier and is maintained independently by the MAH.

4.1.2 Scope

The scope of this chapter is to provide guidance to MAH to create and maintain the PVMF at their site. This describes the different documents to be created, updated, controlled, archived and traceable, whenever required.

4.1.3 Contents of the PVMF

The PVMF should contain all information related to MAH's PV system and cover the following sections:

4.1.3.1 Pharmacovigilance personnel and their responsibilities

A qualified and trained personnel should be authorized by the company management as Pharmacovigilance Officer In-charge (PVOIC) with responsibilities for dealing PV activities at MAH's organization. The PVOIC should be a medical or pharmacy professional trained in the collection and analysis of AE reports. The PVOIC shall be responsible for the following:

- Development of training programes and organizing training for staff of PV department;
- Identification of PV activities and framing of SOPs, revision of SOPs;
- Establishment and maintenance of QMS of PV department;
- The PVOIC should reside in India and respond to queries of regulatory authorities. The information related to the PVOIC provided in the PVMF should include:
  - Contact details (Name, Address, Phone, E-mail);
  - Summary, curriculum vitae with the key information on the role of the PVOIC;
  - A description of the responsibilities stating that the PVOIC has sufficient authority over the PV system in order to promote, maintain

and improve compliance;

- Person-in-charge to work in the absence of PVOIC.

4.1.3.2 Pharmacovigilance Organization Structure

4.1.3.2.1 Marketing Authorization Holder

The Pharmacovigilance system organogram at MAH site should be included in the PVMF. The authorized signatory should be clearly indicated. The description of PV system at MAH site should be provided in PVMF.

4.1.3.2.2 Contract Research Organization (CRO)

If, MAH assigns the responsibilities of PV activities of their vaccine products to any CRO, then the information of the company(ies) including their allied PV departments involved and the relationship(s) between Contract Research Organizations & operational units relevant to the fulfilment of PV obligations should be provided. It should include:

- ❖ The PV organizational structure of the CRO's showing the organogram of the PV department;
- ❖ Name & address of the organization, where the PV functions are undertaken such as collection of AEs, ICSRs processing, preparation & submission of PSURs, signal detection, Risk Management Plan (RMP), post-marketing surveillance and management of safety variations;
- ❖ Delegated activities (contracts and agreements as per Indian law);
- ❖ Service providing system (e.g., medical information, auditors, patient support programme providers, study data management etc.);
- ❖ Commercial arrangements (distributors, licensing partners, co-marketing etc.);
- ❖ Technical providers (hosting of computer systems and validation etc.)

4.1.3.3 Sources of safety data

The PVOIC will be responsible to collect data, reports, publications related to safety of all vaccine products marketed by the MAH. The main sources for safety data will be as follows:

- ❖ Medical information inquiries;
- ❖ "Contact us" emails, website inquiry forms and helpline etc.;

- Vaccine Product market complaints-Receipt, handling and disposal;
- MAH employees involved in PV activities;
- Spontaneous information from patient or their care givers and follow up of information;
- Published literature;
- Spontaneous reporting by HCPs including pharmaceutical sales representatives;
- Reports from internet, digital media or social media;
- Patient-support programmes;
- Reports from National Regulatory Authorities;
- Contract partners involved in PV activities;

4.1.3.4 Pharmacovigilance Processes

4.1.3.4.1 Description

A description and flow-diagram of the entire PV process, data handling, records control and archives of PV performance and covering the following aspects should be included in the PVMF:

- The procedures for ICSR collection, collation, processing, assessment, reporting and follow-up; should clarify the activities;
- Compilation of all ICSRs and preparation & submission of PSURs of new drugs in accordance with the New Drugs and Clinical Trials Rules, 2019 as amended from time to time;
- Review of ICSR, detection of signal (if any), Drug/ vaccine Safety Alerts, CAPA;
- Communication of Drug/ vaccine safety concerns to Consumers, HCPs and the National Regulatory Authorities;
- SmPCs and PILs with history of updates and revisions.

4.1.3.4.2 SOPs should include the following

- Description of the process, data handling and records of PV performance;
- ICSR collection, collation, follow-up, assessment and reporting;
- Risk Minimization Plan for safety concerns identified;
- Causality Assessment of reported AE/AEFI;
- PSUR scheduling, preparation and submission;
- Quality issue, recall or withdrawal of vaccine products;

- ❖ Training procedures, evaluations and documentations;
- ❖ Signal detection and evaluation process;
- ❖ Communication of safety concerns to consumers, HCPs and regulatory authorities;
- ❖ Implementation of safety variations in PILs/SmPCs;
- ❖ Safety data exchange agreements, if any;
- ❖ Safety data archival and retrieval;
- ❖ PV audit & inspections;
- ❖ Routine PV Internal Audit;
- ❖ Quality Control for PV activities;

4.1.3.4.3 Computerized systems and database

The location, functionality and operational responsibility for computerized systems and databases for receiving, collating and reporting safety information should be described in PVMF. Validation status of computer system functionality with change control, if any; nature of testing; back-up procedures should also be described. The MAH can have data collection in Excel spreadsheets to record and track the data.

4.1.3.4.4 QMS in Pharmacovigilance

The QMS should be established in PV activities, which should include:

- ❖ **Document and record control:** The MAHs should retain the soft copy back-up of all PV documents for indefinite time and hard copies for at least 10 years. The MAHs shall maintain an e-logbook for recording primary information received for every Adverse Events reported.
- ❖ **Trainings:** A summary of trainings records and files should be available at the PV site of MAH. Staff should be appropriately trained for performing PV related activities, including any individual, who may receive safety reports.
- ❖ **Auditing:** The QA of the company should supervise/facilitate the internal & external audits of PV system. The audit report must be documented within the quality system; with a brief description of the CAPA associated with the significant findings, the date it was identified and the anticipated resolution date(s) with cross reference to the audit report and the documented CAPA plan(s).

4.1.3.5 Pharmacovigilance System Performance

The key indicators for the performance of PV system e.g., number and quality of ICSRs, CAPA needs to be identified and measured for annual trend analysis.

They should contain evidence of the ongoing monitoring of the PV system performance including compliance of the main PV output. The PVMF should include a description of the monitoring methods applied and contain as a minimum the following:

- An explanation of how the correct reporting of ICSRs is assessed. In the annexure, figures/graphs should be provided to show the timelines of submission;
- A description of any metrics used to monitor the quality of submissions and performance of PV. This should include information provided by the regulatory authority regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timelines of PSUR reporting;
- An overview of the methods used to ensure the timelines of safety variation submissions compared to internal and competent authority deadlines including the tracking of required safety variations that have been identified but not yet submitted;
- Wherever applicable, an overview of adherence to RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to PV.

4.1.4 Annexures to the PVMF

- A list of biological products including the name of the vaccine product, active substance(s) and excipients with approvals;
- A list of contract agreements covering delegated activities including the vaccine products;
- A list of tasks delegated by the PVOIC for PV;
- A list of all completed audits (regulatory as well as internal) and a list of audit schedules.

4.2 Collection, Processing, Reporting of Individual Case Safety Reports by MAH

4.2.1 Introduction

This section highlights the general principles for Collection, Processing & Reporting of Individual Case Safety Reports associated with vaccine products for human use.

4.2.2 Structure & Processes

4.2.3 Collection and Collation of ICSR

The MAHs will collect the Adverse Events of their marketed vaccine from different sources. The AE data collection tool for ICSR reporting to CDSCO by MAH is annexed in appendix D (Annexure 1). The following sources/methods required to be established by MAHs to strengthen spontaneous reporting.

4.2.2.1 Medical inquiries

The MAHs should have a process in place to record all the medical inquiries related to their vaccine and documents including follow-up information or clarifications with a patient/consumer or HCPs. For inquiries that relate to safety of the vaccine, MAHs should ensure that there is a mechanism in place to transfer details of such cases to the PV point of contact.

4.2.2.2 “Contact us”, e-mails and website inquiry forms

The MAH should consider the mechanism(s) by which incoming information via "Contact us" on their MAH portal, through e mail addresses and website inquiry forms is monitored to allow theidentification and transfer of PV data to the designated PV person in an appropriate time frame to meet the regulatory requirement.

4.2.2.3 MAH’s employees

The employees of the MAH designated for the PV work, should be trained timely on the type of the information received and data collected from the various sources. These employees should be well versed in dealing with the information i.e., how to report particular Adverse Events? The data

captured manually by the medical representative during a discussion with HCP regarding an AE or other safety related issue should be retained and he/she should be aware of reporting the same to the PV personnel of the respected MAHs.

4.2.2.3.1 Contractual partners

There could be different types of contractual arrangements existing in the pharmaceutical industry like loan licensing, contract manufacturing, distribution etc. The responsibilities regarding PV activities among partners should be clearly defined in a drug/vaccine safety data exchange agreement. Contractual partners are a potential source of ICSR and mechanisms should be in place for the exchange of these ICSR in an appropriate manner & timeframe to meet regulatory requirements.

4.2.2.3.2 Information on Adverse Events from the internet or digital media

The MAHs should regularly screen relevant websites or digital media (including newspapers) or social media under their management or responsibility for potential reports of Adverse Events. The frequency of the screening should allow for potential valid ICSR to be reported to the competent authorities within the appropriate reporting timeframe based on the date of the information was posted on the website/digital media. MAHs may also consider utilizing their websites/portals to facilitate the collection of Adverse Events.

4.2.2.3.3 Solicited Reports

Solicited reports of suspected AE/AEFI are those derived from organized data collection systems, which include clinical trials, non- interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or HCPs, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected AE/AEFI obtained from any of these data collection systems should not be considered spontaneous.

4.2.2.3.4 Miscellaneous sources for reporting

The MAH should have other methods like e-mail, fax, online submission, mobile app, helpline, postal letters etc. to report Adverse Events. Patient identity should be kept confidential.

4.2.3 Literature Monitoring

The scientific and medical literature is a significant source of information for monitoring the safety and benefit-risk profile of vaccine products, particularly in relation to the detection of new safety signals or emerging safety issues. MAHs should perform monthly literature review of their vaccine products by using electronic literature data base (such as PubMed, Science Direct, Scopus etc.). Any AE identified by this process need to be processed as per spontaneous ICSR. The MAHs are advised to submit vaccine ICSR to CDSCO along with the complete literature reference including Digital Object Identifier (DOI) or copy of full-length article, wherever feasible.

4.2.4 Follow-up of ICSR

When initial ICSR is received, the information on Adverse Event may be incomplete. Thus, the ICSR should be followed up as necessary to obtain the required information for clinical evaluation of the ICSR.

For serious ICSRs, at least two follow-up attempts must be made and documented. For non-serious ICSRs, at least one follow-up attempt must be made and documented. While reporting to CDSCO, the MAH should clearly indicate that the reported ICSR is either initial or follow up.

4.2.5 Processing of ICSR

4.2.5.1 ICSR receipt

4.2.5.1.1 Date of receipt

The MAH should record the date of receipt for each Adverse Events; this applies to both initial notification and any follow-up communication.

4.2.6 Validation of reports

All reports of Adverse Events should be validated by authorized signatories of MAHs before reporting them to National Regulatory Authority i.e. CDSCO.

4.2.7 Reporting of ICSR

Only valid ICSR would qualify for reporting to National Regulatory Authority. Each valid ICSR should have the following minimum criteria for reporting: -

I. An identifiable patient (one or more identifier such as, patient initial, age, gender, weight);

II. An Adverse Event

III. A suspected Vaccine (along with manufacturer details and batch number, including brand name if any);

IV. An identifiable reporter (source);

The fields to describe the above four criteria are as follows: -

4.2.6.1 Identifiable patient should have the following information

- Patient Initials: Write first letters of name & surname e.g., Mukesh Kumar should be written as MK.
- Age or date of birth: Write either the date of birth (DD/MM/YYYY) or age of the patient at the time of an Adverse Event occurred.
- Gender: Male/Female/Transgender
- Weight: In case of adult (in Kg) and in case of infant use value upto two decimals.

Note: If any of this information is available, the ICSR will still be considered. Any one of the above can define the identifiable patient for case processing.

4.2.6.2 An Adverse Event

- Date of onset of adverse event (DD/MM/YYYY)
- Date of stop of adverse event
- Describe adverse event: Provide the description of the event in terms of nature, localization, etc.

