



# MINISTRY OF HEALTH OF UKRAINE

## ORDER

26.09.2016

Kyiv

№ 996

Registered at the Ministry of Justice of Ukraine on December 19, 2016 under № 1649/29779

### **On introduction of changes to some Orders of the Ministry of Health of Ukraine**

According to Bases of the Legislation of Ukraine on Healthcare, Laws of Ukraine “On Medicines”, “On Population Protection against Infectious Diseases”, “On Ensuring Sanitary and Epidemic Safety of the Population” “On the National Programme of Approximation of Ukrainian Legislation to that of the European Union”, Procedure for State Registration (Re-Registration) of Medicinal Products and Amounts of Fees for Their State Registration (Re-Registration) approved by the Decree of the Cabinet of Ministers of Ukraine of May 26, 2005 № 376, item 8 of the Regulations of the Ministry of Health of Ukraine approved by the Decree of the Cabinet of Ministers of Ukraine of March 25, 2015 № 267,

#### **I ORDER:**

1. To substitute words “Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use” in all cases by words “Pharmacovigilance Procedure” in respective cases in the title and text of the Order of the Ministry of Health of Ukraine of December 27, 2006 № 898 “About Approval of Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use” registered at the Ministry of Justice of Ukraine on January 29, 2007 under № 73/13340.
2. To introduce changes to the Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use approved by the Order of the Ministry of Health of Ukraine of December 27, 2006 № 898, registered at the Ministry of Justice of Ukraine on January 29, 2007 under № 73/13340, stating it in the new wording (attached).
3. To delete sub-items 1.4-1.6 of item 1 of the Order of the Ministry of Health of Ukraine of September 16, 2011 № 595 “On Procedure for Prophylactic Vaccination in Ukraine and quality control and use of medical immunobiological products” registered at the Ministry of Justice of Ukraine of October 10, 2011 under № 1159/19897.

Thus, to consider sub-items 1,7, 1.8 as sub-items 1.4, 1.5 respectively.

4. To delete word “, toxoid” from paragraph two of item 5 of the Prophylactic Vaccination Schedule in Ukraine approved by the Order of the Ministry of Health of Ukraine of September 16, 2011 № 595 registered at the Ministry of Justice of Ukraine on October 10, 2011 under № 1159/19897.

5. To delete words “, and adverse reactions or death of persons at using batch(es) of medicinal products” from paragraph six of item 5.2 of section 5 of the Rules of storage and quality control of medicinal products in health facilities approved by the Order of the Ministry of Health of Ukraine of December 16, 2003 № 584 registered at the Ministry of Justice of Ukraine on March 03, 2004 under № 275/8874.

6. To read sub-item 3.2.5 of item 3.2 of section III of the Procedure to Impose a Ban (Temporary Ban) on and to Restore Circulation of Medicinal Product at the Territory of Ukraine approved by the Order of the Ministry of Health of Ukraine of November 22, 2011 № 809 registered at the Ministry of Justice of Ukraine on January 30, 2012 under № 126/20439 as follows:

“3.2.5 negative conclusions on quality of samples from batch or batches of medicinal product suspected of causing the death, unexpected adverse reaction and/or lack of efficacy if there is a causal association according to reports from MoH Ukraine and/or territorial bodies of the State Service of Ukraine for Medicinal Products and Narcotics Control;”.

7. To approve Regulations of Central and Regional Group of Quick Response to AEFI/Tuberculin Diagnostics (attached).

8. To declare as invalid:

1) The MoH Ukraine Order of June 15, 2007 № 325 "On Approval of Quality Parameters of Immunobiological Products (Vaccines and Toxoids)", registered at the Ministry of Justice of Ukraine on July 06, 2007 under № 773/14040;

2) The MoH Ukraine Order of July 24, 2009 № 531 "On Approval of Procedure for Safety and Efficacy Monitoring of Medicinal Products in In-Patient Departments of Health Facilities", registered at the Ministry of Justice of Ukraine on August 17, 2009 under № 774/16790;

9. That the Pharmaceutical Activity and Pharmaceutical Product Quality Administration arranges for the submission of the present order to the Ministry of Justice of Ukraine for the state registration according to the established procedure.

10. I will supervise execution of this order by myself.

11. The order shall take effect from the date of its official publication.

**U. Suprun**  
**Acting Minister**

**AGREED UPON WITH:**  
**K. Liapina**  
**Head, State Regulatory Service of Ukraine**

**I. Suvorova**  
**Acting Head, the State Service of Ukraine for Medicinal Products and Narcotics Control**

**D. Oliinyk**

## **First Deputy Head, Joint Representative Body of Employers at the National Level**

**A. M. Makarenko**

**Director General, SE “Ukrvaktsyna” MoH Ukraine**

**H. V. Osovyi**

**Head, Joint Representative Body of Representative National Confederations of Trade Unions at the National Level**

APPROVED

Order of the Ministry of Health of Ukraine of  
27.12.2006 № 898

(in wording of the MoH Ukraine Order of  
26.09.2016 № 996)

Registered at the Ministry of Justice of Ukraine  
on 19.12.2016 under № 1649/29779

## **PHARMACOVIGILANCE PROCEDURE**

### **I. GENERAL**

1. This Procedure has been elaborated in compliance with Bases of the Legislation of Ukraine on Healthcare, Laws of Ukraine “On Medicines”, “On Population Protection against Infectious Diseases”, “On Ensuring Sanitary and Epidemic Safety of the Population” “On the National Programme of Approximation of Ukrainian Legislation to that of the European Union”, Procedure of State Registration (Re-Registration) of Medicinal Products and Amounts of Fees for Their State Registration (Re-Registration) approved by the Decree of the Cabinet of Ministers of Ukraine of May 26, 2005 № 376, provisions of the Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001, Regulation (EC) № 726/2004 of the European Parliament and of the Council of 31 March 2004 that establish main rules and requirements for pharmacovigilance.

2. The terms used in this Procedure have the following definitions:

Adverse event following immunization/tuberculin diagnostics - any untoward medical occurrence, which is observed following immunization/ tuberculin diagnostics and which does not necessarily have a causal association with the usage of the vaccine and/or tuberculin. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, and symptoms of disease or disease;

Adverse reaction - any unintended and noxious response to a medicinal product; any unintended and noxious reaction to vaccine, tuberculin if it is caused or precipitated by the active component or one of the other components, or may also relate to failures occurring in manufacturing of vaccine, tuberculin including administration devices supplied by the manufacturer;

Benefit – a range of degrees of positive effect of a medicinal product, vaccine, tuberculin on a reduction of severity of the disease course or symptom manifestations, and an intensity of positive pharmacological response to medicinal product administration and its duration.

Benefit-risk balance of medicinal product, vaccine, tuberculin – an assessment of positive therapeutic effects of medicinal product, vaccine, tuberculin against any risks relating to the quality, safety or efficacy of medicinal product, vaccine, tuberculin as regards patients' health or public health;

Bridging summary report – a written report integrating the safety information about a medicinal product, vaccine, tuberculin presented in two or more periodic safety reports on medicinal product, vaccine, tuberculin;

Causality of clinical manifestations of any adverse reaction/adverse event following immunization/tuberculin diagnostics and use of medicinal product, vaccine, tuberculin – a likelihood, which is determined by an established method (WHO qualitative method, Naranjo Scale, Binary method, etc.) according to certain criteria and indicates the association between the adverse reaction/adverse event following immunization/tuberculin diagnostics observed and the use of a medicinal product, vaccine, tuberculin;

Cluster of adverse reactions - two or more cases of adverse reactions associated with use of medicinal product, vaccine or tuberculin, which have similar clinical manifestations related in time, location of health facility and/or batch of medicinal product, vaccine, tuberculin;

Cluster of adverse events following immunization - two or more cases of adverse events following immunization, which have similar clinical manifestations related in time, place of performing immunization/tuberculin diagnostics and type of vaccine, tuberculin administered;

Combination vaccines – vaccines intended for protection against several infectious diseases, which may be caused by different strains, different microorganisms or serotypes of microorganisms;

Company core data sheet (hereinafter - CCDS) of the applicant– a document, prepared by the applicant, containing the safety information on medicinal product, vaccine, tuberculin, proposed indications for use, dosing, peculiarities of use, pharmacology, etc.

