

WHO Guideline on Regulatory Preparedness for Human Pandemic Influenza Vaccines

Post Marketing Surveillance

By

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Presentation outline

- Pharmacovigilance Planning
 - CHMP recommendations
- Industry perspectives on draft WHO guidance

CHMP Recommendations for a Pharmacovigilance Plan

- Part of the Marketing Authorization Application
- Risk Management Plan for a pandemic influenza vaccine
- Adopted by CHMP in November 2006
- Reference EMEA/32706/2007



3270607en.pdf
(120 Ko)

Risk Management Plan- Principles

- Safety specification
 - Important risks identified
 - Potential risks
 - Missing information
- Pharmacovigilance plan
 - Routine PV
 - Additional PV activities
 - Action plan
- Risk minimisation plan
 - SmPC
 - Communication
 - Training/education
 -

Risk Management Plan and Pandemic Influenza Vaccines- General comments

- Pharmacovigilance Plan
 - Routine and additional PV activities during the pandemic period (phase 6 WHO)
 - Preparatory activities
- Evolving document
- Close collaboration between Health Authorities and Manufacturers

Pharmacovigilance Plan

- Routine activities
 - Adverse event collection:
 - Healthworkers and patients
 - Prioritization « encouraged »
 - Standardized data collection form
 - Electronic submission to NCA (E2B)
 - Simplified PSUR-template predefined:
 - Bi-weekly frequency first 3 months of the pandemic
 - Vaccine distribution
 - Focus on serious unexpected events/LT/fatal/AESI, signals
 - Clock start after shipment of the first batch, full PSUR at the end of pandemic

Pharmacovigilance Plan

- **Objective:** serious outcomes, rapid review cycle
- **Routine activities**
 - Signal detection
 - Focus on important new safety signals
 - Use of quantitative methods (measures of disproportionality)
 - No specific threshold recommended
 - Potential bias in interpretation
 - Target groups may differ from country to country
 - Public information
 - Simple and standardized reports of signals, ie, PRR, EBGM or counts, Brighton definition, etc.

Pharmacovigilance Plan

- Additional activities
 - Post licensure evaluation of safety and immunogenicity of final variant after the onset of a pandemic
 - For each MAH-combination possible-
 - Design: prospective cohort study of exposed subjects
 - Cohorts to be identified *prior* to the pandemic period
 - Primary objective: important safety outcomes
 - Simple, rapid generation of data
 - Questions remain to be addressed

Post licensure study (EVM proposal annexed in EMEA/32706/2007)

Indication/Study population	Individuals in priority groups for vaccination with a
Objectives	<p>Primary</p> <ul style="list-style-type: none"> - estimate the incidence of important safety outcomes <p>Secondary</p> <ul style="list-style-type: none"> - a description of the immunogenicity of the final variant pandemic vaccine
Study design	Prospective, active surveillance of vaccinated cohorts.

Characteristics of the active surveillance approach include:

- Implementation in several but not all European countries as a generic study
- remote data entry (RDE) or standardised hard-copy Case Report Forms (CRFs)
- self-reported and health care professional-based outcomes; it might be possible to provide pre-designated health care professionals with pre- and post-vaccination diaries in which to record symptoms on a regular basis
- baseline assessment will take place at the time of enrolment in the study

Post licensure study

Study Individuals in priority groups for vaccination with a pandemic vaccine

Population Age groups

- 6 to 23 months
- 2 to 8 years
- 9 to 17 years
- 18 to <60 years
- 60 years and above

Priority designation

- Health care workers
- Public safety professionals (e.g., police, fire fighters, public utility workers)
- children

Post licensure study

Number of subjects

A total cohort of 9000 study participants will be composed of five age-stratified cohorts:

- 6 to 23 months (n = 500)
- 2 to 8 years (n = 500)
- 9 to 17 years (n = 3000)
- 18 to <60 years (n = 3000)
- 60 years and above (n = 2000)

Solicited Adverse Events of Special Interest

- Neuritis
- Convulsions
- Severe allergic reactions
- Encephalitis
- Vasculitis
- Guillain Barré Syndrome
- Hospitalisations
- Pneumonia

Industry perspectives on draft WHO guidance

- Agreement on need to simplify and harmonize activities
- Methods, tools, and systems to be implemented in the pre-pandemic phase
- Uncertainties regarding the use of the pandemic vaccines have impact on the approach
- Common principles required
- Adaptability is critical!

