WHO Guidance for Vaccine Safety Presentations to the Global Advisory Committee for Vaccine Safety (GACVS)

Rationale for this guidance document

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance. The Committee provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programmes. The Terms of Reference, committee members, topics covered by the GACVS, and committee reports can be found at http://www.who.int/vaccine_safety/committee/en/.

However, there have been instances where only limited and/or incomplete safety information has been available in order for GACVS to formulate its advice to WHO on vaccine safety. Thus, it was agreed that a template be developed that describes the critical safety information to be presented in order for GACVS to make an informed recommendation on the safety of a vaccine. In drafting this template past presentations on vaccine safety to GACVS were taken into consideration. . Documents such as the American Committee for Immunisation Practice (Guidance for Health Economics Studies) and the CIOMS (Guide to Active Vaccine Safety Surveillance) were also consulted. Even though the template is thought to result in a more comprehensive and consistent presentation of safety information, it is acknowledged that safety data and issues are unique to a particular product and thus, presentations may need to be adapted accordingly.

The template has primarily been developed for vaccine manufacturers for the presentation of pre-licensure clinical trials and post-licensure pharmacovigilance vaccine safety data. It is also recognised that while such a template may guide the presentation of safety data this document is not intended to replace existing documentation (such as the International Conference on Harmonisation guidelines for Good Clinical Practice) which detail how clinical trials should be performed and what safety data should be collected. In addition, alternate formats maybe appropriate to the presentation of other vaccine safety topics, such as systematic reviews.

Objective of this guidance document

The objective of this guidance document is to provide to presenters a framework for presentation of safety data that, to the extent possible, includes all relevant safety data for a particular vaccine that the GACVS requires in order to make an informed assessment of safety.

Materials to be presented and timelines for preparation (see Figure 1)

All presenters (internal or external to WHO) to GACVS or one its sub-committees (SC) shall present an electronic presentation and other presentation materials (e.g. handouts) **8 weeks prior** to the

scheduled date of presentation to the WHO secretariat (Contact details to be included). Under extraordinary circumstance, an appeal can be made to the WHO secretariat to submit the report fewer than 8 weeks before the meeting.

The WHO secretariat (if appropriate) will assign a GACVS member to the topic under review who will review the presentation. The WHO secretariat will provide comments and questions in writing to the presenter **6 weeks** in advance of the presentation. These comments will be forwarded to the wider GACVS membership for information and comment, if appropriate. The presenter will have 2 weeks to respond and provide the final presentation to the GACVS secretariat **4 weeks prior** to the planned presentation. This will allow time for at least one round of comments and revisions or responses prior to the material being presented to the GACVS (see Figure 1). The relevant GACVS member will determine, following re-submission, if revisions and responses are sufficient to allow presentation. If differences persist, the GACVS member together with the WHO secretariat will decide if the information will be presented to the GACVS.

Presentation material

A presentation template (see Table 1 below) should include the following information:

1.0 Introduction

The purpose of the introduction is to provide a general overview of the product, current registration and use, and a high level summary of its efficacy or effectiveness so that safety data provided can be viewed in the context of risk/benefit of the vaccine Information of the presenters and their affiliations should also be provided.

a) Affiliations

All presenters and authors shall include their affiliations. A separate section listing any conflicts of interest shall be included for each author. If there are no potential conflicts of interest, a statement to that effect must be included (e.g., Author A: No conflicts of interest). If presenting on behalf of a vaccine manufacturer COI need not be declared.

b) **Overview of product and clinical development**

An overview of the development of the product including efficacy or effectiveness summary(ies) highlighting the key milestones in regard to the acquisition of safety data.

c) **Product characteristics**

An overview of the study product highlighting any product characteristics that could or have led to any safety concerns. This should include any concerns regarding the vaccine antigen, adjuvant or excipient.

2.0 Integrated Summary of Safety (ISS)

The purpose is to provide an ISS with a broad overview of the safety data which should include pre and post licensure data. This should cover the totality of the safety data base with the details of the key clinical trials and post-marketing studies or surveillance.

3 Pre-licensure clinical trials

Multiple pre-licensure trials should be presented as a meta-analysis or systematic review or as synthesised studies (for guidance see https://cioms.ch/shop/product/evidence-synthesis-and-meta-analysis-report-of-cioms-working-group-x/). If there are a limited number of key trials detailed description can be presented. The purpose is to select the key trials/studies that will be used to provide this evidence of safety.

3.1 Methodology

This section should detail the methodology used as this is important to interpreting the safety data. This includes (but is not limited to) the following; Trial design, subject selection, vaccines, comparator and concomitant vaccines, randomisation, stratification, blinding, definitions and period of surveillance for solicited adverse events (AE) and period of surveillance for unsolicited AE (and details of their classification).