Company core safety information (hereinafter - CCSI) of the applicant – a document, prepared by the applicant, containing all relevant safety information contained in the Company Core Data Sheet of the applicant. CCSI of the applicant is used for the purpose of periodic reporting for determining whether an adverse reaction is listed and unlisted in the Company Core Data Sheet of the applicant. Data from CCSI of the applicant are not used for determining whether an adverse reaction is expected or unexpected for submitting reports on cases of adverse reactions;

Cumulative data about cases of adverse reactions after using vaccine, tuberculin – a report summarizing information on adverse reactions following the use of vaccine, tuberculin according to a list of clinical manifestations of adverse reactions after using vaccine, tuberculin and/or their description included in the instructions for medical use of vaccine, tuberculin in the reporting period.

Efficacy of medicinal product – a favourable diagnostic, therapeutic or preventive effect of a medicinal product on the nature of a disease, its course, duration or correction of organism's state or physiological functions according to the indications for use specified in the instructions for medical use;

Efficacy of vaccine – a percentage reduction of controlled infectious diseases in vaccinated persons compared with unvaccinated persons;

Epidemiological investigation form – a form according to which a responsible person of the regional or oblast healthcare structural units provides information on case of infectious disease controlled by specific immunoprophylaxis in vaccinated persons;

Expected adverse reaction - an adverse reaction, the nature or severity of which is consistent with the information on medicinal product, vaccine, tuberculin available in the instructions for medical use for the registered medicinal product/summary of product characteristics for medicinal product, vaccine, tuberculin;

Frequency of cases of adverse reactions to medicinal product, vaccine, tuberculin – a ratio (expressed as a percentage) of the number of patients who developed adverse reaction during the use of medicinal product over a period of time to the number of patients who used the medicinal product, vaccine, tuberculin over the same period of time.

General report about registered cases of infectious disease controlled by specific immunoprophylaxis in vaccinated persons according to epidemiologic investigation form - a report about all registered cases of infectious diseases controlled by specific immunoprophylaxis in vaccinated persons, which is prepared based on data from epidemiological investigation forms for cases of infectious diseases controlled by specific immunoprophylaxis in vaccinated persons;

Grouping of adverse reactions to medicinal product, vaccine, tuberculin according to their frequency:

over 10% - very common;

1-10% - common;

0,1 – 1% - uncommon;

0,01 – 0,1% - rare;

less 0,01% - very rare.

Hospital-based monitoring - the method of getting information about adverse reactions to medicinal product/vaccine which allows a determination of the frequency of adverse reactions and identification of peculiarities of interactions of medicinal products/vaccines in patients of one or more hospitals when for a period of time all hospitalized patients are under control, all prescribed medicinal products/vaccines, and any adverse reactions, which occur, are taken into account;

Immunogenicity of vaccine - the ability of a vaccine to induce a humoral (specified percentage of antibodies) and/or cell-mediated immunity. This measure should be more than 90% (except for influenza vaccines) according to clinical trial data; for combination vaccines each of their components should correspond to this measure;

Information that identifies a case of adverse reaction to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product, and/or adverse event following immunization/tuberculin diagnostics – data on source of information, suspected medicinal product, vaccine, tuberculin, patient, description of adverse reaction/statement of a lack of efficacy/description of adverse event following immunization/tuberculin diagnostics;

International birth date of medicinal product, vaccine, tuberculin – the date of the first marketing authorization for a medicinal product, vaccine, tuberculin, granted to the applicant in any country of the world;

Lack of medicinal product's efficacy – a lack of favorable diagnostic, therapeutic or preventive effect of a medicinal product on determination of the nature of a disease, its course and duration or correction of organism's state or physiological functions according to the indications for use given in instructions for medical use.;

Listed adverse reaction to medicinal product, vaccine, tuberculin - an adverse reaction whose nature or severity is consistent with the information in the applicant core safety information for a medicinal product, vaccine, tuberculin;

Meta-analysis - a method of getting information including one about adverse reactions to medicinal product, vaccine, tuberculin, which uses a statistical analysis to integrate data of several independent studies to monitor medicinal products, vaccines, tuberculin, and adverse reactions in particular those occurring after a long period of time. Any information about the patient from different sources (health facilities where he/she was treated, maternity house, prescriptions, etc.) accumulated throughout his/her life shall be taken into account; this is a basis for preparation of a patient's dossier and further analysis.

Monitoring of prescriptions - a method of getting information about adverse reactions to medicinal product/vaccine based on recording medicinal product/vaccine prescriptions when the number of registered adverse reactions and the number of patients who used a medicinal product/vaccine at any given period of time are defined, thus allowing identification of the relationship between the adverse reaction and the use of a medicinal product/vaccine;

Non-serious adverse reaction - any untoward reaction that does not result in death, is not life-threatening, does not require hospitalization, or prolongation of existing hospitalization, does not result in persistent or significant disability or incapacity, or is not a congenital anomaly/birth defect, and is not any other important medical event.

Other important medical event – a case of adverse reaction, and/or lack of efficacy that may not be immediately life threatening or result in death, or require hospitalization, but may jeopardize the patient or may require intervention to prevent the outcome of adverse reaction, and/or a lack of efficacy;

Periodic safety update report on medicinal product, vaccine, tuberculin – a written report containing periodically updated information on safety of a medicinal product, vaccine, tuberculin;

Pharmacovigilance – activities relating to the detection, collection, assessment, study and prevention of adverse reactions, adverse event following immunization /tuberculin diagnostics or any other problems related to the use of medicinal products, vaccine, tuberculin;

Pharmacovigilance system – a system used by a state or an applicant in order to monitor safety and efficacy of medicinal products, vaccines, tuberculin, and detect any changes in benefit-risk balance;

Pharmacovigilance system master file – a document containing detailed description of the pharmacovigilance system used by the applicant with respect to one or more medicinal products, vaccines, tuberculin;

Post-registration safety and efficacy study of medicinal product, vaccine, tuberculin – any post-registration safety and efficacy study of a medicinal product, vaccine, tuberculin permitted for medical use, which is conducted in order to identify, characterize or assess a safety hazard, confirm the safety profile of the medicinal product, vaccine, tuberculin and/or measure the effectiveness of risk management activities;

Post-registration non-interventional safety and efficacy study of medicinal product, vaccine, tuberculin – a type of post-registration safety and efficacy study of a medicinal product, vaccine, tuberculin where a medicinal product, vaccine, tuberculin is prescribed in accordance with instructions for medical use for a medicinal product, vaccine, tuberculin. The assignment of the patient to the defined treatment group is not decided in advance by a study protocol but falls within current practice and the prescription of the medicinal product, vaccine, tuberculin is separated from

the decision to enroll the patient in the study. In such studies no additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of collected data.

Post-registration non-interventional safety and efficacy study of medicinal product, vaccine, tuberculin (case-control) – a type of post-registration safety and efficacy study of medicinal product, vaccine, tuberculin conducted with two groups of patients, in one of which there are certain iatrogenic diseases or adverse reactions, and in the other there are no similar diseases or adverse reactions in order to detect risk factors for developing iatrogenic diseases or adverse reactions;

Post-registration non-interventional safety and efficacy study of medicinal product, vaccine, tuberculin (cohort) - a type of post-registration safety and efficacy study in which two large selected groups of patients representing those exposed and those not exposed to an investigational medicinal product are observed over a period of time in order to detect adverse reactions, risk factors for developing adverse reactions, etc.;

Post-registration safety and efficacy study protocol for medicinal product, vaccine, tuberculin – a document containing a description, objectives, methodology, procedures, statistical aspects and design of post-registration safety and efficacy study of medicinal product, vaccine, tuberculin, and (if applicable) previously obtained data on investigational medicinal product, vaccine, tuberculin, and justification for this study;

Report on adverse reaction to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product, and/or adverse event following immunization/tuberculin diagnostics at health facilities – an annual report on all cases of adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product, and/or adverse events following immunization/tuberculin diagnostics to be prepared and submitted by any health facility regardless types of ownership, healthcare structural units of the Autonomous Republic of Crimea, the Oblast, Kyiv and Sebastopol city state administrations;

Report form on adverse reaction of medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal product, and/or adverse event following immunization/tuberculin diagnostics – a form according to which doctors, pharmacists, feldshers, obstetricians, chemists, nurses of any health facility regardless of types of ownership informs of any adverse reactions of medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal products, and/or adverse event following immunization/tuberculin diagnostics;

Report on post-registration safety and efficacy study of medicinal product, vaccine, tuberculin – results of post-registration safety and efficacy study of medicinal product, vaccine, tuberculin and their analysis presented in written form;

Risk management plan – a detailed description of the risk management system;

Risk management system - a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to the use of medicinal product, vaccine, tuberculin including the assessment of effectiveness of those activities and interventions;

Risk related to the use of the medicinal product, vaccine, tuberculin – any risk related to the quality, safety or efficacy of medicinal product, vaccine, tuberculin, as regards patients' health or public health, or any risk of undesirable environmental effects;

Safety profile – a set of indices of use of medicinal product, vaccine, tuberculin that allow a determination of a benefit-risk balance of the medicinal product, vaccine, tuberculin;

Serious adverse reaction – any adverse reaction that results in death, is life-threatening, requires hospitalization, or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect, or is other important medical event;

Seroconversion - the production or increase in antibody concentration considered to be a transition from seronegative to seropositive reaction or as a clinically significant increase in predefined level of antibodies, demonstrating the immunogenicity of a vaccine.