4.2.6.3 A suspected pharmaceutical product/ Human Vaccine

The details of suspected vaccine(s) such as vaccine name (brand or generic), Batch No/Lot No., expiry date, marketing authorization holder/ manufacturer details, dose, route, frequency, dates of therapy started & stopped, and indication should be provided. Other details are as follows:

1. **De-challenge & Re-challenge:** Consideration of de-challenge and re-challenge differs for vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious AEFIs often prevent further vaccine administration; hence re-challenge information is only rarely available. De-challenge may not be applicable to vaccines, given their long-term immunological effects**.**

2. **Concomitant drugs/ vaccine:** The details like dose, route, and frequency of all concomitant drugs should be provided in the same manner as that of suspected drugs including self-medication, Over the Counter medication,herbal medications, etc. with therapy dates.

3. **Relevant tests/ laboratory data/ investigation:** Mention relevant laboratory tests /investigation data before & after Adverse Events.

4. **Other relevant history:** The relevant medical history of patient including pre-existing medical conditions (e.g., allergies, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction) and concurrent condition, if any.

5. **Seriousness of the event:** If, any adverse event is seriousin nature, tick the appropriate reason for seriousness as-

   - **Death:** If, the patient died, mention the cause and date of death.
   - **Life-threatening:** If, the patient was at substantial risk of dying at the time of Adverse Events.
   - **Hospitalization /prolongation of existing hospitalization:** If, Adverse Events caused hospitalization or increased the hospital stay of the patient.
   - **Disability:** If, Adverse Events resulted in a substantial disruption of a person's ability to conduct normal life functions.
   - **Congenital anomaly:** If, exposure of the drug/vaccine prior to conception or during pregnancy may have resulted in a birth defect.
   - **Other medically important condition:** When the event does not fitto above conditions, but the event may have put the patient at risk and required medical or surgical intervention to prevent any one of the above conditions.

6. **Outcomes:** Tick the outcome of the adverse event at the time of reporting as-

- **Recovered/resolved:** If, the patient recovered/resolved from the adverse event.
- **Not recovered/ not resolved:** If, the patient did not recover/resolve from the adverse event.
- **Recovering/ resolving:** If, the patient is recovering/resolving from the adverse event.
- **Fatal:** If, the patient died.
- **Recovered/resolved with sequelae:** If, the patient has completely recovered from the adverse event (mention the date of recovery) or recovered with sequelae (e.g., scar).
- **Unknown:** If, the outcome is not known.

4.2.6.4 An identifiable reporter (source)

- **Name & address:** A reporter must mention his/her name, address and contact details. The identity of the reporter will be maintained confidential.
- **Date of report:** Mention the date on which he/she reported the Adverse Events.
- **Reporter qualification:** Qualification of the reporter needs to be mentioned.

4.2.8 Coding of Adverse Event

For the purpose of ICSR reporting (expedited and periodic) to National Regulatory Authority, MAHs are required to code Adverse Events, Indication preferably using latest version of MedDRA.

4.2.9 Reporting time lines

All cases involving serious unexpected adverse reactions/ AEFIs must be reported to the licensing authority (CDSCO) within fifteen days of initial receipt of the information by the applicant (MAH) through email **pharma.covig@cdsco.nic.in**.

All individual case information with respect to AE/AEFI received from India and rest of the world are also to be reported by MAHs along with PSUR report in compliance to section 1. (5).(C)(v) (g) of Fifth Schedule of New Drug and Clinical Trials Rules, 2019 to National Regulatory Authority (CDSCO). PSURs shall be submitted through Online Sugam Portal as per CDSCO Circular vide File no.: PSUR-13011(14)/2/2024-eoffice dated 26.02.2024 and File no.: PSUR-11011(15)/1/2024-eoffice dated 25.06.2024 within prescribed time frame as per New Drug and Clinical Trials Rules, 2019.

Note: The adverse events due to lack of efficacy, medication error, off-label use etc. must also be reported by MAH to National Regulatory Authority.

4.3 Causality Assessment

The MAHs should preferably follow WHO Vaccine AEFI causality assessment scale/ AEFI Surveillance and Response Operational Guidelines 2024 for establishing a causal relationship between the suspected vaccine and Adverse Events by trained Pharmacovigilance Professionals as prescribed in G.S.R. 287 (E) dated 08.03.2016. For said scale, refer ANNEXURE-5.

4.3.5 Special Population

4.3.5.1 Use of a biological product during pregnancy or breast-feeding

Where during pregnancy, a woman has been exposed to any potential teratogenic medication/ vaccine, the follow up should be done till the delivery or child birth to assess the adverse outcome of maternal exposure. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the vaccine product was taken before conception.

Reports of exposure to biological products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationship between any reported Adverse Events and the

exposure to the suspected Human Vaccine.

Individual cases with an adverse outcome associated with a Human Vaccine following exposure during pregnancy are classified as serious reportsand should be reported:

- ❖ Reports of congenital anomalies or developmental delay in fetusor child;
- ❖ Reports of fetal death and spontaneous abortion;
- ❖ Reports of serious suspected adverse reactions/events in the neonate.

However, in certain circumstances, reports of pregnancy exposure with no suspected events may necessitate reporting. This may be a condition of the marketing authorization or stipulated in the risk management plan; for example, pregnancy exposure to Human Vaccine contraindicated in pregnancy or vaccine products with a special need for surveillance because of a high teratogenic potential. A signal of a possible teratogenic effect (e.g., through a cluster of similar abnormal outcomes) should be notified immediately to the National Regulatory Authority.

Note: AEs which occur in infants following exposure to a biological product from breast milk should also be reported.

4.3.5.2 Use of a biological product in pediatric or elderly population

The collection of safety information in pediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a HCPs, or consumer in order to be able to identify potential safety signals specific to a particular population.

4.3 Preparation and Submission of Periodic Safety Update Report

4.3.1. Introduction

The Periodic Safety Update Report is a document for evaluation of the benefit- risk profile of a vaccine products submitted by the MAH at defined time points as per Drugs and Cosmetics Act, 1940 and New Drugs & Clinical Trials Rules, 2019 there under during the post-marketing phase.

4.3.2. Objective

This chapter defines the recommended format, content and timelines of PSUR submission in conformity with New Drugs and Clinical Trials Rules-2019 of the Drugs and Cosmetics Act, 1940. PSURs are intended to be submitted to national regulatory authority i.e. CDSCO in order to monitor the safety and efficacy of vaccine products marketed in India.

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of new or emerging information on the risks and benefits of the vaccine products in approved indications. The PSUR, is therefore, a tool for post-marketing evaluation at defined time points in the life cycle of a vaccine product.

4.3.3. Post marketing assessment of New Drugs

(1) When a new drug is approved for marketing, assessment of safety and efficacy of the drug/vaccine are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

(2) In actual clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, concomitant drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed. Therefore, subsequent to approval of a new drug, the new drug shall be closely monitored and post marketing assessment of its benefit-risk profile shall be carried out.

(3) A person intending to import or manufacture any new drug for sale or distribution shall have a pharmacovigilance system in place for collecting, processing and forwarding the adverse event report to the Central Licensing Authority emerging from the use of the new drug imported or manufactured or marketed by the applicant in the country.

(4) The pharmacovigilance 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 event reports.

(5) Post marketing assessment of new drug may be carried out in different ways as under: -

(A) Phase IV (Post marketing) trial- Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety and efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population. In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines. In such study, the study drug/ vaccine may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the new drug free of cost, to the satisfaction of the Central Licensing Authority and the ethics committee.

(B) Post marketing surveillance study or observational or non-interventional study for active surveillance- Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licensing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package

insert. In such studies, the study drugs/ vaccine is the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable in such cases as drugs/ vaccines are already approved for marketing.

(C) Post marketing surveillance through periodic safety update reports- As part of post marketing surveillance of new drug the applicant shall furnish PSURs in accordance with the procedures as follows;

i. The applicant shall furnish PSURs in order to-

a) report all relevant new information from appropriate sources;

b) relate the 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 shall be made to product information in order to optimize the use of product.

ii. Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one periodic safety update reports. Within the single periodic safety update reports separate presentations of data for different dosage forms, indications or separate population need to be given.

iii. All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The periodic safety update reports shall be submitted every six months for the first two years after approval of the new drug is granted to the applicant. For subsequent two years — the periodic safety update reports need to be submitted annually. Central Licensing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty 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 fifteen 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. **Vaccines and Biologicals are always considered as New Drug, unless specified, otherwise, by the Licensing Authority.**

iv. New studies specifically planned or conducted to examine a safety issue should be described in the periodic safety update reports.

v. A PSUR should be structured as follows:

(1) Title Page: The title page of periodic safety update reports should capture the name of the vaccine; reporting interval; permitted indication of such vaccine; date of permission of the vaccine; date of marketing of vaccine; licensee name and address.

(2) Introduction: This section of periodic safety update reports should capture the reporting interval; vaccine intended use, mode of action, therapeutic class, dose, route of administration, formulation and a brief description of the approved indication and population.

(3) Current worldwide marketing authorization status: This section of periodic safety update reports should capture the brief narrative over view including details of countries where the vaccine 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.

(4) Actions taken in reporting interval for safety reasons: This section of periodic safety update reports 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 licence holder, sponsor of a clinical trial, regulatory authorities, data monitoring committees, or ethics committees.

(5) Changes to Reference Safety Information (RSI): This section should include any significant changes in reference safety information within the reporting interval. Such changes include information relating to contraindications, warnings, precautions, adverse events, and important findings from ongoing and completed clinical trials and significant non-clinical findings, if any.

Note: Even if there is no significant change in RSI (Prescribing Information Leaflet & Company Core Data Sheet/Summary of Product Characteristics), MAHs should submit recent dated approved RSI.

(6) Estimated patient exposure: This section of periodic safety update reports should provide the estimates of the size and nature of the population exposed to the vaccine. Brief descriptions of the methods used to estimate the subject or patient exposure should be provided,

6.1. Cumulative subject exposure in clinical trial

This section of the PSUR should include the following information in tabular format as referred below:

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational vaccine product, placebo, and/or active comparator(s) since the date of first approval for conducting an interventional clinical trial in any country (Refer Appendix-B, Table 01).
- More detailed cumulative subject exposure in clinical trials should be presented, if available (e.g. sub- grouped by age, sex, and racial/ethnic group) important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered (Refer Appendix-B, Table No. 02 & 03);
- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.

- If, clinical trials have been or are being performed in special population (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate.
- When, there are substantial differences in the time of exposure between subjects randomized to the investigational vaccine product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or - years).
- New drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of AE/AEFI, particularly, when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- If, the SAEs from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- For individual trials of particular importance, demographic characteristics should be provided separately, if available.

6.2 Cumulative and interval patient exposure from marketing experience from India

Interval patient exposure refers as the patient exposure occurring between two data lock points of PSUR. Separate estimations should be provided for interval exposure and, when possible, cumulative exposure (since the date of marketing authorization) from India. (Refer Appendix- B, Table No. 04 and 05). The estimated number of patients exposed should be provided, when possible, along with the method(s) used to determine the same. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. If applicable, data of special population and vulnerable population should be identified

and submitted. The data should be presented according to the following categories:

6.2.1 Post-approval exposure

An overall estimation of patient exposure should be provided. In addition, the data should be presented by indication, sex, age, dose, formulation, and region, wherever applicable. Depending upon the product, other relevant variables, such as vaccinations, etc. should be described. Whenever, there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible. Some industries may be running some programmes for ensuring patient safety such as patient support programme, if in this programme, any safety concern or serious AE/AEFI is observed, it should also be communicated to CDSCO.

6.2.2 Post-approval use in special population

Where the approved vaccine has been used in special population, the cumulative estimated patient exposure should be provided with method of calculation.

Sources of such data may include non-interventional studies designed to obtainthis information, such as registries.

The following are the examples of special population:

- Pediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;
- Patients with other relevant co-morbidity;
- Patients with disease severity different from that studied in clinical trials;
- Sub-population carrying relevant genetic polymorphism(s);
- Patients of different racial and/or ethnic origin;
- Any other vulnerable population.

6.2.3 Other post-approval use

If the MAH becomes aware of any specific pattern of use of a vaccine product, which may be relevant for assessment of product safety, a brief description should be provided. Examples of such patterns of use are new drug abuse, misuse (such as use of antibiotics in viral infection) and use beyond that recommended in the reference product information.

6.3 Cumulative and interval estimated patient exposure from marketing experience from rest of the world

The estimations should be provided separately for interval exposure(since the data lock points of the previous PSUR) and, when possible, cumulative exposure from the date of approval in the rest of the world. (Refer Appendix-B, Table 06 and 07). The data should be presented as mentioned in the section 6.2.