3.2 Results

The safety results presented needs to be comprehensive. In brief, the cohort that were included in the safety analysis needs to be described and details provided about those who did not complete the trial or study. When presenting adverse event data the number of subjects (n-numerator and denominator) as well as the percentages (%) in each group need to be presented within the vaccine group and comparator group. The adverse event data should also be presented as a rate per XX administered doses, as an absolute event rate difference as well as a relative difference (or risk ratio). Differences should be statistically analysed with reporting of 95% Confidence Intervals. Serious Adverse Events (particularly any deaths) and Adverse Events of Special Interest, if appropriate, should be covered in detail with a case narrative. This should include, if relevant, a causality assessment, with details of how this was performed.

Special risk groups are of particular interest. This includes pregnant women and those with immunodeficiency disease – particularly HIV. These groups may have been excluded from vaccination but safety data obtained from any inadvertent administration to these groups or the availability of any registers is important. The safety data on concomitant vaccine use (if available) should be detailed.

4 Post-licensure safety studies

Multiple post-licensure studies/trials or AEFI surveillance data should be presented as collated data. If there are a limited number of key studies detailed description can be presented. The purpose is to select the key trials/studies that will be used to provide evidence of safety.

4.1 Methodology

This section should detail the study or surveillance methodology used as this is important to interpreting the post-licensure safety data. The method of collecting AEFI data and their classification needs to be described.

4.2 Results

The safety results presented needs to be comprehensive. In brief, the cohort and population that were included in the safety analysis needs to be described. Special risk groups are of particular interest. This includes pregnant women and those with immunodeficiency disease – particularly HIV. These groups may have been excluded from vaccination in pre-licensure clinical trials but safety data obtained from any inadvertent or deliberate administration to these groups or the availability of any registers is important. Any trial or study limitations must be discussed.

5.0 Future studies and Risk Management Plans (RMP)s

Any important identified risks, important potential risks or missing information should be presented. Future or ongoing trials, studies or pharmacovigilance activities that address safety concerns identified in past studies should be detailed. If results of these are unavailable then the timelines when this data will become available should be detailed. Any RMP should be summarised.

6.0 Conclusion and discussion

This should summarise the presentation and may also include specific questions to be addressed by GACVS.

7.0 Publications and material of relevance

Results must be discussed in relation to other similar studies if such studies are available. Any supporting documentation can be provided in this section – preferable in soft copy.

Guidelines for the presentation of Essential Safety Information to the Global Advisory Committee for Vaccine Safety (GACVS)

	Area to be addressed	Information to be provided	Examples / tips
1.0 Introduction			
	Information to be provided by presenters	Presenters names and affiliations Declared COI	If presenting on behalf of a vaccine manufacturer COI need not be declared
	Overview of product and clinical development	Include an overview of; • Key mile-stones in vaccine development • Product indication • Target population • Summary of effectiveness including important immunogenicity results and any available clinical endpoint efficacy data (in brief) • List countries where marketing is authorised • WHO prequalification status • Current use specify by region and country including use in clinical trials, compassionate use or similar programmes and post-marketing))	Summarise in 1-2 slides Demonstrate on a time-line Include key studies Effectiveness, immunogenicity and efficacy data should NOT be presented in detail

	Area to be addressed	Information to be provided	Examples / tips
	Product characteristics	Summarise production methods List of vaccine components • Antigen(s) • Adjuvant • Excipients Detail any particular novel aspects to the vaccine development (identified in pre-clinical studies), manufacture or constitution that may have safety implications	If a novel vaccine vector or adjuvant is used additional safety data should be presented, when available (for example, safety data from studies using the adjuvant with a different vaccine antigen)
2.0 Integrated Summary of Safety			
	Pre-licensure clinical trials Post-Marketing surveillance	Should include the following; • Size of safety data base • Key safety clinical trials • Key post-marketing safety information • Highlight any safety issues	…

	Area to be addressed	Information to be provided	Examples / tips
3.0 Pre-licensure clinical trials			
3.1 Methodology **If possible present pre-licensure trials as a meta-analysis or collated studies.** **If there are a limited number of key trials detailed description can be presented.**	Trial design	Overall trial design	Should be summarised in a Table
	Subject selection	Population (s) from which the trial participants were selected Groups excluded from trials	Important to detail if risk groups eg Pregnant, lactating, HIV +ve subjects, were included
	Vaccines, comparator and concomitantly administered vaccines	Description of comparator vaccine/placebo and concomitantly administered vaccines.	If placebo used, describe constituents of the placebo.
	Randomisation and stratification	Method of subject randomisation and stratification	State if the vaccinated and comparator groups equivalent in all respects-other than the intervention
	Blinding	Blinding of subjects and researchers	Sufficient blinding to prevent any potential biases in assessing safety outcomes
	Reactogenicity and Adverse Events (AE)	Description of which AE were solicited in a specified period Case definitions for local and systemic reactogenicity, Serious	Detail if case definitions were according to the CIOMS, Brighton Collaboration or