Seroprotection - an antibody titer protecting against an identified infection(s);

Signal – an information that arises from one or multiple sources (including observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between a medicinal product, vaccine, tuberculin and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action;

Source documents – outgoing documents, data and records (e.g., case histories, hospital records, laboratory notes, memos, subjects' diaries or evaluation checklists, medicinal product dispensing records, recorded data from automated instruments (printouts), verified and authenticated copies or transcripts of sound tracks, microfiches, reversed images, microfilms or magnetic carriers, X-ray films, administrative documents, records kept at the pharmacy, laboratory and instrumental diagnostics department of health facilities);

Suspected medicinal product, vaccine, tuberculin – a medicinal product, vaccine, tuberculin, medical use of which is causally associated with clinical manifestations of any adverse reaction and/or lack of efficacy, and/or adverse event following immunization/tuberculin diagnostics occurred at its use.

Time interval following use of vaccine, tuberculin – an interval following immunization/tuberculin diagnostics ranging from day 1 to 24 months and depends on type of vaccine, tuberculin, and for most of them is 30 days;

Unexpected adverse reaction - an adverse reaction, the nature or severity of which is not consistent with the product information for medicinal product, vaccine, tuberculin contained in instructions for medical use/summary of products characteristics for medicinal product, vaccine, tuberculin);

Unlisted adverse reaction of medicinal product, vaccine, tuberculin – an adverse reaction whose nature or severity of manifestations is not consistent with the information in the applicant core safety information on medicinal product, vaccine, tuberculin. These adverse reactions include those whose nature, severity of manifestations, specificity or outcome is not consistent with the information in the applicant core safety information on medicinal product, vaccine, tuberculin, including reactions related to a specific pharmacological group of medicinal products, vaccines, tuberculin, which have not occurred at using the medicinal product, vaccine, tuberculin;

Vaccination (inoculation, active/passive immunization) – an artificial induction of immunity in humans to specific infectious diseases by injection of vaccine or immunoglobulin;

Vaccination failure - may be defined based on clinical manifestations of infectious disease with a laboratory confirmation of an absence of markers of this disease protection. Primary failure of vaccination can be due to non-production of its intended effect (lack of seroconversion or seroprotection), secondary one – due to congenital and/or acquired defects of immune system or inappropriate administration of the vaccine prescribed;

3. Other terms used in this Procedure are applied based on definitions specified in Bases of the Legislation of Ukraine on Health Care, Laws of Ukraine “On Medicines”, “On Population

Protection against Infectious Diseases”, “On Ensuring Sanitary and Epidemic Safety of the Population” and other healthcare regulations.

For pharmacovigilance purposes, personal data shall be processed according to the Law of Ukraine “On Personal Data Protection”.

## **II. GENERAL CONCEPTS OF PHARMACOVIGILANCE**

1. In Ukraine pharmacovigilance is ensured by application of international standards, observing rules and requirements established by this Procedure, and envisages a formation and functioning of pharmacovigilance system.

2. The pharmacovigilance system shall be established within the health care system on the national level and by the applicant of medicinal product, vaccine, tuberculin.

3. The pharmacovigilance system within the health care system shall be used to:

1) collect information on the risks of medicinal products, vaccines, tuberculin as regards patients’ or public health, in particular information referring to adverse reactions to medicinal products, vaccines, tuberculin, lack of efficacy of medicinal products, adverse event following immunization/tuberculin diagnostics (hereinafter – AEFI) (classification of AEFI is given in Annex 1 to this Procedure), and any other issues related to safety and efficacy of use of medicinal products, vaccines, tuberculin;

2) give a substantiated assessment of any information on risks relating to medicinal products, vaccines, tuberculin as regards the impact on patients’ or public health;

3) elaborate measures to prevent or minimize risks relating to medicinal products, vaccines, tuberculin;

4) apply regulatory measures affecting the validity of registration certificate for a medicinal product, vaccine, tuberculin, if applicable.

4. For pharmacovigilance purposes the Ministry of Health of Ukraine:

1) shall involve medical workers, applicants, patients and/or their legal representatives, etc.;

2) shall establish a procedure for performance of activities by heads of healthcare structural units of the Autonomous Republic of Crimea, the Oblast, Kyiv and Sebastopol city state administrations (hereinafter - healthcare structural units), heads of all health facilities regardless of types of ownership (hereinafter – health facilities), doctors, pharmacists, feldshers, obstetricians, chemists, nurses (hereinafter – medical workers), and rules, requirements to be observed by applicants of medicinal products, vaccines, tuberculin and their obligations stated in this Procedure;

3) shall regulate relations between structures involved in the process governing a circulation of medicinal product, vaccines, tuberculin.

5. Public Enterprise “The State Expert Center of the Ministry of Health of Ukraine” (hereinafter – the Center) shall perform pharmacovigilance activities according to the legislative requirements.

In the healthcare system pharmacovigilance shall be performed at local, administrative territorial and central levels, and in the pharmaceutical sector – by applicants.

6. In order to exercise the powers relating to pharmacovigilance entrusted to it the Center:

1) shall take measures to optimize the submission of report forms on adverse reaction to medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal product, and/or AEFI (hereinafter – report form) and information on other issues relating to safety and efficacy of medicinal products, vaccines, tuberculin by medical workers to the Center including through involving the Center’s representatives for pharmacovigilance in administrative territorial units in this process.

2) shall promote the submission by patients and/or their legal representatives of reports on adverse reaction of medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal product, and/or AEFI and information on other issues relating to safety and efficacy of the use of medicinal products, vaccines, tuberculin through any available means;

3) shall take appropriate measures to obtain accurate and verifiable data for the evaluation of report forms on adverse reaction of medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal product, and/or AEFI, and other issues relating to safety and efficacy of medicinal products, vaccines, tuberculin;

4) shall inform the public of important data on safety and efficacy of the use of medicinal products, vaccines, tuberculin through any available means;

5) shall perform an audit of applicant’s pharmacovigilance system;

6) shall inform the Ministry of Health of Ukraine on applicants who fail to meet rules, requirements and obligations stated in this Procedure.

7. The applicant shall set up and operate a pharmacovigilance system(s).

8. For pharmacovigilance purposes the applicant:

1) shall have (permanently and continuously) at his disposal an authorized qualified person responsible for pharmacovigilance (hereinafter - QPPV);

2) shall create, maintain and make available on the Center’s request a pharmacovigilance system master file (hereinafter - PSMF);

3) shall operate a risk management system for a medicinal product, vaccine, tuberculin (if applicable);

4) shall monitor the outcome of risk minimization measures which are contained in the risk management plan or which are conditions for issuing the registration certificate;

5) shall update the risk management system and monitor pharmacovigilance data to detect new risks, changes to known risks, changes to the benefit-risk balance of medicinal products, vaccines, tuberculin;

6) shall perform a regular audit of his own pharmacovigilance system(s).

9. Each pharmacovigilance system of the applicant may have only one QPPV. If a QPPV does not reside in Ukraine a single contact person responsible for pharmacovigilance (hereinafter – CPPV) who resides and operates in Ukraine and is accountable to QPPV shall be assigned at the territory of Ukraine

10. The applicant shall submit to the Center information on QPPV, CPPV, namely: full name, contact details, document (copy of diploma) evidencing a medical or pharmaceutical education, and document confirming power of QPPV, CPPV.