Industry perspectives on draft WHO guidance

- Routine pharmacovigilance activities
 - Must be harmonized across countries
 - Data collection form
 - List of adverse events of special interest (AESIs)
 - Case definitions for AESIs, et al
 - Prioritization « encouraged » ie, SAE
 - Periodic reports –frequency, templates

Industry perspectives on draft WHO guidance

- Additional activities
 - Multiple challenges
 - Scientific
 - Choice of study designs and analyses
 - Need for harmonization
 - Background rates of AESIs by age, other risk factors
 - Strategic
 - Implementation decisions
 - Policy makers

Industry perspectives on draft WHO guidance

- Choices of study designs and analyses (line 1877-1926)
 - Pragmatic choices must be made
 - Harmonization necessary

Randomized clinical trials	First wave individuals, before pandemic (prepandemic, pandemic vaccines ?) Randomization ? Control group? Size? (important safety outcomes) rapid generation of data ?
Prospective cohort with a control group	Identification of comparison group biggest challenge; unvaccinated (ie, general population) persons may be available but some issues (logistic problems etc..)
Prospective cohort without a control group	Use of historical comparisons not ideal; comparison to general population rates. Basically, a registry of vaccinated persons
Case control study	Not good for rapid generation of data or signal detection, needs large sample size, eg, tens of thousands to detect doubling of risk of 0.1%

Industry perspectives on draft WHO guidance

- Large computerized databases: topics for discussion
 - Country specific
 - Availability
 - Selected practices (vaccinated persons or not)
 - Size limitations
 - Predefined systems or de novo creation
 - Assessability of data, transparency

Industry perspectives on draft WHO guidance

- Analyses by:
 - Vaccines, brand, pooled data
 - Interpandemic, pre-pandemic, pandemic
 - Age group, other groups at risk
 - Countries, region, global

Industry perspectives on draft WHO guidance

Needs:

- Clearly defined leadership and coordination
- Agreement on proposal
- Harmonisation with other, eg, EMEA proposals
- New database vs. utilisation of existing one(s)
- Mechanisms for funding
 - Registries have large start-up/maintenance costs
- Compliance by individual countries
- Timelines and milestones

Back up

Table 1. Priority groups considered for vaccination in a pandemic

	Austria	Czech	Estonia	France	Greece	Ireland	Italy	NL	Norway	Slovakia	Sweden	UK
Health care personnel	X	X	X	X	X	X	X	X	X	X	X	X
First responders	X	X	X			X	X		X	X		X
Public utility workers	X		X		X		X		X			
High risk of complications	X			X	X	X	X	X	X	X	X	X
Household contacts of high-risk											X	
Elderly										X	X	X
Children						X	X				X	X
Adolescents							X					
Healthy adults							X				X	
Pregnant women											X	
Long-term care facilities		X			X				X	X		
Crowded areas (e.g. schools)					X							
Transport workers	X	X	X							X		
Selected industries										X	X	X
Entire population	X								X		X	X

No priority groups specified for: Belgium, Cyprus, Finland, Lithuania, Luxembourg, Portugal, Spain

Outline of study procedures

Visit	VISIT "DAY 0"	VISIT DAY 21	VISIT "DAY 42"	VISIT "DAY 180"
Informed consent	X			
Check inclusion criteria	X			
Demographics	X			
Medical history	X			
Vaccination	variable	x		
Serologic testing (immuno subset)	X	x	y	
Collection of diary		x	y	X
Record any concomitant medication/vaccination		x	x	X
Reporting of Serious Adverse Events		x	y	X
Recording of unresolved adverse events				X
Study Conclusion				X