	Area to be addressed	Information to be provided	Examples / tips
		Adverse Events (SAE) Adverse Events of Special Interest (AESI), AESI Definitions used for severity grading for all events	other definitions used Severity grading scales for individual solicited AEs as well as overall severity grading scales for unsolicited AEs, SAEs and AESI.
		Ascertainment of events	Detailed information about detection of AE, SAE, AESI and in particular the method of surveillance for solicited and unsolicited events
		Duration of surveillance post-vaccination	Detailed information about duration of AE, SAE, AESI surveillance
	Statistical analysis plan	Specify if pre-specified safety hypotheses to evaluate specific outcomes (e.g., febrile seizures; intussusception).	
3.2 Results **If possible present pre-licensure trials as a meta-analysis or collated studies.**	Description of cohorts/population used for analysis	Total numbers of individuals enrolled in the cohort– vaccinated and comparator populations Number of individuals that completed the trial or study – per protocol population (PP) Number of individuals that were enrolled but did not complete –	CONSORT flow diagram

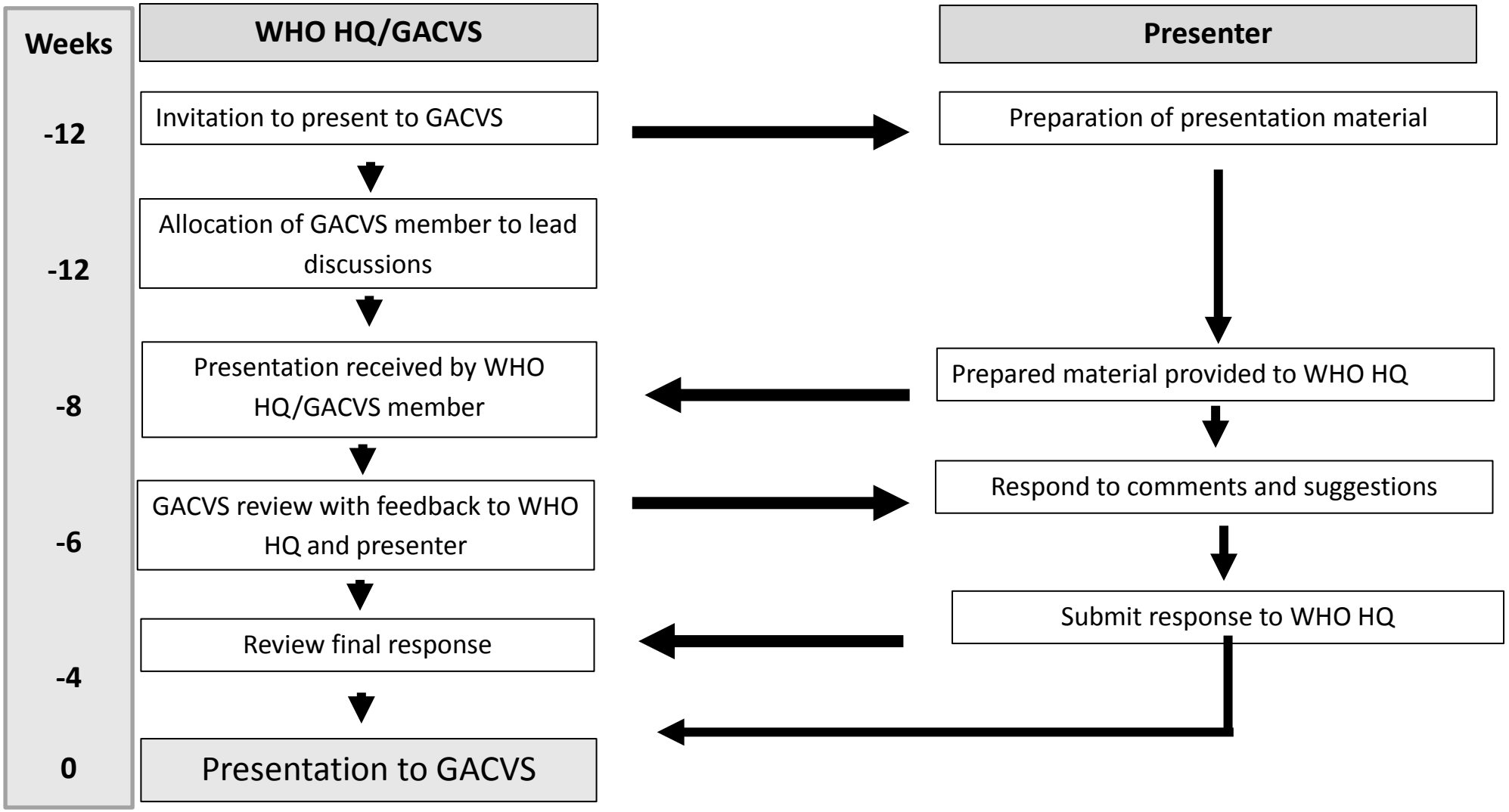
	Area to be addressed	Information to be provided	Examples / tips
If there are a limited number of key trials detailed description can be presented.		intention to treat (ITT) Number of individuals that were treated “all treated as treated”	
	Safety results overview	Reported as vaccinated vs comparator group Number (n) of enrolled subjects included in the safety analysis Include total n (%) of Solicited AE, SAE and AESI Specifically detail SAE n (%) of deaths, hospitalisation, disability etc Unsolicited AE, SAE, AESI should be presented according to a prespecified classification system (e.g., MedDRA)	
	Stratification of Adverse events	Stratification by age, gender,ethnic/racial group or other factors if appropriate	
	Reporting as comparisons between groups	Report as Relative Risk (RR) or absolute event rate difference between vaccinated and comparator vaccine or other appropriate statistical tests	
	Details of all SAE, AESI, death in vaccinated and comparator groups	Detail details time to onset of event, severity, outcome	This can be tabulated including case narratives