### **III. RECEIPT AND EXCHANGE OF INFORMATION ON SAFETY AND EFFICACY OF MEDICINAL PRODUCT, VACCINE, TUBERCULIN**

1. Information on safety and efficacy of a medicinal product, vaccine, tuberculin shall come to the Center from:

- 1) medical workers;
- 2) legal and natural persons performing an economic activity on medical practice;
- 3) health facilities;
- 4) applicants;
- 5) patients and/or their legal representatives according to report form on adverse reaction of medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal product, and/or adverse event following immunization/tuberculin diagnostics to be submitted by patient and/or his legal representative, which is given in Annex 2 to this Procedure;
- 6) the State Service of Ukraine for Medicinal Products and Narcotics Control and its territorial bodies;
- 7) the Center's representatives for pharmacovigilance in administrative territorial units;
- 8) World Health Organization (hereinafter - WHO), the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), the Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA), the federal health department of Canada (Health Canada), the Therapeutic Goods Administration of Australia (TGA), the Swiss Agency for Therapeutic Products (Swissmedic), the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) and other international organizations and agencies;
- 9) official information sources and periodicals;
- 10) other sources.

2. The Center shall submit information on safety and efficacy of medicinal products, vaccines, tuberculin to:

- 1) the State Service of Ukraine for Medicinal Products and Narcotics Control (in hard copy or electronic form):

copies of obtained report forms on unexpected adverse reactions, adverse reactions resulted in a patient's death, cluster of adverse reactions, and/or lack of efficacy of medicinal product (except for vaccines, tuberculin), if there is a causal association between them and use of the medicinal product (except for vaccines, tuberculin) – within 48 hours after receipt of information, which confirms a causal association between them and use of the medicinal product (except for vaccine, tuberculin), by the Center;

copies of obtained report forms on a cluster of adverse reactions and/or serious adverse reactions relating to failures occurring in manufacturing of vaccine, tuberculin including administration device supplied by the manufacturer of vaccine, tuberculin, if there is a causal association between them and use of the vaccine, tuberculin – within 48 hours after receipt of information, which confirms a causal association between them and use of the vaccine, tuberculin, by the Center.

If the deadline day for submitting information is a day-off or holiday the information shall be submitted the next working day;

2) the applicant (concerning medicinal products, vaccines, tuberculin, which he represents at the pharmaceutical market of Ukraine:

on unexpected adverse reactions, adverse reactions resulted in a patient's death, cluster of adverse reactions, and/or lack of efficacy of medicinal products (except for vaccines, tuberculin), if there is a causal association between them and use of the medicinal product (except for vaccines, tuberculin) – within 48 hours after receipt of information, which confirms a causal association between them and use of the medicinal product (except for vaccines, tuberculin), by the Center;

on a cluster of adverse reactions and/or serious adverse reactions relating to failures occurring in manufacturing of vaccine, tuberculin including administration device supplied by the manufacturer of vaccine, tuberculin, if there is a causal association between them and use of the vaccine, tuberculin – within 48 hours after receipt of information, which confirms a causal association between them and use of the vaccine, tuberculin, by the Center;

on adverse reactions of medicinal product, vaccine, tuberculin, and/or lack of efficacy of medicinal product, and/or AEFI, information about which was submitted to the Center over a period of time - upon his request.

If the deadline day for submitting information is a day-off or holiday the information shall be submitted the next working day;

3) Ministry of Health of Ukraine:

upon the request;

annually in the form of report – until March 1 next year. If March 1 is a day-off or holiday the report shall be submitted the next working day;

annually in the form of report on registered cases of infectious diseases controlled by specific immunoprophylaxis in vaccinated persons – until March 20 next year. If March 20 is a day-off or holiday the report shall be submitted the next working day;

quarterly in the form of report on cumulative data about cases of adverse reactions after using vaccine, tuberculin - till the 30<sup>th</sup> day of the month after the reporting month. If the 30<sup>th</sup> day of the month after the reporting month is a day-off or holiday the report shall be submitted the next working day;

copies (in hard copy and/or electronic form) of obtained report forms on unexpected adverse reactions, adverse reactions resulted in a patient's death, cluster of adverse reactions, and/or lack of efficacy of medicinal products (except for vaccine, tuberculin), if there is a causal association between them and use of the medicinal product (except for vaccine, tuberculin) – within 48 hours after receipt of information, which confirms a causal association between them and the use of the medicinal product (except for vaccine, tuberculin), by the Center;

copies (in hard copy and/or electronic form) of obtained report forms on a cluster of adverse reactions and/or serious adverse reactions relating to failures occurring in manufacturing of vaccine, tuberculin including administration device supplied by the manufacturer of vaccine, tuberculin, if there is a causal association between them and use of the vaccine, tuberculin, and copies of protocol of investigation and establishment of a causal association between serious and/or cluster of AEFI/tuberculin diagnostics and use of vaccines, tuberculin (hereinafter – AEFI investigation

protocol) according to the form given in Annex to the Regulations of central and regional group of quick response to AEFI/tuberculin diagnostics approved by MoH Ukraine Order of September 26, 2016 № 996 - within 48 hours after receipt of information, which confirms a causal association between them and use of vaccines, tuberculin, by the Center;

copies (in hard copy and/or electronic form) of obtained report forms on immunization/tuberculin diagnostics programme error-related AEFI during use of vaccine, tuberculin if information according to the AEFI investigation protocol is available - within 48 hours after receipt of information, which confirms a causal association between them and use of vaccine, tuberculin, by the Center;

copies (in hard copy and/or electronic form) of obtained report forms on AEFI (fatal case) registered within 30 days following immunization/tuberculin diagnostics - within 48 hours after receipt of a report form by the Center;

If the deadline day for submitting information is a day-off or holiday the information shall be submitted the next working day;

#### 4) Central Group of Quick Response:

copies (in hard copy and/or electronic form) of obtained report forms on AEFI containing information on clinical manifestations not specified in the instructions for medical use or a List of clinical manifestations of adverse reactions after using vaccines, tuberculin (hereinafter – List of clinical manifestations) (annex 3), Time intervals between use of vaccine, tuberculin and clinical manifestations of adverse reactions (hereinafter – Time intervals) (annex 4), report forms, which became a basis for generating a signal - within 48 hours after receipt of information, which confirms a causal association between such AEFI and use of a batch(es) of vaccine, tuberculin, by the Center;

copies (in hard copy and/or electronic form) of obtained report forms on AEFI (fatal case) registered within 30 days following immunization/tuberculin diagnostics - within 48 hours after receipt of a report form by the Center;

copies (in hard copy and/or electronic form) of obtained report forms on immunization/tuberculin diagnostics programme error-related AEFIs during use of vaccine, tuberculin if information according to the AEFI investigation protocol is available - within 48 hours after receipt of information, which confirms a causal association between them and use of vaccine, tuberculin, by the Center;

If the deadline day for submitting information is a day-off or holiday the information should be submitted the next working day;

#### 5) WHO;

6) upon the request of natural and legal persons regardless of types of ownership in the cases envisaged by legislation.

3. The State Administration of Ukraine on Medicinal Products and Narcotics Control shall submit to the Center (in hard copy and/or electronic form) all obtained report forms (including AEFI and information on fatal case) regardless of their source - within 48 hours after receipt of them. If the deadline is a day-off or holiday the information shall be submitted the next working day.

4. The Center shall analyze information submitted by the State Administration of Ukraine on Medicinal Products and Narcotics Control according to item 3 of this section, and submit results of

this analysis to the State Administration of Ukraine on Medicinal Products and Narcotics Control within 48 hours after receipt of the above information. If the deadline is a day-off or holiday the information shall be submitted the next working day.

5. Territorial bodies of the State Administration of Ukraine on Medicinal Products and Narcotics Control shall give the Center's representatives for pharmacovigilance in administrative territorial units and the State Administration of Ukraine on Medicinal Products and Narcotics Control copies (in hard copy and/or electronic form) of all obtained report forms - within 48 hours after receipt of them. If the deadline is a day-off or holiday the information shall be submitted the next working day.

6. The Center's representatives for pharmacovigilance in administrative territorial units shall submit to the Center report forms and/or their copies (in hard copy and/or electronic form):

on cases of adverse reactions which resulted in patient's death, and/or lack of efficacy of medicinal products - within 48 hours after receipt of them;

about any other cases of adverse reactions - within 15 days after receipt of them.

If this deadline is a day-off or holiday the information shall be submitted the next working day.