7. Presentation of individual case histories

This section of Periodic Safety Update Reports should include the individual case information available to a license holder and provide brief case narrative, medical history, indication treated with suspect drug, causality assessment. Provide following information:

7.1 Reference prescribing information

In this section, updated reference prescribing information of a new drug should be provided by the MAH.

7.2 Individual cases received from India

The CIOMS & Line-listing of ICSRs should contain the information such as: age, gender, seriousness criteria, AE/AEFI start/stop date, therapy start/stop date of suspected/concomitant drug/vaccine, dose, route of administration, and indication of suspected/concomitant drug/vaccine, relevant past medical history, outcome & causality assessment in tabulated form as annexed in Appendix D (Annexure 1& 2).

7.3 Individual cases received from rest of the world

In this section Individual cases received from rest of the world should be provided by the MAH same as above 7.2.

7.4 Cumulative and interval summary tabulations of Serious Adverse Events from clinical investigations

This section of the PSUR should provide a brief narration of the serious adverse events as mentioned in the Appendix B that provides a cumulative summary tabulation of SAE reported in the MAHs, clinical trials, from the first authorization to conduct a clinical trial in any country worldwide to the data lock point of the current PSUR. The MAHs should explain any omission of data (e.g., clinical trial data might not be available for vaccine products marketed for many years). The tabulation(s) should be organized by SOC, for the new drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables.

This section should not serve to provide analyses or conclusions based on the SAEs.

- Appendix B, Table 8 provides cumulative tabulations of SAEs from clinical trials.
- While tabulating SAEs from clinical trials only those criteria should be used which are defined in NDCT Rules, 2019. This should not include non- serious adverse events.
- The causality assessment, where has been done should also be mentioned as related and not-related.
- While coding SAE (Table 8) and AE/AEFI (TAB), Preferred Term (PT) and System Organ Class (SOC) should be used.

7.5 Cumulative and interval summary tabulations from post marketing data sources

This section of the PSUR should provide background for the Appendix that provides cumulative and interval summary tabulations of AE/AEFI

from the date of marketing authorization to the data lock point of the current PSUR. The tabulation should include:

- ❖ Serious and non-serious AE/AEFI from spontaneous ICSR, including reports from HCPs, consumers, scientific literature, and regulatory authorities
- ❖ Serious adverse events from non-interventional studies
- ❖ Solicited reports of serious AE/AEFIs

For special issues or concerns, additional tabulations of adverse events can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the data presented (Refer Appendix-B, Table 09).

8. Studies

This section of periodic safety update reports should capture the brief summary of clinically important emerging efficacy or effectiveness and safety findings obtained from the licence holder, 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

8.1 Completed clinical study

A brief summary of clinically important safety and efficacy findings obtained from completed trial during the reporting interval should be provided. This information can be presented in a narrative format or as a synopsis (Refer ICH- E3). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

8.1.1 Ongoing clinical study

If the manufacturer and/or importer is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unbinding of subjects with Adverse Events), this sub- section should briefly summarize the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

8.1.2 Long-term follow-up

Wherever applicable, this sub-section should provide information from long-term follow-up of subjects from clinical trials of new drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products, tissue engineering and biotech products). These are referred as Advanced Therapy Medicinal Products (ATMPs).

8.1.3 Other therapeutic uses of biological product

This should include clinically important safety information from other programmes, if and when conducted by the manufacturer and/or importer that follow a specific protocol (e.g., expanded access programmes, compassionate use programmes, particular patient uses and other organized data collection).

8.2 Findings from non-interventional Studies

This section should summarize relevant safety information or information with potential impact on the benefit or risk evaluations, from MAH - sponsored non-interventional studies that became available during the reporting interval (e.g., observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from new drug utilization studies, when applicable to multiple regions.

8.3 Information from other clinical trial sources

8.3.1 Other clinical trials

This sub-section should summarize information accessible with reasonable effort from any other clinical trial/study sources to the MAH during the reporting interval (e.g. including results from pooled analyses or meta-analyses of randomized clinical trials, and safety information provided by co-development partners or from investigator-initiated trials).

8.3.2 Medication errors

This sub-section should summarize relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. This information may be received by the manufacturer and/or importer via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

8.4 Findings from non-Clinical Studies

This section should summarize major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval.

8.5 Findings from literature

This section should summarize new and significant safety findings, either published in the scientific literature, Alerts published by USFDA/EMEA or other regulatory agencies, relevant to the approved vaccine product that the manufacturer and/or importer became aware of during the reporting interval.

Literature searches for PSUR should be as wide as possible and should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.

This should include:

Pregnancy outcomes (including termination) with or without adverse outcomes

- Use in pediatric populations
- Compassionate supply, named patient use

- ❖ Lack of efficacy
- ❖ Asymptomatic overdose, abuse or misuse
- ❖ Medication error where no adverse events occurred Important non-clinical safety findings

9. Other Information

This section of PSURs should include the details about signal and Risk Management Plan in place by licence holder (if any).

(a) Signal and risk evaluation: In this section, licence holder will provide the details of signal and risk identified during the reporting period and evaluation of signals identified during the reporting period.

(b) Risk management plan: In this section, licence holder willprovide the brief details of safety concern and necessary action taken by him to mitigate these safety concerns.

9.1 Lack of efficacy in controlled clinical trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy (ies), for vaccine products intended to treat or prevent serious or life-threatening illnesses could reflect a significant risk to the treated population and should be summarized in this section.

9.2 Late-breaking information

This section should summarize information on potentially important safety and efficacy/effectiveness findings that arise within 15 days after the data lock point of the PSUR in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the manufacturer and/or importer, a data monitoring committee, or a regulatory authority has taken for the safety reasons.

Any significant change proposed to the reference product information which has occurred after the data lock point of the report, but before submission should also be included in this section, where feasible. Such changes could include a new contraindication, warning/precaution, or new AE/AEFI.

9.3 Overview of signals: new, ongoing, or closed

- A new signal is a signal that the MAH became aware of during the reporting interval. A new clinically important information on a previously closed signal that became available during the reporting period of the PSUR (i.e., a new aspect of a previously refuted signal or recognized risk likely to warrant further action to verify) would also constitute a new signal. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PSUR. Examples would include new information on a previously:
- Closed and refuted signal, which would result in the signal being re-opened; Identified risk which is indicative of a clinically significant difference in the severity of the risk, e.g., transient increase in liver enzymes are identified risks and new information is received indicative of a more severe outcome such as hepatic failure; neutropenia is an identified risk and a well-documented and unconfined case report of agranulocytosis is received;
- Identified risk for which a higher frequency of the risk is newly found, e.g.,in a sub population; and
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimization activities.

Refer Appendix-C, include a tabular listing of all signals ongoing or closed at the data lock points of the PSUR.

When a regulatory authority has requested that a specific safety concern (not considered a signal) be monitored and reported in a PSUR, the MAH should summarize the result of the analysis of such safety concern in this section even if it is negative.

10. Overall Safety Evaluation

10.1 Benefit Evaluation

This section of PSURs should capturethe overall safety evaluation of the drug/ Vaccine based upon its risk benefit evaluation for approved indication.

The purpose of this section is to provide:

- ❖ Important identified risks;
- ❖ Important potential risks;
- ❖ Important missing information.
- ❖ In case a signal was indicated in previous interval report and now has been refuted because of new evidences which resulted in closure, should be specifically mentioned here.
- ❖ An evaluation of new information with respect to previously recognized identified and potential risks
- ❖ An updated characterization of important potential and identified risks, where applicable and
- ❖ A summary of the effectiveness of risk minimization activities (if any) in any country or region, which may have utility in other countries or regions.

These evaluations of subsections should not summarize or repeat information presented in previous sections of the PSUR, but should instead provide an interpretation of the information, with a view towards characterizing the profile of those risks assessed as important.

10.2.1 Important baseline efficacy/effectiveness information

This section summarizes information on the efficacy/effectiveness of the vaccine product as of the beginning of the reporting interval, and provides the basis for the benefit evaluation. This information should relate to the approved indication(s) of the vaccine product listed in the reference product information

For vaccine products with multiple indications, population, and/or routes of administration, the benefit should be characterized separately by these factors, wherever relevant. The level of detail provided in this section should be sufficient to support the characterization of benefit in PSUR and the benefit-risk assessment.

10.2.2 Newly identified information on efficacy/ effectiveness

Wherever necessary, for some product's new information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section.

New information about efficacy/effectiveness in uses other than the approved indication(s) (off-label use) should not be included, unless relevant for the benefit-risk evaluation in the approved indication.

Information on additional indications approved during the reporting interval should also be included in this section. New information on efficacy /effectiveness might also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines, emergence of resistance to anti- infective agents.

10.2.3 Characterization of benefits

This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications. When there are no new relevant benefit data, this sub-section should provide a characterization of the information in sub-section "Important baseline efficacy and effectiveness information".

When there is a clear information about the benefit and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this sub-section should be provided. This sub-section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, as follows:

- A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across clinical trials/studies
- New information that challenge the validity of a surrogate endpoint, if used
- Clinical relevance of the effect size
- Generalizability of treatment response across the indicated patient population, e.g., information that demonstrates lack of treatment effect in a sub-population
- Adequacy of characterization of dose-response

- ❖ Duration of effect
- ❖ Comparative efficacy

A determination of the extent to which efficacy findings from clinical trials are generalizable to patient populations treated in medical practice.

10.2.4 Benefit risk analysis evaluation

This section should provide an integration and critical analysis of the key information. This section also provides the benefit-risk analysis, and should not simply duplicate the benefit and risk characterization presented in subsections mentioned above.

10.2.5 Benefit-Risk context- medical need and important alternatives

This sub-section should provide a brief description of the medical need for the vaccine product in the approved indications, and summarize alternatives (medical, surgical, or other; including no treatment).

10.2.6 Benefit-Risk analysis evaluation

A benefit-risk balance is specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible. The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should consider the following points:

- ❖ Whereas previous sections included all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections shouldbe carried forward for integrationin the benefit-risk evaluation.
- ❖ Consider the context of use of the vaccine product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated.

- ❖ With respect to key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non- responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all.
- ❖ With respect to risk, consider its clinical importance, e.g., nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.
- ❖ The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be described.
- ❖ Provide a clear explanation of the methodology and reasoning used for benefit-risk evaluation:
- ❖ The assumptions, considerations, and judgement or weighing that support the conclusions of the benefit-risk evaluation, should be clear.
- ❖ If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
- ❖ Economic considerations (e.g., cost-effectiveness) should not be included in the benefit-risk evaluation.

Note: When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-risk analysis is warranted.

Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

11. Conclusion

This section of PSURs should provide the details on the safety profile of drug(s)/ Vaccine(s) and necessary action taken by the license holder in this regard.

Based on the evaluation of the cumulative safety data, and the benefit-risk analysis, the manufacturer and/or importer should assess the need for further

changes to the reference product information and propose changes as appropriate. In addition, and as applicable, the conclusion should include preliminary proposal(s) to optimize or further evaluate the benefit-risk balance, for further discussion with the national regulatory authority. This may include proposals for additional risk minimization activities. These proposals should also be considered for incorporation into the Risk Management Plan.

12. Appendix

The appendix includes the copy of marketing authorization in India, copyof prescribing information, RMP, adverse events Line listings in standard format (India & Global), CIOMS forms with narrative of Individual Case Safety Report.

4.4. Quality Management System at MAH Site

4.4.1. Introduction

This Chapter contains guidance for the MAHs for the establishment, maintenance, performance, performance and quality assurance of PV system.

4.4.2. Scope

This guidance document is applicable to all MAHs who hold marketing authorization for manufacture or import of vaccine products in Indian market.

4.4.3. Structures and Processes

4.4.3.1 Pharmacovigilance system

All MAH should have the PV system which should comply with the quality management system including requirements of NDCT Rules 2019, revised Schedule M of the Drugs & Cosmetics Act, 1940, and Rules made thereunder.

The PV system at MAH should have an organogram describing PV personnel's roles and responsibilities, procedures, processes and resources, including management of resources, compliance and records.

4.4.3.2 Quality Management System (QMS) of PV

The QMS in PV is a framework of policies, procedures and system necessary to ensure quality related to detection, assessment, understanding, evaluation and prevention of adverse events on vaccine products.