	Area to be addressed	Information to be provided	Examples / tips
	Causality assessment	Causality assessment for SAE and AESI	Detail methodology of causality assessment
	n (%) of AE,SAE, AESI leading to discontinuation	Reported as vaccinated vs comparator groups	
	AE, SAE, AESI in risk groups	Safety in risk groups needs to be evaluated separately	
	Pregnancy	n (%) with pregnancies during entire study period n (%) of subjects with pregnancy around vaccination (-30 pre-natal to +45 days post-natal) N (%) with known pregnancy and perinatal outcomes	Use Brighton CD for pregnancy outcomes
	Limitations	Limitations of each clinical trial	
	Conclusion	Overall conclusions regarding safety for each clinical trial, meta-analysis or collation of trials	

	Area to be addressed	Information to be provided	Examples / tips
4.0 Post-licensure safety studies			
4.1 Methodology **Post-licensure safety studies or surveillance. If possible present these as collate studies**	Study design or surveillance activities	Study design or description of surveillance	Should be summarised in a Table
	Subject selection	Cohort or populations studied	Important to detail if risk groups eg Pregnant, lactating, HIV +ve subjects, were included
	Concomitantly administered vaccines	Description of concomitantly administered vaccines.	If placebo used, describe constituents of the placebo.
	Adverse Events Following Immunisation (AEFI)	Description of AEFI Case definitions for AEFI, Serious AEFI, Adverse Events of Special Interest (AESI), AESI Definitions used for severity grading	Detail if case definitions were according to the CIOMS, Brighton Collaboration or other definitions used Severity grading scales for individual solicited AEs as well as overall severity grading scales for unsolicited AEs, SAEs and AESI.

	Area to be addressed	Information to be provided	Examples / tips
	Statistical analysis used	Specify if pre-specified safety hypotheses to evaluate specific outcomes (e.g., febrile seizures; intussusception).	
4.2 Results **Post-licensure safety studies or surveillance. If possible present these as collate studies**	Safety results overview	Number (n) of individuals included in the cohort or study population Include total n (%) of AEFI, SAE and AESI Specifically detail n (%) of deaths, hospitalisation, disability etc AEFI should be presented according to a prespecified classification system (e.g., MedDRA)	
	Limitations	Limitations of surveillance	
	Conclusion	Overall conclusions regarding safety for each clinical trial, meta-analysis or collation of trials	
5.0 Future studies and Risk Management Plans (RMP)			
	Safety concerns	Important identified risks, important potential risks or missing information should be summarised	May have been identified in a Risk Management Plan (RMP - European)

	Area to be addressed	Information to be provided	Examples / tips
	Post-marketing trials/studies or pharmacovigilance activities	Ongoing or planned trials/studies or pharmacovigilance studies to address the limitations	Include the timelines for expected findings
	Risk Management Plan	Risk minimisation strategies included in RMP	
6.0 Summary and Conclusion			
	Overall summary	To include specific questions to the GACVS	
7.0 Appendices, publications and material			
	To support safety data	Include • Peer reviewed articles • Regulatory documentation • Package Insert (PI).	Provide electronic references where possible


Weeks
WHO HQ/GACVS
Presenter
-12
Invitation to present to GACVS
Preparation of presentation material
-12
Allocation of GACVS member to lead discussions
-8
Presentation received by WHO HQ/GACVS member
Prepared material provided to WHO HQ
-6
GACVS review with feedback to WHO HQ and presenter
Respond to comments and suggestions
-4
Review final response
Submit response to WHO HQ
0
Presentation to GACVS