7. The Center shall submit report forms on adverse reactions, and/or lack of efficacy of medicinal products, which resulted in patient's death, to healthcare structural units within 48 hours after receipt of them. If the deadline is a day-off or holiday the information shall be submitted the next working day.

8. Healthcare structural units when obtain reports forms or their copies (in hard copy and/or electronic form) on adverse reactions, and/or lack of efficacy of medicinal products, which resulted in patient's death shall submit this information to the relevant clinical expert commission, which makes a clinical expert evaluation of the medical assistance and medical service quality as regards adverse reactions and/or lack of efficacy of medicinal products, which resulted in patient's death, within 48 hours after receipt of such information. If the deadline is a day-off or holiday the information shall be submitted the next working day.

9. A clinical expert evaluation of medical assistance and medical service quality as regards adverse reactions and/or lack of efficacy of medicinal products, which resulted in patient's death, shall be performed by a clinical expert commission involving the Center's representatives for pharmacovigilance from the respective administrative territorial unit and other specialists by arrangement.

10. Based on the results of its work the clinical expert commission shall draw up a protocol and conclusions on adverse reactions and/or lack of efficacy of medicinal products, which resulted in patient's death, and submit them to the Ministry of Health of Ukraine, the Center, and the State Administration of Ukraine on Medicinal Products and Narcotics Control within 24 hours of drawing up them. If the deadline is a day-off or holiday the information shall be submitted the next working day.

#### **IV. PROCEDURE FOR PERFORMANCE OF PHARMACOVIGILANCE ACTIVITIES BY HEADS OF HEALTHCARE STRUCTURAL UNITS, HEADS OF HEALTH FACILITIES, AND MEDICAL WORKERS**

1. Heads of healthcare structural units:

1) shall appoint a responsible person for drawing up a report according to primary medical record form № 69 “Report on cases of adverse reactions of medicinal products, vaccines, tuberculin and/or lack of efficacy of medicinal products and/or adverse events following immunization/tuberculin diagnostics at health facilities for 20\_\_\_” (hereinafter – Form № 69) given in Annex 5 to this Procedure within the timeline stated in subitem 2 of this item (a cumulative report shall be drawn up based on data from Form 69 that are submitted by responsible persons for pharmacovigilance of health facilities according to Form № 69 within the timeline specified in subitem 2 of item 3 of this section);

2) shall ensure a timely submission to the Center of the report according to Form № 69 till January 30 of the year after the reporting year to be signed by a head of appropriate healthcare structural unit (in hard copy and electronic form (Excel table)). Postal and e-mail addresses shall be specified on the cover page of Form № 69 (a cumulative report according to Form № 69 (in hard copy)) shall be submitted to the Center with a cover letter at the address specified in Form № 69. A cumulative report according to Form № 69 (in electronic form)) shall be sent at the address specified in Form № 69)

3) shall ensure a timely submission to the Center of AEFI investigation protocols and report forms according to the form given in Annex 6 to this Procedure;

4) shall appoint a responsible person for drawing up a general report about registered cases of infectious disease controlled by specific immunoprophylaxis in vaccinated persons according to epidemiological investigation forms (hereinafter – general report) using template given in Annex 7 to this Procedure. The general report shall be drawn up based on epidemiological investigation forms about cases of infectious disease controlled by specific immunoprophylaxis (hereinafter - epidemiological investigation form) using template given in Annex 8 to this Procedure;

5) shall ensure a timely submission of a general report (in electronic form) to the Center till January 30 of the year following the reporting year. A general report shall be sent to electronic address specified in instructions for completing it;

6) shall ensure quarterly a timely submission of cumulative data on cases of adverse reactions after using vaccine, tuberculin (hereinafter – cumulative data) (in hard copy or electronic form) with a cover letter signed by a head of appropriate healthcare structural unit according to the form given in the List of clinical manifestations) at the postal and electronic addresses specified in instructions for drawing up cumulative data till the 10th day of the month following the reporting month. If the deadline is a day-off or holiday the cumulative data shall be submitted the next working day;

7) shall hear biannually a report on status of submission by medical workers of information about cases of adverse reactions to medicinal products, vaccines, tuberculin, lack of efficacy of medicinal products, AEFI at the meetings of healthcare structural unit’s boards;

8) introduce the Center’s representative for pharmacovigilance in administrative territorial units to certification commissions at the subordinated healthcare structural units (by arrangement).

2. A head of State Enterprise “Ukrvaktsyna” of the Ministry of Health of Ukraine (hereinafter – Ukrvaktsyna) shall appoint a responsible person for drawing up and submitting report on quantitative distribution of vaccines by administrative territorial units to the Center according to the form given in Annex 9 to this Procedure within 48 hours after receipt of a written request from it.

3. Heads of health facilities shall appoint a deputy chief doctor for medical work (or other person with a higher medical or pharmaceutical education) to be a person responsible for pharmacovigilance, and ensure:

1) timely submission of report forms and information on any other issues related to safety and efficacy of use of medicinal products, vaccines, tuberculin by medical workers within timelines specified in item 9 of this section;

2) timely submission to an appropriate healthcare structural unit of a report according to Form N 69 (except for table 1001) till January 20 of the year following the reporting year (in hard copy and electronic form (Excel table)). A report according to Form N 69 (in hard copy and electronic form) with a cover letter signed by a head of health facility shall be sent to postal and electronic addresses of appropriate healthcare structural units;

3) timely submission to healthcare structural units of primary medical record form № 058/o “Expedited notification of infectious disease, food poisoning, acute professional poisoning, uncommon reaction to immunization” approved by MoH Ukraine Order of January 10, 2006 № 1 registered at the Ministry of Justice on June 08, 2006 under № 686/12560 (hereinafter – notification of infectious disease) in the case of infectious disease occurring in the patient vaccinated against relevant infection within 12 hours after detecting such patient.

4. A health facility’s person responsible for pharmacovigilance:

1) shall draw up standard operating procedures for taking measures in the case of occurring adverse reactions to medicinal product, vaccine, tuberculin, lack of efficacy of medicinal product, AEFI, and familiarize medical workers with them;

2) shall record report forms;

3) shall draw up a report according to Form № 69 (except for table 1001) and submit to an appropriate healthcare structural unit within the term specified in subitem 2 of item 3 of this section. A report according to Form № 69 shall be drawn up based on data of report form copies submitted by medical workers of a health facility. A report according to Form № 69 (except for table 1001) (in hard copy and electronic form (Excel table)) with a cover letter signed by a head of health facility shall be sent to postal and electronic addresses of relevant healthcare structural unit;

4) shall collaborate with the Center’s workers responsible for pharmacovigilance in administrative territorial units on pharmacovigilance-related issues (analysis of adverse reactions at using medicinal products, vaccines, tuberculin, lack of efficacy of medicinal products, AEFI, detection of bias, training, etc.);

5) shall promote to implementation of risk minimization measures relating to medicinal products, vaccines, tuberculin;

6) record adverse reactions after using vaccines, tuberculin;

7) draw up and submit to a responsible person of a healthcare structural unit cumulative data about cases of adverse reactions after using vaccine, tuberculin monthly till the 5<sup>th</sup> day of the month following the reporting month using a template given in the List of clinical manifestations. If the deadline is a day-off or holiday the cumulative data about cases of adverse reactions after using vaccine, tuberculin shall be submitted the next working day. Cumulative data (in hard copy and electronic form (Excel table)) with a cover letter signed by a head of health facility shall be sent to postal and electronic addresses of an appropriate healthcare structural unit.

5. Heads of health facilities shall ensure a submission of copies of a health facility’s primary medical records upon the Center’s request.

6. Medical workers shall inform:

1) patients (parents or legal representatives) about those adverse reactions, which may occur at using medicinal products and the need for seeking medical attention at a health facility if their health state is getting worse after using medicinal product;

2) persons who are subject to immunization, tuberculin diagnostics (parents or legal representatives) on those adverse reactions, which may occur after using a certain vaccine, tuberculin, and the need for seeking medical attention at a health facility if their health state is getting worse following immunization/tuberculin diagnostics.

7. Medical workers shall detect:

1) adverse reactions to medicinal product, vaccine, tuberculin, lack of efficacy of medicinal product, any worsening of health state and any other safety and efficacy concerns related to medicinal product, vaccine, tuberculin if a patient, vaccinated person or person undergone to tuberculin diagnostics seeks medical attention at a health facility;

2) AEFI and other safety and efficacy concerns related to vaccine, tuberculin if a patient, vaccinated person or person undergone to tuberculin diagnostics seeks medical attention.