The quality management system is based on the following activities:

- **Quality planning:** Establishing structures of PV system, planning, effective integration and consistent processes for safety;
- **Quality adherence:** Carrying out tasks and responsibilities in accordance with quality requirements such as collection of ICSRs, completeness of report, case narrative, data management, causality

assessment, signal management, etc.;

- **Quality control and assurance:** By monitoring the parameters described under quality adherence;
- **Quality improvements:** Taking Corrective and Preventive measures, as and when required, to ensure patient safety.

4.4.3.3 Requirements and Responsibilities of QMS at MAH site

MAH should have a sufficient number of competent and appropriately qualified, and trained personnel for the performance of PV activities.

In case, where MAH has completely outsourced the PV activities, through a valid contract, the outsourced agency/institution should comply with the above statement. It should be notified to CDSCO with authorized legal documents.

The responsibility of adhering to PV QMS will ultimately lie with MAH.

The managerial staff in the organization should be responsible for compliance of PV Guidance Document for MAH's Vaccine Products.

4.4.3.4 Training of MAH personnel for PV

The personnel involved in PV activities should receive induction (within one month of joining and continued trainings with proper evaluation of performance, thereafter. The organization should maintain the training plans and records of trainings. The organization should keep identifying the continued training needs.

4.4.3.5 Facilities and equipment for PV

Achieving the required quality for the conduct of PV processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, Information Technology (IT) systems and storage space (electronic). They should be located, identified, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for PV System. Facilities and equipment which are critical for the conduct of PV should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.

4.4.4. Specific quality system procedures and processes

4.4.4.1. Compliance management by MAH

For the purpose of compliance, MAHs should have specific quality system procedures and processes in place in order to ensure the following:

- Continuous monitoring of PV data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the MAH.
- Scientific evaluation of all information on the risks of vaccine products in regards to patients or public health, in particular to their adverse events in human beings arising from use of the product within or outside the terms of its marketing authorization or associated with occupational exposure
- Submission of accurate and verifiable data on all AEFIs to the regulatory authority within the legally required time-limits
- Quality, integrity and completeness of the information submitted on the risks of vaccine products, including processes to avoid duplicate submissions and to validate signals
- Effective communication with regulatory authority, including communication on new or changed risks, the PVMF, risk management systems, PSURs and CAPAs.

4.4.4.2. Record management

The MAH shall record all PV information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information. As part of a record management system, specific measures should, therefore be taken at each stage in the storage and processing of PV data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorized personnel respecting the medical and administrative confidentiality of the data. The electronic copies of the PV records should be stored indefinitely. It is expected that the MAHs should retain the soft copy back-up of all PV documents for indefinite time and hard copies for at least 10 years. The MAHs shall maintain an e-logbook for recording primary information received for every Adverse Events reported.

4.4.4.3. Documentation of the quality system

All elements, requirements and provisions adopted for the quality system should be documented in a systematic and orderly manner in the form of written policies and procedures. For the requirements of documenting the quality system.

4.4.4.4. Critical PV processes

The following PV processes should be considered as critical:

- Benefit-risk evaluation;
- Establishing, assessing & implementing risk management systems and evaluating the effectiveness of risk minimization;
- Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of ICSRs from any source;
- Signal management;
- Scheduling, preparation (including data evaluation and quality control), submission and assessment of PSURs;
- Interaction between the PV and product quality defect systems;
- Communication about safety concerns between MAHs and licensing authority in particular notifying changes to the benefit-risk balance of vaccine products;
- Communicating information to patients and HCPs about changes to the benefit-risk balance of vaccine products for the aim of safe and effective use of vaccine products;
- Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the regulatory authority;
- Implementation of variations to marketing authorizations for safety reasons according to the urgency required;
- Provisions for events that could severely impact on the organization's staff and infrastructure in general or on the structures and processes for PV in particular; and

- ❖ Back-up systems for urgent exchange of information within an organization, amongst organizations sharing PV tasks as well as between MAHs and competent authorities.

4.4.4.5. Monitoring the effectiveness of QMS in PV

The QMS in PV should be continuously monitored for its effectiveness by the MAH through the following processes:

- ❖ System reviews by those responsible for management
- ❖ Audits
- ❖ Compliance monitoring
- ❖ Inspections
- ❖ Evaluating the effectiveness of actions taken with biological products for the purpose of minimizing risks and supporting their safe and effective use in patients.

The organization may use performance indicators to continuously monitor the good performance of PV activities in relation to the quality requirements. The requirements for the quality system itself are laid out in this Chapter and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system at regular intervals with the frequency and the extent of the reviews to be determined in a risk-based manner.

Reviews of the quality system should include the review of SOPs and work instructions, deviations from the established quality system, audits and inspections reports as well as the use of the indicators referred to above.

4.4.4.6. Responsibilities of the MAH in relation to the PVOIC for PV

The pharmacovigilance 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 AEFI/AE reports.

A qualified and trained personnel should be authorized by the company management as Pharmacovigilance Officer In-charge (PVOIC) with responsibilities for dealing PV activities at MAH's organization. The PVOIC should be a medical or pharmacy professional trained in the collection and analysis of

AE reports. The PVOIC shall be responsible for the following:

- ❖ Development of training modules and organizing training for staff of PV department;
- ❖ Identification of PV activities and framing of SOPs, revision of SOPs;
- ❖ Establishment and maintenance of QMS of PV department;

The PVOIC should reside in India and respond to queries of regulatory authorities including PvPI, IPC whenever required. The information related to the PVOIC provided in the PVMF should include:

- ❖ Contact details (Name, address, phone, e-mail);
- ❖ Summary, curriculum vitae with the key information on the role of the PVOIC;
- ❖ A description of the responsibilities guaranteeing that the PVOIC has sufficient authority over the PV system in order to promote, maintain and improve compliance;
- ❖ Details of Person-in-charge to work in the absence of PVOIC;

4.5. Audit & Inspection of Pharmacovigilance System at MAH Site

4.5.1. Introduction

This chapter provides insights into planning, conducting, reporting and follow-up of PV inspections by regulatory authorities/officials responsible for inspection.

4.5.2. Objectives

The objectives of PV audits and inspections are as below:

- To verify by examination and evidence, the appropriateness of the implementation and operation of the PV system including its quality systems.
- To assess and establish that the MAH has qualified personnel, robust system and facilities to conduct PV activities
- To identify, record and address non-compliance, which may pose a riskto public health
- To take regulatory action, wherever considered necessary based on the result of the inspections/audits.

The results of an inspection will be provided to the inspected MAH, who will be given the opportunity to comment on any non-compliance identified. Any non-compliance should also be rectified by the MAH within stipulated time period through the implementation of CAPA plan.

4.5.3. Inspection Types

The Inspections of PV can be routine or targeted to MAHs suspected of being non-compliant.

4.5.3.1. Routine inspection

These are planned and informed inspection of the PV system of MAH. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet the regulatory PV obligations for the marketed vaccine products in India.

4.5.3.2. Targeted inspections

These inspections are conducted as and when there is trigger and the regulatory authority determines that inspection is the only way. Triggering factors for such type of inspections are as below (**but not limited to**):

- ❖ Continuous delays or omission and poor-quality reporting of ICSRs/PSURs/RMPs.
- ❖ Failure to provide the asked information or data within the deadline specified by regulatory authority.
- ❖ Delays or failure to carry out specific obligations related to the monitoring of vaccine product safety, identified at the time of the marketing authorization.
- ❖ Delays in the implementation or inappropriate implementation of CAPAs.
- ❖ Sudden vaccine product withdrawal and recall.
- ❖ Any major changes in PV system.
- ❖ Any emerging safety issue relating to any drug/ vaccine product held by the MAH.

4.5.4. Inspection Procedure

4.5.4.1. Inspection Planning

PV inspection should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. Arisk-based approach to inspection planning will enable the frequency and scope of inspections to be carried out.

The PV inspection team will comprise CDSCO Officials and representative from PvPI & other experts if required.

The inspection will be planned based on the following:

- ❖ Compliance history identified during previous PV inspections, if any.
- ❖ Re-inspection date recommended by the inspectors as a result of

compliance of previous inspection submitted by MAH,

- ❖ MAH with sub-contracted/ outsourced/ Third Party PV activities (qualified person responsible for PV functions in India, reporting of safety data, etc.) and multiple firms employed to perform PV activities;
- ❖ Changes to the PV safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- ❖ Changes in contractual arrangements with PV service providers or the organizations at which PV is conducted;
- ❖ Delegation or transfer of PVMF management.

4.5.4.2. Organization to be inspected

Any party carrying out PV activities in whole or in part, on behalf of, or in conjunction with the MAH may be inspected, in order to confirm their capability to support the MAH's compliance with PV obligations.

4.5.6. Regulatory Actions:

In the event of non-compliance, the regulatory authority shall take the necessary measures to ensure that a MAH is in compliance with NDCTR-19 of D&C Act 1940 and Rules made thereunder.

4.6. Submission of Risk Management Plan

4.6.1. Introduction

At the time of marketing authorization, information on the safety of a biological product is relatively limited as the clinical studies are carried out in relatively small number of subjects, restricted population in terms of age, gender, ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up.

A biological product is authorized on the basis that at the time of authorization, the benefit-risk balance is positive. The product may have multiple risks of varying degree associated with it and individual risks will vary from product to product. All actual or potential risks might not have been identified at the time of initial authorization. Many risks will only be discovered and characterized during post- marketing phase.

The aim of Risk Management Plan (RMP) is to document the risk management system considered necessary to identify, characterize and minimize a vaccine product's important risks. The Risk Minimization strategy involves continuous monitoring of efficacy and safety profile-Risk Identification, Risk Assessment, Risk Characterization, Risk Communication and Risk Mitigation.

4.6.2 Objective

- Identification and characterization of risk to update the safety profile of the vaccine product(s);
- Indicate how to characterize further the safety profile of the vaccine product(s);
- Document measures to prevent or minimize the risks associated with a vaccine product, including an assessment of the effectiveness of interventions;
- Document post-marketing obligations that have been imposed as a condition of the marketing authorization;
- Document any change in the risk profile of a vaccine product(s) after marketing authorization.

The RMP document is a dynamic, stand-alone document which should be updated throughout the life-cycle of vaccine products.

The License holder will provide the details of safety concern and necessary actions taken by him to mitigate any safety concern in the applications of PSUR.

4.6.3. Description of RMP

4.6.3.1. Vaccine product overview

The MAH should provide an overview of a vaccine product including:

- Active Pharmaceutical Ingredient(s) information, name of MAH, date and country of first launch/authorization worldwide (if applicable), chemical class, indication (s), mechanism of action, route of administration, pharmaceutical form and strength.
- Information on the excipients used in the formulation of a vaccine product should be provided.
- Administrative information on the RMP such as data lock point, date submitted and version number of all parts of RMP.

4.6.3.2. Safety specifications

The MAH should provide a synopsis of the safety profile of a vaccine product(s) and should include, what is known and unknown about the vaccine product(s) safety. The safety specification consists of following subsections:

4.6.3.2 Epidemiology, indication (s) and target population(s)

This section should include incidence, prevalence, mortality and relevant co- morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin.

4.6.3.2.2. Non-clinical part of the safety specifications

This section should present a summary of important non-clinical safety findings like toxicity related information, interactions etc.

4.6.3.2.3. Clinical trial exposure

This section includes the data on the patients studied in clinical trials. This should be stratified for relevant categories (age, gender, indication, ethnicity, exposure to special population-pediatric, geriatric etc.) and also by the type of clinical trial.

4.6.3.2.4. Populations not studied in clinical trials

This section describes, which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population. Limitations of the clinical trials should also be presented in terms of the relevance of exclusion criteria such as pediatric population, geriatrics population, pregnant/lactating women, hepatic /renal impairment patients etc.

4.6.3.2.5. Post-marketing experience

This section should provide information on the number of patients exposed during post-marketing phase; how the vaccine product has been used in clinical practice, labelled and off-label use including use in the special populations mentioned above? This should also include any action taken by any regulatory authority/MAH for safety reason.

4.6.3.2.6. Identified and potential risks

This section provides information on the important identified and potential risks associated with the use of a vaccine product and potential AE/AEFI associated with other vaccine and pharmaceutical products, foods, other substances, and the important pharmacological class effects.

The risk data should include frequency, public health impact, risk factors, preventability, potential mechanism, evidence source/strength.

4.6.3.2.7. Summary of the safety concerns

At the end of the RMP document, summary of the "Safety concerns/measures" of vaccine products should be provided.