8. Medical workers shall timely submit to the Center report forms on any adverse reaction to medicinal product, vaccine, tuberculin, lack of efficacy of medicinal product and AEFI within timelines specified in item 9 of this section.

9. A report form shall be submitted in hard copy and/or electronic form. Electronic template for a report form can be found at <https://aisf.dec.gov.ua>. A report form copy shall be submitted to a health facility's person responsible for pharmacovigilance in order to draw up a report according to Form № 69.

A report form shall be submitted to the Center within the following timelines:

for non-serious adverse reaction/AEFI at using medicinal product - within 90 days;

for serious adverse reaction/AEFI at using medicinal product - within 15 days;

for lack of efficacy at using medicinal product - within 48 hours;

for adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal products, and/or AEFI/tuberculin diagnostics, which resulted in patient's death – within 48 hours.

If the above deadlines are a day-off or holiday the information shall be submitted the next working day.

10. Doctor shall enter information about adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal products, and/or AEFI/tuberculin diagnostics to primary medical records.

11. Medical workers shall submit reports forms on AEFI after using vaccines, tuberculin within 48 hours after registering AEFI to the Center and groups of quick response of appropriate healthcare structural units (hereinafter – regional group of quick response). If the deadline is a day-off or holiday the information shall be submitted the next working day.

12. A report form shall be submitted to the Center and regional group of quick response in hard copy and/or electronic form. A report form copy shall be submitted to a health facility's person responsible for pharmacovigilance in order to draw up a report according to Form № 69.

13. Requirements for setting up, composition and objectives of regional and central groups of quick response to AEFIs are set forth in the Regulations of Central and Regional Group of Quick Response in Managing AEFI/Tuberculin Diagnostics approved by MoH Ukraine Order of September 26, 2016 № 996.

14. Medical workers of a health facility, where vaccination is performed, shall monitor and submit information on cases of infectious disease controlled by specific immunoprophylaxis occurred in the vaccinated persons.

If a case of infectious disease is detected medical workers shall complete primary medical record (notification of infectious disease) and submit it to a healthcare structural unit within 12 hours after detecting such a disease. If the deadline is a day-off or holiday the information shall be submitted the next working day.

15. When a report on infectious disease is obtained a responsible person of the healthcare structural unit shall perform an epidemiological investigation in place where a disease occurs/is detected.

If during the epidemiological investigation a case of infectious disease is confirmed to occur in the person vaccinated against the relevant infection a responsible person of a healthcare structural unit shall complete an epidemiological investigation form within 48 hours of the date of confirmation. If the deadline is a day-off or holiday the information shall be submitted the next working day.

16. A responsible person of healthcare structural unit shall draw up a general report based on data from epidemiological investigation forms. The general report in electronic form with a cover letter shall be submitted to Center at the electronic address specified in instructions for completing it annually till January 30 of the year following the reporting year.

## **V. PERFORMANCE OF PHARMACOVIGILANCE ACTIVITIES BY APPLICANT**

### **1. General requirements for applicant's pharmacovigilance system**

1. The applicant shall set up, provide and ensure functioning a pharmacovigilance system in his disposal in Ukraine that is a compulsory condition for medicinal product, vaccine, tuberculin circulation at the territory of Ukraine.

2. The applicant's pharmacovigilance system shall include elements, which allow a safety monitoring of medicinal product/vaccines, tuberculin and identification of any changes in benefit-risk balance, namely:

1) availability of a QPPV at applicant's disposal. If an applicant resides in Ukraine a QPPV shall be on the applicant's staff. If a QPPV does not reside in Ukraine a single CPPV at the territory of Ukraine subordinated to the applicant's QPPV shall be appointed. QPPV and CPPV details in Ukraine shall be included in the applicant's PSMF. QPPV/CPPV in Ukraine shall have higher medical or pharmaceutical education (pharmacist, clinical pharmacist). If QPPV/CPPV in Ukraine has only pharmaceutical education he/she shall have a possibility to consult the person with higher medical education (if necessary). Each pharmacovigilance system may have only one QPPV/CPPV in Ukraine. A procedure for QPPV and/or CPPV substitution if he/she is absent shall be provided for;

2) existence of an organizational structure of the pharmacovigilance system, its update and maintenance;

3) documenting all procedures and processes;

- 4) developing and ensuring the functioning of databases used by the applicant for pharmacovigilance related purposes;
- 5) involving (if applicable) other legal and/or natural persons and enterprises, institutions, organizations in pharmacovigilance by entering into contractual relationship;
- 6) provision of the applicant's staff training for performing pharmacovigilance related activities;
- 7) establishing a quality system of pharmacovigilance;
- 8) document management with regard to pharmacovigilance including storage and archiving;
- 9) creation and maintenance of the risk management system.

3. QPPV/CPPV in Ukraine have responsibilities related to (but not limited to):

- 1) establishment and maintenance of the system of collection, assessment and submission of information on adverse reactions, lack of efficacy, AEFI, other data relating to safety and efficacy of medicinal product, vaccine, tuberculin, and any other data needed to assess risk and benefit of medicinal product, vaccine, tuberculin including the quality system to the Center;
- 2) drawing up (for CPPV, if applicable) and/or submission of periodic safety update reports (hereinafter - PSUR) according to the frequency of submitting PSURs for medicinal products, vaccines, tuberculin by an international non-proprietary name of active pharmaceutical ingredient or combination of active pharmaceutical ingredients (hereinafter – frequency of submitting PSUR) (annex 10);
- 3) drawing up (for CPPV, if applicable) and/or submission of risk management plans;
- 4) submission upon any Center's request of additional information needed for assessment of the benefit-risk balance of medicinal product, vaccine, tuberculin including data relating to the volume of sales of medicinal product or estimate of the population exposed to medicinal product, vaccine, tuberculin;
- 5) ensuring submission of any data relevant to the benefit-risk assessment of medicinal product, vaccine, tuberculin including information on post-registration safety and efficacy studies of medicinal product, vaccine, tuberculin;
- 6) notifying the Center, taking the appropriate measures and introducing appropriate changes and additions to the safety information for a medicinal product, vaccine, tuberculin included in its instructions for medical use/summary of product characteristics in the case of detection of previously unknown unsafe properties of medicinal product, vaccine, tuberculin, which resulted or may result in serious sequela for human health and life or shift in the benefit-risk balance toward risk, which have become known to QPPV/CPPV;
- 7) ensuring the applicant's staff training for performing pharmacovigilance related activities;

4. In the case of changes in the pharmacovigilance system the applicant shall update it, maintain and submit PSMF, a document, which includes a detailed description of the pharmacovigilance system used by the applicant with respect to one or more medicinal products, vaccines, tuberculin upon the Center's request. PSMF shall be compiled according to the structure given in Annex 11 to this Procedure, and contain information on:

- 1) QPPV/CPPV;

- 2) the organisational structure of the applicant, including the pharmacovigilance system, which ensures collection, determination, evaluation and submission of reliable information on adverse reactions, lack of efficacy, AEFI, and any other data necessary for assessment of benefit-risk balance of medicinal product, vaccine, tuberculin;
- 3) natural and/or legal persons involved in the performance of pharmacovigilance activities by the applicant;
- 4) sources of safety data related to the use of medicinal products, vaccines, tuberculin;
- 5) list and brief description of the functionality of databases used by the applicant for the performance of the pharmacovigilance activities;
- 6) pharmacovigilance processes including a list of standard operating procedures used for pharmacovigilance, description of documents related to pharmacovigilance, including those kept in the archives, other types of documents related to pharmacovigilance;
- 7) pharmacovigilance system performance;
- 8) quality system for the performance of pharmacovigilance activities, including a description of the applicant's staff training system giving the information on training taking into account functions of the applicant's staff with a brief description of the applicant's responsibilities to assure quality of the pharmacovigilance system, including the pharmacovigilance system audit and audit of natural and/or legal persons involved in the performance of pharmacovigilance activities by the applicant.

## **2. Requirements for reporting adverse reactions to medicinal products, vaccines, tuberculin and/or lack of efficacy of medicinal products by applicant**

1. While the applicant submits reports on adverse reactions to medicinal products, vaccines, tuberculin and/or lack of efficacy of medicinal products he shall submit to the Center by any means on a timely basis:

- 1) reliable information on all serious adverse reactions to medicinal products, vaccines, tuberculin, registered during their use in Ukraine and medically confirmed, which became known to him, if there is a causal association between adverse reactions and use of the medicinal product, vaccine, tuberculin – within 15 days following the day of the receipt of such information;
- 2) reliable information on all non-serious adverse reactions to medicinal products, vaccines, tuberculin, registered during their use in Ukraine and medically confirmed, which became known to him, if there is a causal association between adverse reactions and use of the medicinal product, vaccine, tuberculin – within 90 days following the day of the receipt of such information;
- 3) reliable information on all unexpected serious adverse reactions to medicinal products/vaccines,/tuberculin, which resulted in patient's death or was life threatening, on any cases of suspected transmission of an infectious agent via a medicinal product, registered at the territory of other country and medically confirmed, which became known to him, if there is a causal association between them and use of the medicinal product, vaccine, tuberculin – within 15 calendar days following the day of the receipt of such information;
- 4) reliable information on failures occurring in manufacturing of vaccine, tuberculin including administration device – within 48 hours of the receipt of such information.

If the deadline day for submitting information is a day-off or holiday, the information shall be submitted the next working day;

5) information on any other cases of adverse reactions to medicinal products, vaccines, tuberculin registered at the territory of other country, and which became known to him – as part of the next PSUR for medicinal product, vaccine, tuberculin;

6) reliable information on cases of lack of efficacy, which were registered in Ukraine, and occurred when:

life-threatening diseases or critical conditions are treated, unless the reporter (primary source) has specifically stated that the lack of efficacy was due to disease progression and was not related to the medicinal product;

vaccines are used;

contraceptives are used.

Information shall be submitted within 15 calendar days following the day of its receipt. If the deadline day for submitting information is a day-off or holiday the information shall be submitted the next working day;

7) information on any other identified cases of lack of efficacy of the medicinal product, which became known to him – as part of the next PSUR.

2. Reports on adverse reactions to medicinal products, vaccines, tuberculin and/or lack of efficacy of medicinal products shall be submitted together with the information specified in item 7 of this chapter in hard copy and/or electronic form, which can be found at <https://aisf.dec.gov.ua>.

3. The applicant shall submit a report on adverse reaction to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product to the Center in the form of information on adverse reaction to medicinal product, vaccine, tuberculin and lack of efficacy of medicinal product that occurs in a single patient at a specific point of time.

4. The applicant shall take into account reports on cases of adverse reactions to medicinal products, vaccines, tuberculin and/or lack of efficacy of medicinal product received by him electronically or by any other appropriate means from patients and/or their legal representatives or medical workers.

5. The applicant shall collaborate with the Center in the detection of duplicates of reports on adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product.

6. The minimum information in a report on case of adverse reaction to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product shall include at least an identifiable reporter, an identifiable patient, an adverse reaction/lack of efficacy, and a suspected medicinal product(s), vaccine(s), tuberculin(s).

7. When the applicant submits a report on case of adverse reaction to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product he shall submit all available information on each particular case, including:

1) administrative information (type of report, date, unique case report identification number, and, unique reporter's identifier; date information was first received from source, and date of receipt of the most recent information (full precision date should be used); other identifiers and their sources, and references to additional available documents held by sender of the report on adverse reaction to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product, if applicable);

2) literature reference(s) in accordance with international and national publication requirements – for information on adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product (according to data from literature sources) including a comprehensive English or Ukrainian summary of the article. If the article is written in English, its summary translation into Ukrainian shall be provided. Upon the Center’s request the applicant that transmitted the initial report shall provide a copy of the relevant article taking into account the copyright restrictions, and a full translation of that article into Ukrainian if the article is written in English.

3) type, name and sponsor’s number or registration number of a safety and efficacy study of medicinal product, vaccine, tuberculin - for reports on adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product observed during this non-interventional study;

4) information on primary source (s) (information that identifies a report source, including a name of the country where the reporter resides, and his professional qualifications);

5) information identifying the patient and parent in the case of a parent-child report, including age at the time of the onset of the adverse reaction/lack of efficacy, age group, gestation period when reaction/event was observed in the foetus, weight, height or gender, last menstrual date and/or gestation period at time of the onset of adverse reaction/lack of efficacy;

6) patient’s relevant medical history and concurrent conditions;

7) the trade name (s) of the medicinal product (s)/vaccine(s)/tuberculin suspected to be related to the occurrence of the adverse reaction and/or lack of efficacy, including concomitant medicinal products, vaccines, tuberculin or, where the name is not known, the active pharmaceutical ingredient(s), and any other characteristics that allow for the identification of the medicinal product(s)/vaccine(s)/tuberculin, including the name of the applicant/manufacturer, number of registration certificate, country where medicinal product, vaccine, tuberculin is registered, pharmaceutical form and route of administration, indication for use in the case, dose administered, start date and end date of administration, action(s) taken for elimination of adverse reaction manifestations, including drug therapy, effect of the dechallenge and rechallenge for suspect medicinal products/vaccine(s);

8) for biological medicinal product(s), the batch number(s). A follow-up procedure shall be in place to obtain the batch number where it is not specified in the initial report;

9) concomitant medicinal products, vaccines, tuberculin which are not suspected to be related to

the occurrence of the adverse reaction/lack of efficacy, and past-medical drug therapy for the patient (and for the parent), where applicable;

10) information on the suspected adverse reaction(s)/lack of efficacy (start date and end date of the or duration, seriousness, outcome of the suspected adverse reaction(s)/lack of efficacy at the time of last observation of the patient, time intervals between beginning of suspect medicinal product, vaccine, tuberculin administration and start of reaction/lack of efficacy, the terms and data specified in the documents relating to adverse reaction(s)/lack of efficacy which were used by a primary source for description of adverse reaction (s)/lack of efficacy, and a country at the territory of which the adverse reaction(s) and/or lack of efficacy occurred.

11) results of tests and procedures relevant to the investigation of the patient;

12) date and reported cause(s) of death, including autopsy-determined cause(s) of death;

13) description of the case (any relevant information is given, if possible).

The information should be presented in a logical time sequence (development of the situation over time, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained, any relevant autopsy and post-mortem findings; information on a causal association between manifestations of adverse reaction/lack of efficacy and use of suspect medicinal product, vaccine, tuberculin; reason for nullifying or amending the report on adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal product).

8. The applicant shall record the details necessary for obtaining follow-up information on adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy of medicinal products. The follow-up of reports shall be adequately documented.

### **3. Requirement for submission of periodic safety update reports by applicant**

1. An applicant shall submit to the Center a full periodic safety update report according to the structure of PSUR for medicinal product, vaccine, tuberculin and its completion requirements set out in Annex 12 to this Procedure. PSUR shall be submitted in hard copy, annexes of the PSUR may be submitted in electronic form. Full PSUR shall be submitted in Ukrainian or English with frequency specified in item 2 of this chapter. In case of submission of the periodic safety report in English Section III "Actions taken in the reporting interval for safety reasons", Section IV "Changes to reference safety information", Section XVIII "Integrated benefit-risk analysis for registered indications" and Section XIX "Conclusions and actions" or other sections that contain such information shall be submitted in Ukrainian. Section XVI "Signal and risk evaluation" and Section XVII "Benefit evaluation" of PSUR shall be submitted in Ukrainian upon the Center's request.

2. PSUR shall be submitted with the following frequency:

1) for the medicinal product registered in Ukraine as the first country of the world or first registered in any country of the world – every 6 months during the first 2 years (regardless of the placing of medicinal product on the market), once a year for the following 2 years and at three-yearly intervals thereafter starting from the date of the registration of medicinal product. If the timeline for submission of PSUR specified in this sub-item coincides with the timeline in accordance with the frequency of submission of periodic safety reports a periodic safety report shall be submitted in accordance with the frequency of submission of PSUR;

2) or in accordance with the frequency specified in the registration certificate, when issued, as per subitem 1 of item 3 of this chapter;

3) or in accordance with the timeline as per the frequency of submission of PSUR;

4) for medicinal products to be registered after this Order taking effect - in accordance with the timelines as per the frequency of submission of PSUR, or at the applicant's option but not less frequently than as established by legislation;

5) upon request of the Center.

3. PSUR shall be submitted for all medicinal products except for generic medicinal products, medicinal products with well-established medicinal use, traditional herbal and homeopathic medicinal products unless the submission of PSUR for such medicinal products is:

1) a condition for issuing registration certificate;

2) requested by the Ministry of Health of Ukraine and/or the Center on the basis of concerns relating to pharmacovigilance data or due to the lack of PSUR for an active pharmaceutical ingredient after the registration certificate has been granted (for example, when the effect of registration certificate of the reference medicinal product has been suspended in Ukraine);

3) the timelines are determined by the frequency of submission of PSUR.