4.6.3.3. PV activities

MAH should list the various PV activities involved to identify a new safety concern or further characterize known safety concerns or investigation of potential safety concerns, whether it is real or not and how missing information will be sought? PV activities can be divided into routine PV activities and additional PV activities. For each safety concern, the MAH should list their planned PV activities for that concern. PV plans should be proportionate to the risks of the product. If routine PV is considered sufficient for post-marketing safety monitoring, without the need for additional actions (e.g. safety studies) "routine PV" should be carried out against the safety concern.

4.6.4 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 Management Action Plan (MAP) could improve the product's benefit-risk balance. The characteristics to be weighedmight include the

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

4.6.5 Preventability of adverse effects

Serious adverse effects that can be minimized or avoided by preventive measures around drug/ vaccine 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:

- ❖ Targeted education and outreach: targeted education and outreach to communicate risks and appropriate safety behaviors to healthcare practitioners or patients.
- ❖ Reminder systems: processes or forms to foster reduced-risk prescribing and use, and
- ❖ Performance-linked access systems: that guide prescribing, dispensing, and use of the product to target the population and conditions of use most likely to confer benefits and to minimize particular risks.

4.6.6 Targeted education and outreach

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

(a) When routine risk minimization is known or likely to be insufficient to minimize product risks or

(b) 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:

i. Patient education that includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are sometimes called consent forms.
ii. HCPs training programs that include testing or some other documentation of physicians' knowledge and understanding.
iii. Enrolment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.
iv. Limited number of doses in any single prescription or limitationson refills of the product.
v. Specialized product packaging to enhance safe use of the product.

vi. Specialized systems or records that are used to attest that safety measures have been satisfied (e.g. Prescription stickers, physician attestation of capabilities).

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

4.6.8 Selecting and Developing the Best Tools:

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 burden some 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.

4.6.9 Risk minimization activities

The MAH should have the approved & updated Package inserts, Product labelling, Product Information Leaflet (PIL), pack size, risk minimization activities. The MAH should also consider when appropriate to have additional Risk minimization activities like educational material, communication letter to HCPs etc.

For each safety concern, the following information should be provided:

- Objectives of the risk minimization activities;
- Routine risk minimization activities;
- Additional risk minimization activities (if any), individual objectives and justification,
- How the effectiveness of each (or all) risk minimization activities will be evaluated in terms of attainment of their stated objectives?
- What the target is for risk minimization? i.e. what are the criteria for judging success?
- Milestones for evaluation and reporting.

5. PROCEDURES FOR IMPLEMENTING AN EFFECTIVE PHARMACOVIGILANCE SYSTEM

(a) Obligations for MAH:

In accordance with the Govt. Gazette Notification No. GSR 227 (E) dated March, 19th March 2019, 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 AE/AEFI.

Hence, the MAHs 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 MAHs should appoint as per the norms laid down in Fifth Schedule of New Drugs and Clinical Trials Rules 2019 under Drugs & Cosmetics Act 1940 a qualified and trained personnel with duly given responsibilities for continuously monitoring of the vaccine products at his disposal

(b) AEFI Case Reporting:

Documented standard procedure should compile but not be limited to the following:

I. Provisions for timely and thorough review to determine whether the complaint represents an AE/AEFI;
II. Personnel responsible to receive the incoming correspondence (phone calls, letter, email, etc.) relating to potential AE/AEFI through product complaints;
III. How an unique identifier is assigned to each case; and
IV. Clear and defined processes on AE/AEFI complaint, evaluation and follow-up.

c) Manufacturers and importers should have in place systems and procedures for the receipt, handling, evaluation and reporting of AE/AEFIs that are adequate to effectively sustain AEs/AEFI reporting. All cases involving serious unexpected adverse reactions must be reported to the licencing authority within fifteen 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.

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.

d) MAHs should have in place adequate procedures for AE/AEFI receipt, handling, evaluation and reporting and should include but not be limited tothe following.

- **i.** Requirement to report to CDSCO within 15 days of receipt by the MAH, reports of serious AE/AEFI occurring within India, and serious unexpected AE/AEFI occurring outside of India and any unusual failure in efficacy for new drugs occurring within India, if applicable;
- **ii.** Address all the specific Indian regulatory requirements such, as when notification is required, serious and non-serious adverse events, unusual failure in efficacy of new drugs, if applicable, retention of all records associated with AE/AEFIs, etc.;
- **iii.** Requirement to have a qualified health care professional to evaluate and assess AE/AEFI reports, including the process to review AEs.
- **iv.** Identifying the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse events) for submitting a case;
- **v.** Identifying key personnel who are responsible for forwarding the AE reports to the Licensing Authority;
- **vi.** Procedure on how complaints and AEs are tracked/logged in;
- **vii.** Procedure on how the MAH is to be notified of foreign serious unexpected AEs/AEFIs;
- **viii.** The responsibilities for the final approval of AE/AEFI evaluation and appropriate follow-up;

ix. Requirement to conduct a critical analysis of AE reports received and preparation of a summary report on an annual basis, or at the request of the Licensing Authority (CDSCO). As per Para 6.11 of part I Good Manufacturing Practices For Pharmaceutical Products: Main Principles of Schedule M revised vide G.S.R. No. 922(E) dated 28th December 2023 of Drugs and Cosmetics Act and Rules, the licensee shall have a Pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the AEFI/AEs emerging from the use of drugs/ vaccines manufactured or marketed or imported by the licensee. The licensee shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the AEFI/AEs emerging from the use of drugs/ vaccines manufactured or marketed by the licensee.

e) Importers should have in place adequate procedures for AE/AEFI receipt, handling, evaluation (for determination of complaints or AE/AEFI) and forwarding AE/AEFI to the MAH and should include but not be limited to the following:

i. Procedure on how complaints and AE/AEFI are tracked/logged in;

ii. Procedure on how complaints are assessed in order to determine if it is an AE/AEFI;

iii. Identifying key personnel who are responsible for forwarding the AE/AEFI reports to the MAH; Requirement to report AE/AEFI 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 Fifth Schedule of New Drugs and Clinical Trials Rules 2019 of Drugs and Cosmetics Rules.

iv. Requirement to follow up with the MAH to ensure that AE/AEFI have been assessed and sent to Drugs Controller General (India), if required;

v. Requirement to maintain records of all AE/AEFI received and AE/AEFI sent to the MAHs and subsequent correspondence; and ensure that as

per Drugs and cosmetics Rules, As per Para 6.11 of part I Good Manufacturing Practices For Pharmaceutical Products: Main Principles of Schedule M revised vide G.S.R. No. 922(E) dated 28th December 2023of Drugs and Cosmetics Act and Rules, the licensee shall have a Pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the AEFI/AEs emerging from the use of drugs/ vaccines manufactured or marketed or imported by the licensee reports of serious- AEFI/AEs resulting from the use of a drugs/ vaccines along with comments and documents are forthwith reported to concerned Licensing Authority (CDSCO).

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

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

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

i) Changes to procedures should be tracked and documented.

j) Deviations from procedures relating to pharmacovigilance activities should be documented

k) 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 New Drugs and Clinical Trials Rules 2019. Copies of the procedures should be readily available to the inspector/ regulator.

l) MAHs

i. The AE/AEFI 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.

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

iii. For AE/AEFI reports that qualify for expedited reporting, the 4

minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse event) for submitting a case are met.

iv. 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).

v. A qualified health care professional evaluates and assesses AE/AEFI to determine whether the AE/AEFI qualifies for expedited 15-day reporting.

m) Reports of AEFI cases from 2 or more sources

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

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

iii. Multiple copies of the same AE/AEFI reports should be nullified within the

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

v. Documented procedure and process should be in place describing when AE/AEFI reports may be nullified.

vi. Documentation related to nullified cases should be retained.

vii. Additional information received for previously submitted AE/AEFI reports

viii. Upon receipt of follow-up information, AE/AEFI reports should be re-evaluated.

ix. Follow-up information received for previously submitted AE/AEFI 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.

x. All reportable AE/AEFI that have been upgraded to serious upon receipt of follow- up information are to be sent to Licensing Authority within the prescribed timelines

xi. Rationale for changing the seriousness of an AE/AEFI report should

be documented.

xii. 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.

n) Reporting of AE/AEFI data

All AEs shall be reported to Licensing Authority (CDSCO) in accordance with New Drugs Clinical Trials Rules 2019.

o) Importers

All suspected AE/AEFI 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 New Drugs Clinical Trials Rules2019, if required.

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

p) Literature SearchMAHs

i. 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.

ii. AE/AEFI found during literature searches should be classified according to their seriousness and expectedness. These assessments should be retained and be well documented.

iii. AE/AEFI reports from the scientific and medical literature must be reported to Licensing Authority in accordance with the New Drugs Clinical Trials Rules 2019.

iv. Results of the literature searches should be documented.

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

q) Periodic Internal Audit

MAHs and Importers

An Internal Audit program that covers all departments that may receive AE/AEFI reports or that are involved in pharmacovigilance activities may help to ensure compliance with the appropriate sections of the News and Drugs and Clinical Trials Rules 2019 applicable to AEFI/AEs reporting. Internal Audit programs should be in

place and should include but not be limited to the following;

I. A comprehensive written procedure that describes the functions of the Internal Audit program.

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

III. Reports on the findings of the Internal Audit and on corrective actions. These reports should be reviewed by appropriate senior MAH management. Corrective actions should be implemented in a timely manner.

r) Periodic Internal Audit should be conducted by personnel independent from the pharmacovigilance department and that are suitably qualified to perform and evaluate the inspections.

s) Personnel and Training

MAHs and Importers

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

i. Should have knowledge of all applicable sections of the D&C Act 1940 and Rules made there under, New Drug and Clinical Trials Rules 2019 and GCP Guidelines related to the AEs reporting requirements, and of key pharmacovigilance activities performed as part of the MAH's pharmacovigilance system.

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

iii. 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.

iv. All personnel involved in pharmacovigilance activities should be aware of the principles of pharmacovigilance that affect them, and all personnel should receive relevant training.

v. When responsible personnel are absent, qualified personnel should be appointed to carry out their duties and functions.

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

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

viii. Consultants and contractors should have the necessary qualifications, training, and experience to fulfill their New Drugs Clinical Trials Rules 2019.

t) Contractual Agreements

MAHs and Importer

i) 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 labeland should include;

a. who is responsible for determining if a complaint is a potential AE/AEFI,

b. Who is responsible to report AE/AEFI,

c. 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,

d. Who is responsible for conducting literature searches?

e. 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).

f. To notify other party if changes to procedures are made.

ii) In the case of foreign MAHs, the contractual agreement should specify to send known AE/AEFI to the local MAH in a timely manner so as to promote compliance with regulatory reporting obligations.

iii) 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 AE/AEFI data to the importer in a timely manner.

iv) All records (including, but not limited to, contractual agreements and safety data/ AE/AEFI data) should be available on the premises of the MAH and the importer for auditing purposes

v) 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.

vi) Contractual agreement should be shared and signed off by each party.

vii) Contractual agreement should be reviewed periodically in order to reflect current regulations and practices.

u) Validation of Computerized Systems

MAHs, Importer, and all parties involved in pharmacovigilance activities who use an electronic system.

Data of the validation of system(s) used for recording, evaluating, and tracking complaints and AE/AEFI should be available.

Computerized systems should be validated and systems are periodically and suitably backed up at predefined intervals. It should be identified what electronic data and records will be collected, modified, imported and exported, archived and how they will be retrieved and transmitted. Electronic source data, including the audit trail should be directly accessible by investigators, monitors, auditors, and inspectors without compromising the confidentiality of participants' identities.

6. DEFINITIONS

A. Adverse Event (AE)

Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a Human vaccine /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 followsimmunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

C. Adverse Drug Reaction (ADR)

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

II. 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. Market Authorization Holder (MAH)

For the purpose of this guidance document means the manufacturer or the importer of the drug/ vaccine, who has valid manufacturing or import license.

E. Cluster

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

F. 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.

G. 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/ vaccine in question set out.

- In the case of a licensed product, in the summary of productcharacteristics (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.

H. 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 productcharacteristics (SmPC) for that product.
- In the case of any other investigational medicinal product, in the IBrelating to the trial in question.

I. Third Party

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

7. REFERENCES

1 ICH Guideline. E2E: Pharmacovigilance Planning;

2 Drugs and Cosmetics Act 1940 & Rules 1945– Fifth Schedule of New Drugs and Clinical Trials Rules 2019;

3 Guidance for Industry – Development and Use of Risk Minimization Action Plans – US FDA;

4 National AEFI Surveillance & Response Operational Guideline 2024;

5 WHO AEFI Guidelines;

6 Pharmacovigilance Guidance Document for Marketing Authorization Holders of Pharmaceutical Products;

7 Good Pharmacovigilance Practices (GVP) Guidelines.

Appendix: A

Annexure-1:

CASE REPORTING FORM (CRF)

To be filled by doctor and sent to District Immunization Officer within 24 hours *Mandatory Field

AEFI Case ID: IND (AEFI) / ST / DST / YR / NUM (from SAFE-VAC, for all vaccines except COVID-19 vaccines)

AEFI Case ID: IND (CO-AEFI) / ST / DST / YR / NUM (from Co-WIN - SAFE-VAC, for COVID-19 vaccines)

Section A: Reporter and notifier details

Name of doctor reporting / filling this form*: Contact phone number*: E mail*: Place of present posting*: Designation*: Address of present posting:	Reporting Date: __ __ / __ __ / __ __ __ __ (date when this form is prepared) Date case visited and examined / interviewed: __ __ / __ __ / __ __ __ __ (date when the case visited or interviewed)
Notified by (Name)*: Date notified: __ __ / __ __ / __ __ __ __ (date when the case informed to reporting doctor)	Designation of notifier (please circle): ASHA / AWW / Health worker / Government doctor / Private practitioner or hospital / Parent / Community / Media / Others Specify: _____
Address of session site*: Village or Urban area: Block Name: District: State:	Place of Vaccination*: Govt Health Facility / Outreach / Private Health Facility / Others (specify): _____ Source of vaccine: Government supply / Privately purchased / Others (specify): _____
Date of Vaccination*: __ __ / __ __ / __ __ __ __ Time of Vaccination: __ __ : __ __ AM/PM	Vaccination in*: Routine Immunization / Campaign (MI, Pulse Polio, MR, JE, COVID 19) / Others (specify):_____ Type of Session Site: Fixed / outreach / mobile / school / others (specify):_____

Section B : Patient details

Patient Name*																			

Date of Birth * DD/MM/YYYY	Age: _____ years ___ Months ___ days	Sex*	Male / Female

Mother's Name																			
Spouse / Father / Guardian's name*																			

Complete Address* with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*

P	I	N	-							P	H	O	N	E*	-											

For women in reproductive age group:

1. Status of pregnancy at the time of vaccination: Yes / No / Don't know
2. If Yes, duration of pregnancy at the time of vaccination: 1-3 months / 4-6 months / 7-9 months
3. Lactating at the time of vaccination: Yes / No / Don't know

Section C : Details of vaccine(s) and diluent(s) administered to the AEFI case during this session (to be filled by MO incharge or DIO of area where vaccination took place)

Name of vaccines administered to this case (write vaccine & diluent details in separate rows)*	Dose no. (birth / zero / 1st / 2nd / 3rd / booster 1 / booster 2 / campaign)*	Name of Manufacturer / Brand Name*	Batch / Lot No.*	Mfg. date	Expiry date	Date & Time of vaccine reconstitution / opening vaccine vial	No. of **OTHER** beneficiaries who received vaccine from **SAME** vial in this session

Section D : Details of adverse event(s)

1. Type of Adverse Event: Serious / Severe
2. If serious AEFI specify: Death / Hospitalization / Cluster / Persistent or significant disability / Congenital anomaly or birth defect / Media, community or parental concern

If this is a part of a cluster*: Yes / No / Unknown

If yes number of other cases in the cluster _____ Cluster ID (as generated by SAFE-VAC):

Adverse event(s) - clinical* (TICK AS MANY AS APPLICABLE):

☐ Severe local reaction	☐ Fever	☐ Seizures	☐ Injection site abscess
☐ Sepsis	☐ Encephalopathy	☐ Toxic shock syndrome	☐ Thrombocytopenia
☐ Allergic reaction	☐ Anaphylaxis	☐ Intussusception	☐ Lymphadenitis
☐ Acute Flaccid Paralysis	☐ Hypotonic Hypo-responsive Episode (HHE)	☐ Unexplained Death	☐ Anxiety reaction

Additional for COVID vaccine

☐ Joint pain / swelling of recent onset	☐ Painful single limb swelling	☐ Chest pain / fainting / palpitation
☐ Recent ECG / Echo / angiography changes	☐ Breathlessness / difficulty in breathing / worsening of existing respiratory problem	
☐ Altered sensorium / Loss of consciousness	☐ Acute disseminated encephalomyelitis	☐ Guillain-Barre syndrome
☐ Meningoencephalitis	☐ Mono-neuropathy / Poly-neuropathy	☐ Rashes
☐ Loss of taste / smell	☐ Acute liver injury / Acute Liver Failure	☐ Chilblain-like lesions /vasculitis
☐ Acute kidney injury / Acute Renal Failure / Hematuria / Oliguria / Edema of legs / Hypertension		☐ Lymphadenopathy
☐ Coagulation / bleeding disorder (Thromboembolism, Hemorrhage)		
☐ Worsening of existing disease (Cardiac / Respiratory / Liver / Kidney / Diabetes etc.)		☐ Others (specify).....

Pregnancy related events

☐ Maternal death ☐ Fetal loss (abortion) ☐ Premature delivery ☐ Still birth ☐ Neonatal mortality ☐ Congenital anomaly in newborn

Date & Time of first symptom*: DD / MM / YYYY at ___:___AM/ PM	Hospitalization (In-patient admission)*: Yes / No
Name and address of hospital:	
Date & Time of hospitalization*: DD / MM / YYYY at ___:___AM / PM	Hospital Reg. No. (OPD/Admission/Bed Head Ticket):
If hospitalized, outcome*: Discharged / Still Hospitalized / Left Against Medical Advice (LAMA) / Absconded / Referred / Death / Brought dead	
Current status of patient*: Recovered completely / recovered with sequalae / still under treatment / death / unknown	
Date & Time of Death*: DD / MM / YYYY (if died) at ___:___AM / PM Place of death: Home / Hospital / On the way to hospital / Others	Post mortem done: Yes / No / Unknown Date of Post mortem: DD / MM / YYYY
Describe AEFI (sequence of events, signs and symptoms after vaccination) *:	
Signature and name of Reporting Medical Officer:	

Section E: Decision making details

District Immunization Officer to complete and submit in **SAFE-VAC / Co-WIN SAFE-VAC (for COVID-19 vaccines)** within 24 hours of receiving the above information. SAFE-VAC: https://safevac.nhp.gov.in; Co-WIN - SAFE-VAC:

Date report received at District level: __ __/ __ __/ __ __ __ __

Date investigation planned: __ __/ __ __/ __ __ __ __

DIO/ District Nodal Person *(Officer forwarding this report)*

Name ..... Designation..... Mobile No*: .....

Email id*: ..... Signature..... Date/ Seal: .....

Complete Office address (with Pin code) .....

.....

For any support or help, write to: aefiindia@gmail.com; safevac.chi@gmail.com

Annexure-2:

CASE INVESTIGATION FORM (CIF)

(To be submitted in SAFE-VAC / Co-WIN – SAFE-VAC within 21 days of notification) *Mandatory Field

AEFI Case ID : IND (AEFI) / ST / DST / YR / NUM (from SAFE-VAC, for all vaccines except COVID-19 vaccines)

AEFI Case ID : IND (CO-AEFI) / ST / DST / YR / NUM (from Co-WIN - SAFE-VAC, for COVID-19 vaccines)

Section A: Basic details (Please refer to CRF of this case for personal details of patient)

Name of the Lead Investigator*:	Designation*:
Contact phone number* : E mail*:	Date of case visit and investigation: __ __ / __ __ / __ __ __ __ (date when the case was contacted/investigated)
Address of session site*: Village or Urban area: Block Name: District: State:	Place of Vaccination*: Govt Health Facility / Outreach / Private Health Facility / Others (specify): _____ Source of vaccine: Government supply / Privately purchased / Others (specify): _____
Date of Vaccination*: __ __ / __ __ / __ __ __ __ Time of Vaccination: __ __ : __ __ AM/PM	Vaccination in*: Routine Immunization / Campaign (MI, Pulse Polio, MR, JE, COVID 19 / Others (specify):_____ Type of Session Site: Fixed / outreach / mobile / others (specify):_____

Section B : Patient details

Patient Name*:				
Date of Birth of patient * DD/MM/YYYY	Age: _____ years ___ Months ___ days	Sex*:	Male	Female
Mother's Name:				
Spouse/Father's Name:				
Complete Address* with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*:				
PIN: Phone:				

For women in reproductive age group:

1. Status of pregnancy at the time of vaccination: Yes / No / Don't know
2. If Yes, duration of pregnancy at the time of vaccination: 1-3 months / 4-6 months / 7-9 months
3. Lactating at the time of vaccination: Yes / No / Don't know

Section C : Details of vaccine(s) and diluent(s) administered to the AEFI case during this session (to be filled by MO incharge or DIO of area where vaccination took place)

Name of vaccines received (write vaccine & diluent details in separate rows)*	Dose no. (birth / zero / 1st / 2nd / 3rd / booster 1 / booster 2 / campaign)*	Name of Manufacturer/Brand name*	Batch / Lot No.	Expiry date*	Mfg. date	Date & Time of opening vaccine vial / vaccine reconstitution	No. of **OTHER** beneficiaries who received vaccine from **SAME** vial in this session

Date & Time of first symptom*: DD / MM / YYYY at ___:___AM/ PM	Hospitalization*: Yes / No
Name and address of hospital:	
Date & Time of hospitalization*: DD / MM / YYYY at ___:___AM / PM	Hospital Reg. No. (OPD/Admission/Bed Head Ticket):

Date & time of death*: DD / MM / YYYY (if died) at ___:___AM/ PM Place of death: Home / Hospital / On the way to hospital / Others	Post mortem done: YES / NO / Unknown If done, date of post mortem: DD / MM / YYYY
If hospitalized, outcome *: Discharged / Still Hospitalized / Left Against Medical Advice (LAMA) / Absconded / Referred / Death / Brought dead	
Current status of patient*: Recovered completely / recovered with sequalae / still under treatment / death / unknown	
Describe AEFI (sequence of events, signs and symptoms after vaccination)*:	

Section D **Relevant patient information prior to immunization:**

Criteria	Finding	Provide details here if "yes" marked to any question@
Any past history of similar reaction event (without vaccination)?	Yes / No / Unknown	
Any adverse event after previous vaccination(s)	Yes / No / Unknown	
Any history of allergies for drugs, vaccine, food or other products?	Yes / No / Unknown	
Any concomitant medication at the time of vaccination, if any (If yes, name the drug, indication, doses, treatment dates/duration)?	Yes / No / Unknown	
Any pre-existing illness / comorbidity / congenital disorder?	Yes / No / Unknown	
Any pre-existing acute illness 30 days prior to vaccination?	Yes / No / Unknown	
Any history of hospitalization 30 days prior to vaccination (mention reason)?	Yes / No / Unknown	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unknown	
Has the patient tested COVID-19 positive prior to this vaccination? If yes- Type of test (RTPCR/Rapid test/CBNAAT/TRUNAAT): Date of the test:	Yes / No / Unknown	
Has the patient been in contact with a COVID-19 positive individual within 30 days prior to vaccination?	Yes / No / Unknown	
Has the patient developed symptoms compatible with COVID-19 in the past?	Yes / No / Unknown	

If patient is an infant or baby born to pregnant woman vaccinated during pregnancy, give birth details:	Remarks
1. Birth Weight:	
2. Duration of pregnancy ☐ Full term ☐ Pre-mature ☐ Postdated ☐ Unknown	
3. Place of birth ☐ Home delivery ☐ Institutional ☐ Unknown	
4. Delivery procedure ☐ Normal ☐ Caesarian ☐ Assisted with forceps/vacuum ☐ Unknown	
5. Any antenatal / postnatal complications: Yes / No / Unknown; if yes please specify	

Section E **Detailed clinical assessment, investigation, diagnosis and treatment of reported AEFI case@**

@Instructions:

- *In case of Unexplained Death in infant* - please fill Verbal Autopsy form as per the guidelines
- *If patient has taken medical care* - attach copies of all available documents (including OPD prescriptions, prescription for concomitant medication, case sheet, discharge summary, laboratory/investigation reports and post mortem reports, if available) and then complete additional information NOT AVAILABLE in the attached documents
- *If patient has not taken any medical care* - obtain history, examine the patient and write down your findings below (add additional sheets as required)

Source of information (✓ *all that* apply): ☐ AEFI Case Reporting Form ☐ Examination by the investigator ☐ Medical case records ☐ AEFI Verbal autopsy form ☐ Interview with patient / caregiver ☐ Telephonic enquiry with patient / caregiver ☐ Interview with treating physician ☐ Other_____

Date of examination: Signs and Symptoms:

Consciousness: Alert / Drowsy / Unconscious / Other (specify and describe) .....

Vitals: Pulse ..... Temperature ..... Respiratory rate ..... BP ..... Weight .....

Skin: Rash/Cyanosis/Petechiae/Pallor/Jaundice/Others (specify and describe) .....

COVID-19 test status after vaccination (if conducted, with date and type of test)

Test conducted: Y / N If Y, date of test: Test result: Positive / Negative / Not known Type of test:

Has anyone in the family of the patient tested COVID 19 positive after vaccination? Y/N. If Y, then date of test:

Has the patient developed symptoms compatible with COVID 19 infection after vaccination? Y/N. If Y, then date of test:

Systemic examination findings (mention the important positive and negative findings):

Treatment provided:

Provisional / Final diagnosis (as per the treating doctor and/or the Investigation team [encircle one] , if no medical care received):

Section F Investigation at vaccination site

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												
	Number of vaccine vials used												

1. Sequence of patient -
   a. At session site on day of vaccination:
      ☐ Within the first half beneficiaries at the session site ☐ Within the last half beneficiaries the session site ☐ Unknown
   b. For a multi dose vaccine vial (since the vial has been opened):
      ☐ Within the first half beneficiaries of the vaccine vial ☐ Within the last half beneficiaries of the vaccine vial ☐ Unknown

   If required, sequence of vaccination of all subjects (affected and not affected) should be established and mentioned on a separate sheet

2. Multidose vials administered to the case		No. of beneficiaries vaccinated from each vial on session day	No. of beneficiaries vaccinated from same vial since opening or reconstitution	No. of times each vial was issued to sessions before being issued to this session
a.				
b.				
c.				
d.				
e.				

3. Is this case a part of a cluster?	Yes / No / Unknown
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 / Unknown
C If no, Number of vials used in the cluster	

4. If similar events have been reported from other session sites, comments:

Immunization practices at the place (s) where concerned vaccine was used (based on observations and assessment)				
5. **Syringes and Needles Used:**				
• Were/Are AD syringes used for immunization? • If no specify the type of syringes:				Yes / No / Unknown
Specific key findings/additional observations and comments:				
6. **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
• Were/Are the diluents used same as recommended by the manufacturer?		Yes	No	NA
7. **Vaccine handling and vaccination** (examine the available used vaccine vials and observe an immunization session, if needed)				
• Noncompliance to recommendations for use of this vaccine (e.g. any contraindication ignored?)				Yes / No / Unknown
• Wrong selection of the beneficiary(ies) (e.g. NOT age appropriate for the vaccine)				Yes / No / Unknown
• Unsterile condition of the vaccine (ingredients) or diluent administered (sterile/unsterile)				Yes / No / Unknown
• Abnormal vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances, etc.)				Yes / No / Unknown
• Error in vaccine reconstitution/preparation by the vaccinator (e.g., wrong product, wrong diluent, improper mixing, improper syringe filling etc.)				Yes / No / Unknown
• Date and time of opening the vial clearly NOT mentioned on the vials being used in the session under observation				Yes / No / Unknown
• Error in vaccine handling (break in cold chain during transport, storage and/or immunization session etc.)				Yes / No / Unknown
• Error in vaccine administration (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?				Yes / No / Unknown
Specific key findings/additional observations and comments:				

Section G Cold Chain and Transport (Answer the following based on observations and assessment)	
Last vaccine storage point:	
• The temperature of the ILR/vaccine storage refrigerator monitored (thermometer and documentation)	Yes / No
○ If, 'yes', any deviation outside of 2- 8°C after the concerned vaccine vial was received at cold chain point	Yes / No
○ If, 'yes' attach relevant monitoring documents separately	
• Correct procedure of storing vaccines, diluents and syringes followed	Yes / No / Unknown
• Any other item (other than vaccines and diluents) available in the refrigerator or freezer	Yes / No / Unknown
• Partially used reconstituted vaccines available in the refrigerator	Yes / No / Unknown
• Unusable vaccines (expired, no label, VVM stage 3 & 4, frozen) available in the refrigerator	Yes / No / Unknown
• Unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) available in the store/refrigerator	Yes / No / Unknown
Specific key findings / additional observations and comments:	
Vaccine Transportation:	
• Type of vaccine carrier used	4-icepacks / 2-icepacks / other
• Conditioned ice-pack used in the vaccine carrier	Yes / No / Unknown
• Vaccine carrier sent to the session site on the same day of vaccination	Yes / No / Unknown
• Vaccination carrier returned from the session site on the same day of vaccination	Yes / No / Unknown
• All empty/partially used/unused vaccine vials (and diluents) return to cold chain point on the same day of vaccination	Yes / No / Unknown
• Comment on vaccine handling (any error, e.g. Break in cold chain during transport, storage and/or immunization session etc.)?	
Specific key findings/additional observations and comments:	

Section H Community Investigation (Please visit locality and interview parents/ others)

Any similar events reported recently in the locality? Yes / No/ Unknown
If Yes, Describe:

If Yes, How many events / episodes and the category of people affected (children, adults, any specific locality/area)?

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

Other findings beyond vaccine or vaccination:

Section I District AEFI Committee Review

a)	*What was the provisional diagnosis of the case concluded by the District AEFI committee?*		
b)	*Please describe the events, clinical and epidemiological findings in support of provisional diagnosis.*		
c)	*Any biological product sent (CSF, Blood, urine, tissue extracts) for testing? Note: for AEFI resulting within 28 days following JE vaccine, send sample of CSF, Serum to nearest NIV lab in Pune or Gorakhpur or Mumbai*		
d)	Did the district AEFI committee recommend sending vaccine samples for quality testing?	Yes	No
e)	Was local drug inspector involved in collecting additional samples?		
f)	Specify any other relevant investigation done and attach reports.		

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

Based on the investigation, answer the following: *(Please provide explanation in the remark column for any 'yes')*

A	Could the vaccine given to this patient have quality defect or is substandard or falsified?	Yes / No / Unable to assess	Remark
B	In this case, was there an error in prescribing or non-adherence to recommendations for use of this vaccine? (e.g. use beyond the expiry date, wrong recipient etc.)	Yes / No / Unable to assess	Remark
C	In this case, was the vaccine (ingredients) or diluent administered in an unsterile manner?	Yes / No / Unable to assess	Remark
D	In this case, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	Yes / No / Unable to assess	Remark
E	When this case was vaccinated, was there an error in vaccine reconstitution / preparation by the vaccinator (e.g., wrong product,	Yes / No / Unable to assess	Remark

	wrong diluent, improper mixing, improper syringe filling etc.?		
F	In this case, was there an error in vaccine handling? (e.g. Break in cold chain during transport, storage and/or immunization session etc.)?	Yes / No / Unable to assess	Remark
G	In this case, was the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes / No / Unable to assess	Remark
H	In this case, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety etc.)?	Yes / No / Unable to assess	Remark

Section J: Attached copies of reports / documents etc. with this Case Investigation Form:

S. No.	List of document copies received (check appropriate box)	Available and submitted with CIF	Will be available, pending for submission	Not applicable	Applicable, but not available	Remarks (if any)
1.	Case Reporting Form (CRF)					
2.	Hospital patient treatment records / hospital discharge summary *(in case of hospitalized cases)* / doctor's OPD prescription / day care treatment record / OPD treatment record)					
3.	Doctor's prescription / treatment record for past / preexisting illness					
4.	Any clinical laboratory test report (Pathology / Microbiology / Hematology / Blood / CSF / Urine / AFP / any radiology imaging report / EEG report, etc.)					
5.	Post Mortem Report – preliminary *(in case of death)*					
6.	Post Mortem Report – final *(in case of death)*					
7.	Verbal Autopsy Form (in case of unexplained death/ not hospitalized)					
8.	Laboratory result of vaccine (if sent for testing)					
9.	Laboratory result of syringes/other drugs (if sent for testing)					
10.	Any other document relevant to case					

District AEFI Committee members

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

Section K: DIO/ RCHO/ District Nodal Person *(Officer forwarding this report)*

DIO/ DRCHO/ District Nodal Person *(Officer forwarding this report)*

Name ..... Designation..... Mobile No*: .....

Email id*: ..... Signature..... Date/ Seal: .....

Complete Office address (with Pin code) .....

.....

District Immunization Officer to complete and submit in SAFE-VAC / Co-WIN SAFE-VAC (for COVID-19 vaccines) within 21 days of receiving the above information. SAFE-VAC: https://safevac.nhp.gov.in; Co-WIN - SAFE-VAC: https://www.cowin.gov.in/

For any support or help, write to: aefiindia@gmail.com; safevac.chi@gmail.com

Annexure-3:

Serious AEFI Case Notification Form – ADR Monitoring Center*	
ICSR No. _____	**Reporting Format No.**
Name & address of ADR Monitoring center (AMC):	
Patient Name	
Age: _____	Sex: Male/Female
Father/Husband's Name	
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: __ __ / __ __ / __ __ __ __ Address of health facility where vaccinated (include name of village/urban area, block, DISTRICT and STATE)#:	
Name of vaccines with dose received (if known)	
Date of first symptom (D D M M Y Y Y Y)	Time of first symptom (H H M M) (AM/PM)
Hospitalization:(No/ Yes) Date- (D D M M Y Y Y Y)	Time of hospitalization (H H M M) (AM/PM)
Name and address of hospital (if hospitalized):	CR No./MRD No _____
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) (AM/PM)
Describe AEFI (signs and symptoms):	
Name & signature of AMC Coordinator/ Medical officer: Email: Contact No.	
*Date form sent to District Immunization Officer# (where patient was vaccinated)- __ __ / __ __ / __ __ __ __	
*Date form sent to State Immunization Officer# (where patient was vaccinated)- __ __ / __ __ / __ __ __ __	
*Date form sent to PVPI, Ghaziabad- __ __ / __ __ / __ __ __ __	
*Date form sent to Immunization Division / AEFI Secretariat (aefiindia@gmail.com)- __ __ / __ __ / __ __ __ __	
Name & signature of Pharmacovigilance Associate: E mail: Contact number:	

#The case is to be notified to the DIO of the district where the vaccine was administered.
***This form should be scanned and emailed simultaneously to DIO, SEPIO, PVPI and AEFI Secretariat.**

Annexure-4

AEFI – LABORATORY REQUEST FORM (LRF)

(To be completed by Drug Inspector/DIO. Vaccine/logistics sample should be sent with LRF)

AEFI category (Encircle): **Death / Hospitalized / Cluster / Disability/Others(specify)**_____

State		Case ID IND (AEFI) / Year / Serial No.	State Code / District Code /
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	Age (in Months): (in days, if < 1 month) .....Days	----- months	Sex (please tick)	☐ 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	(	AM	PM	)							

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	Quantity	Name of Manufacturer	Batch No.	Manufacturi	Expiry

c) For Biological sample/specimen: (CSF, Blood, Urine, tissue samples etc including post-mortem tissue samples if any)

S no.	Type of sample	Date	Laboratory name

2. Test requested:
3. Preliminary clinical diagnosis 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 EPI Officer				
State Cold Chain Officer				
District Immunization Officer (DIO)				
Immunization Division (MoHFW)				
Others (specify)				

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

Landline No. :	Fax No.:	Email Id:

Annexure-5

AEFI Causality Assessment Form-2023 (National)

NATIONAL ID	STATE		DISTRICT
PATIENT'S NAME	**VACCINE (S) GIVEN**		**REASON FOR REPORTING**
VACCINATION BY (ROUTINE / CAMPAIGN)	**DATE OF BIRTH**	**AGE**	**DATE OF DEATH**
DATE OF VACCINATION	**DATE OF FIRST SYMPTOMS**	**DATE OF HOSPITALIZATION**	**OUTCOME**

Status of Case documents availability

(1) CRF (Yes / No) (2) CIF (Yes / No) (3) Hospital records (Yes / No/ NA) (4) Post Mortem (Yes / No /NA)

(5) Verbal Autopsy (Yes / No /NA) (6) State CA (Yes / No) (7) Other documents (Yes / No / NA).....

Documents availability checked & printed by - Name: ..... Date: ..... Signature: .....

Case documents Screening status

Case screened by : Name: ..... Date: ..... Signature: .....

Is this case a part of Cluster: Yes / No / NA, If Yes, Reported cluster / Indentified cluster No. of cases:

Final status of Case : F0 / F1 (If F0, mention reason) : .....

Case Summary:

Details of causality assessment by CA Sub & National committee (To be filled after CA Meeting)

	Valid Diagnosis	Classification
1. Valid Diagnosis & CA classification given by state AEFI committee		
2. Valid Diagnosis & CA Classification given by CA Sub committee experts		

3. Whether conclusion of CA Sub committee expert is consistent with conclusion of State AEFI Committee ? a) YES b) NO c) NA

If no, reason there of .....

4. Remarks (Quality review feedback by sub committee to State).....

Final Status of Causality Assessment

Details	Date		Status	Remarks (If F3 / F4)
Case discussed in CA Sub committee meeting			F2 / F3	
Case discussed in CA Sub committee meeting			F2	
Case discussed in NACM			F4 / F6	
Case discussed in NACM			F6	

STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Step 1 (Eligibility)

Name Of the Patient	Name of one or more vaccines administered before this event	What is the valid Diagnosis?	Does the diagnosis meet a case definition?
«CHILD»			
Create your question on causality here Has the_____vaccine/vaccination caused_____(the event for review in step 2-valid diagnosis)			

Is this case eligible for causility assessment? Yes / No; If, "Yes", proceed to step 2

Step 2 (Event Checklist) ✓ (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	☐☐☐☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐☐☐☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	☐☐☐☐	
Vaccine quality		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐☐☐☐	
Immunization error		
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐☐☐☐	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐☐☐☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety (Immunization Triggered Stress Response - ITSR)		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event?	☐☐☐☐	
IV. Other qualifying factors for classification		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	☐☐☐☐	
2. In this patient did such an event occur in the past independent of vaccination?	☐☐☐☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐☐☐☐	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	☐☐☐☐	
5. Was this patient taking any medication prior to the vaccination?	☐☐☐☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐☐☐☐	

Y: Yes N: No UK: Unknown NA: Not applicable or Not available

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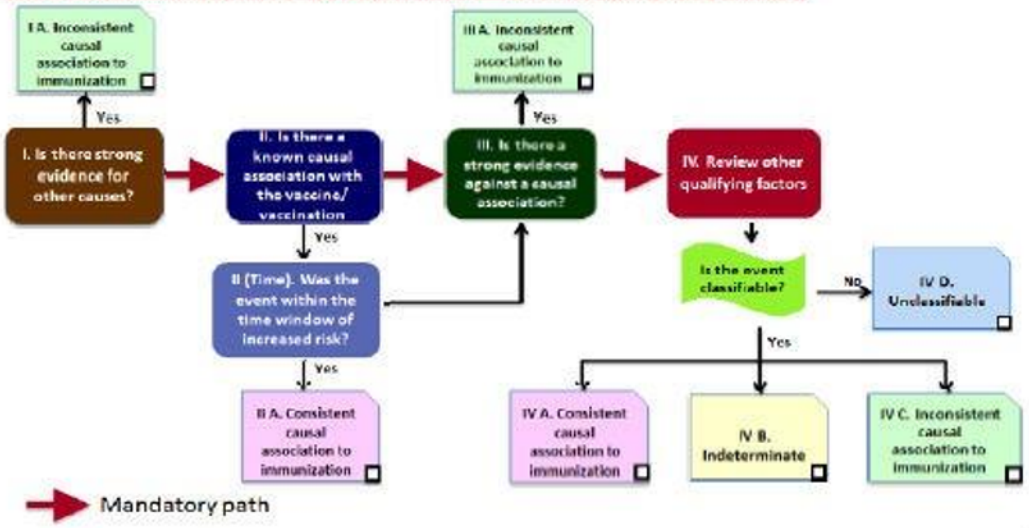
Step 3 (Algorithm) review all steps and ✓ all the appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply

Adequate information available

A. Consistent with 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 (ITSR**)

B. Indeterminate

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

C. Inconsistent with causal association to immunization

C. Coincidental

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

Adequate information not available

☐ **Unclassifiable**

Specify the additional information required for classification :

Tick Reason for Unclassifiable:

1. Supporting documents (Hospital Records/ Post Mortem- Histopathology, Chemical analysis/ Verbal autopsy) not available
2. Documents are available but inadequate information in records.
3. Standard Reporting format (CRF/PCIF/FCIF) not available (incomplete documents)

*B1. This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

Summarize the classification logic in the order of priority:

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

With available evidence, we could NOT classify the case because:_____

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Level of certainty as per Brighton's Classification (with reason for the same)

Feedback on the case for District / State / Others (specify):

S.N.	Name of Experts	Signature	Date
1			
2			
3			
4			

Appendix B

Example of summary tabulations

Note: *These examples can be modified by manufacturer and/or importer to suitspecific situations, as appropriate.*

Table 01: Estimated cumulative subject exposurefrom clinical trials

Treatment	Number of Subjects
Biological product	
Comparator	
Placebo	

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomization schemes for ongoing trials.

Table 02: Cumulative subject exposure to "New Drug"from completed clinical trials by age and sex*

	Number of Subjects		
Age Range	**Male**	**Female**	**Total**

Table 03: Cumulative subject exposure to "New Drug" from completed clinical trials by racial/ethnic group*

Racial/Ethnic Group	Number of Subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

*Data from completed trial as of [date]

Table 04: Cumulative exposure from marketing experience from India

Indication	Sex		Age				Dose / Strength			Formulation		
	Male	Female										
Overall												
Indication 1												
Indication 2*												

Includes cumulative data obtained from month/day /year through month/ day/ year, where available.

Table 05: Interval exposure from marketing experience from India

Indication	Sex		Age				Dose/ Strength			Formulation		
	Male	Female										
Indication 1												
Indication 2*												

Includes interval data obtained from month/day /year through month/day/year, wherever available

Table 06: Cumulative exposure from marketing experience from rest of the world

Indication	Sex		Age				Dose/ Strength			Formulation			ROW (which ever applicable)				
	Male	Female											EU	Japan	Mexico	US/Canada	Other
Overall																	
Indication 1																	
Indication 2*																	

Includes cumulative data obtained from month/day/year through month/day/year,where available

Table 07: Interval exposure from marketing experience from rest of the world

Indication	Sex		Age				Dose/ Strength			Formulation			ROW (which ever applicable)				
	Male	Female											EU	Japan	Mexico	US/Canada	Other
Indication 1																	
Indication 2*																	

Includes interval data obtained from month/day/year through month/day/year, wherever available

Table 08: Cumulative tabulations of Serious Adverse Events fromclinical trials

System OrganClass	Investigational Product		Active Comparator		Placebo*	Causality Assessment (Related (R) and Notrelated (NR)
Preferred Term	Listed	Not Listed	Listed	Not Listed		
Blood and lymphatic system disorders						
Anemia						
Bone Marrow Necrosis						
Cardiac						
disorders						
Tachycardia						
Ischemic cardiomyopathy						

Table 09: Number of AE/AEFIs using the term (System Organ Class (SOC) and preferred term (PT) from Post-Marketing Sources

	Report Sources (Literature, Spontaneous, solicited or any other)					Non-interventional post-marketing sources	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative		Interval	Cumulative
SOC 1							
PT							
SOC 2							
PT							

Appendix C

Tabular Summary of Safety Signals that were ongoing or closed during the reporting Interval (Reporting Interval: DD-MM-YYYY to DD-MM-YYYY)

Signal term*	Datedetected @	Status (ongoing or closed)#	Date closed (for closed signals)*	Source of Signal**	Reason for evaluation & summary of key data @@	Method of signal evaluation	Action(s) taken or planned##
Stroke	MM/YYYY	Ongoing	MM/YYY	Meta analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
Thrombosis with Thrombocytopenia Syndrome	MM/YYY	Closed	MM/YYY	Spontaneous case reports & one case report in Phase IV trial	Rash already an identified risk SJS not reported in pre authorization CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset	Targeted follow up of reports with site visit to one hospital. Full review of cases by manufacturer and/or importer dermatologist and literature searches	RSI updated with a Warning and Precaution DHPC sent to oncologists Effectiveness survey planned 6 months post DHPC. RMP updated.

***Signal term:** A brief descriptive name of a medical concept for the signal. The description may evolve and be refined as the signal is evaluated. The concept and scope may, or may not, be limited to specific term(s), depending on the source of signal.*

*@ **Date detected (month/year):** Month and year the manufacturer and/or importer became aware of the signal.*

***#Status:** Ongoing: Signal under evaluation at the data lock point of the PSUR. Provide anticipated completion date, if known; closed: Signal for which evaluation was completed before the data lock point of the PSUR*

***Note:** A new signal of which the manufacturer and/or importer became aware during the reporting interval may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PSUR.*

*$ **Date closed (month/year):** Month and year when the signal evaluation was completed.*

****Source of signal:** Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous Adverse Event Reports, clinical trial data, scientific literature, non-clinical study results, or information requests or inquiries from a regulatory authority.*

*@@ **Reason for evaluation:** A brief summary of key data and rationale for further evaluation.*

*## **Actions taken or planned:** State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed. Otherwise leave blank for ongoing signals.*

Appendix D

Annexure- 1

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Annexure- 2
Standard Line-listing (excel) Format as per CIOMS Form

Excel Column	Standard Line listing Content	
A	Sr. no.	
B	Case UID	
C	Year	
D	Country	
E	Reaction Information	Pt. Initials (if available)
F		Age (Years)
G		Weight (Kg)
H		Male/ Female
I		Reaction/ Event Onset Date
J		Describe Reaction/ Event (DD/MM/YYYY)
K		Adverse Event Preferred Term (PT)
L		System Organ Class (SOC Name)
M		Relevant tests/ laboratory data with dates, if any
N		Event Listed/ Non-Listed
O		Event Serious/ Non-Serious
P		SAE Category (PATIENT DIED, HOSPITALIZATION, LIFE THREATENING, DISABILITY, CONGENITAL ANOMALY, OTHER MEDICALLY SIGNIFICANT)
Q	Suspected Drug(s)/ Vaccine Information	Suspected Drug(s)/ Vaccine
R		Antigen/ API Name
S		Daily Dose (ml/mg/gm)
T		Route of Administration
U		Indication for use
V		Therapy Dates (from/to) (DD/MM/YYYY)
W		Therapy Duration
X		Did Reaction/Event Abate after Stopping Drug/Vaccine
Y		Did Reaction/Event reappear after re-introduction?
Z		Batch/ Lot Number
AA	Concomitant Drug(s)/ History	Concomitant Drugs/ Vaccines
AB		Dates of Concomitant Drugs/ Vaccines (DD/MM/YYYY)
AC		Other Relevant History
AD	Manufacturer/ or MAH Information	MAH Name & Address
AE		MFR Control No.
AF		Report Source (HCP, STUDY, LITERATURE, REGULATORY AUTHORITY, OTHER)
AG		Report Type (Initial/ Follow-up)
AH		Date of this Report (DD/MM/YYYY)
AI	Outcome	Recovered, Recovering, Not recovered, Fatal, Recovered with sequelae, Unknown
AJ	Event Summary	Reporter Verbatim
AK		Case Narrative
AL		PvOI/PSUR Comments
AM	Causality	Reporter Causality
AN		Company Causality
AO		Causality as per AEFI Surveillance & Response Operational Guidelines or WHO AEFI Classification i.e., A(A1,A2,A3,A4), B (B1,B2), C or unclassifiable
AP	Date of initial receipt of the information received by the applicant/ MAH (DD/MM/YYYY)	
AQ	Date of submission of CIOMS Form to CDSCO (via email/Hard File) by Applicant/ MAH (DD/MM/YYYY)	
AR	Remarks (if any)	

Note: Do not merge the excel cells, do not let cells blank, if information is not available, NA shall be filled. Global & India specific data may be entered in same excel sheet as country option is provided in "D" column.

Central Drugs Standard Control Organization,
Ministry of Health and Family Welfare,
Directorate General of Health Services,
Government of India

FDA Bhawan, ITO, Kotla Road, New Delhi -110002