Applicants of the medicinal products, where periodic safety reports are no longer required to be submitted routinely, shall continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts on the benefit-risk balance or the product information given in the instructions for medical use/summary of product characteristics of the medicinal product.

4. Periodic safety report shall be prepared and submitted according to the following timelines:

1) within 70 calendar days of the data lock point (day 0) - for PSUR covering reporting intervals up to 12 months (including reporting intervals of exactly 12 months);

2) within 90 calendar days of the data lock point (day 0) - for PSUR covering reporting intervals in excess of 12 months;

3) within the timeline normally specified in the request - for PSUR to be submitted upon the request;

4) within 90 calendar days of the data lock point (day 0) – for PSUR in other cases.

5. To change the frequency and/or dates of submission of PSUR the applicant shall submit an application for introduction of changes into registration materials during the validity period of registration certificate according to the procedure established by legislation of Ukraine. This refers to cases when the applicant expresses a wish to submit a PSUR with other frequency but not less frequently than the timeline specified by legislation.

6. For the re-registration of the medicinal product, vaccine, tuberculin in Ukraine, in addition to the documents required for the expert evaluation of materials for the state re-registration of the medicinal product, vaccine, tuberculin according to legislation of Ukraine the applicant shall submit to the Center cumulative safety data related to medical use of medicinal product, vaccine, tuberculin in Ukraine covering the validity period of the last registration certificate according to the form given in Annex 13 to this Procedure.

7. Unless otherwise specified in the provisions relating to the frequency of submission of PSUR, and if the frequency of submission of PSUR is not specified as a condition for issuing the registration certificate, a single PSUR shall be prepared by the applicant for all medicinal products containing the same active pharmaceutical ingredient (hereinafter – API). A PSUR shall cover all indications, routes of administration, dosage forms and strengths, irrespective of whether such medicinal products, vaccines, tuberculin is/are registered under different trade names and according to different types of applications for registration. Where relevant, data relating to a particular indication, dosage form, route of administration or strength shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly.

8. Unless otherwise specified in the provisions relating to the frequency of submission of PSUR, and if the frequency of submission of PSUR is not specified as a condition for issuing the registration certificate, and if the API that is the subject of the PSUR is also registered as a component of a fixed combination medicinal product, the applicant shall either submit a separate

PSUR for the combination of APIs which are registered by the same applicant, with cross references to the single-API PSUR(s), or provide the combination data within the single-API PSUR.

9. PSUR shall contain:

1) summaries of data relevant to the benefits and risks of the medicinal product(s), vaccine(s), tuberculin, including results of all studies with a consideration of their potential impact on the registration certificate;

2) a scientific evaluation of the benefit-risk balance of the medicinal product(s), vaccine(s), tuberculin, which shall be based on all available data, including data from clinical trials in unregistered indications and populations.

3) all data relating to the volume of sales and any data in possession of the applicant relating to the volume of prescriptions written for medicinal product(s), vaccine(s), tuberculin, including an estimate of the population exposed to the medicinal product(s), vaccine(s), tuberculin.

The PSUR shall be based on all available data and shall focus on new information on safety of medical use of medicinal product(s), vaccine(s), tuberculin for the reporting interval. The PSUR shall provide an accurate estimate of the population exposed to the medicinal product, vaccine, tuberculin including all data relating to the volume of sales and volume of prescriptions for medicinal product(s), vaccine(s), tuberculin. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the applicant, including the results of non-interventional or drug utilisation studies.

10. The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the benefit-risk assessment.

11. The PSUR shall contain conclusions as to the need for some actions, including changes and amendments to the instructions for medical use/summary of product characteristics for the medicinal product(s), vaccine(s), tuberculin, for which the PSUR is submitted.

12. If the introduction of changes into instructions for medical use/summary of product characteristics for the medicinal product(s) is necessary the applicant shall submit an application for introduction of changes to the registration materials during the validity period of registration certificate within 60 calendar days in accordance with the Procedure for Conducting Expert Evaluation of Materials Pertinent to Medicinal Products, which are Submitted for State Registration (Re-Registration) and Expert Evaluation of Materials about Introduction of Changes to the Registration Documents during the Validity Period of Registration Certificate, approved by the MoH Ukraine Order of 26 August 2005 № 426, registered with the Ministry of Justice of Ukraine of October 07, 2015 under № 1210/27655 (in wording of MoH Ukraine Order of July 23, 2015 № 460) (hereinafter – Procedure for Conducting Expert Evaluation).

13. The applicant before publishing safety information on medicinal product(s) including letters addressing healthcare professionals, the general public, medical and/or pharmaceutical workers shall agree upon this information with the Ministry of Health of Ukraine and/or the Center except for cases requiring an urgent publication of such information provided the Ministry of Health of Ukraine and/or the Center is notified about this simultaneously.

#### **4. Requirements to risk management system in applicant's pharmacovigilance system**

1. The applicant shall establish and maintain a risk management system in the pharmacovigilance system.
2. The applicant shall establish and submit to the Center risk management plans:
  - 1) for all new applications for registration of medicinal products including generic medicinal products (except for traditional and homeopathic medicinal products, which are registered under the simplified procedure according to the Procedure for conducting expert evaluation);
  - 2) for variations requiring new registration, in particular new dosage form, new route of administration, new manufacturing process for biotechnological medicinal product, pediatric indications and other substantial changes in indications, etc.;
  - 3) in the case of obtaining/detecting new data, which have an impact on the benefit-risk balance of the medicinal product, currently approved specification, pharmacovigilance plan, risk minimization measures or their effectiveness, or within 60 days after receipt of key results pertinent to pharmacovigilance or risk minimization;
  - 4) in the case of re-registration, when the risk management plan is required based on results of assessment of the benefit-risk balance according to the provisions of Annex 15 to the Procedure for conducting expert evaluation;
  - 5) upon request of the Center within 60 days after its receipt.
3. If while preparing a periodic safety report the need for introduction of changes into risk management plan occurs (as the result of new safety data and/or other data being received), the updated version of the risk management plan shall be submitted together with a PSUR. In this case a separate variation application for submission of a risk management plan shall be submitted.
4. For those medicinal products that do not require a preparation of risk management plans according to subitem 1 of item 2 of this chapter the applicant shall maintain a specification file of important identified risks, important potential risks, and missing information in order to prepare PSUR.
5. The risk management plan may be prepared for medicinal products, vaccines containing the same API and belonging to the same applicant and be subject, where appropriate, to the same risk management plan unless otherwise imposed as a condition for issuing the registration certificate.
6. Risk management plan shall be submitted as a separate document according to the structure given in Annex 14 to this Procedure or other structure containing modules, sections similar to those given in Annex 14 to this Procedure including information on risk minimization measures, summary of the risk management plan, pharmacovigilance plan. The risk management plan shall be submitted in hard copy, its annexes may be submitted in electronic form. While preparing the risk management plan the instructions for completing it, which are given in Annex 14 to this Procedure, shall be followed depending on a type of application for registration of medicinal product. The risk management plan shall be submitted in Ukrainian or English. In the case of submission of the risk management plan in English Part V “Risk minimisation measures”, Part VI “Summary of the risk management plan” shall be submitted in Ukrainian. Module SVIII “Summary of the safety concerns”, part III “Pharmacovigilance plan”, part IV “Plans for post-registration efficacy studies” shall be submitted in Ukrainian upon request of the Center. Each submission of the risk management plan shall have a distinct version number and shall be dated.

A risk management plan shall contain:

an identification or characterisation of the safety profile of the medicinal product(s)/vaccine(s)/tuberculin;

an indication of how to characterise further the safety profile of the medicinal product(s)/vaccine(s)/tuberculin;

a documentation of measures to prevent or minimise the risks associated with the medicinal product(s)/vaccine(s)/tuberculin, including an assessment of the effectiveness of those interventions;

a documentation of post-registration obligations that have been imposed as a condition of the registration certificate.

7. Where a risk management plan refers to post-registration studies, it shall indicate whether those studies are initiated, managed (by the applicant voluntarily or pursuant to obligations).

8. A risk management plan shall contain the summary of the risk management plan.

Where a risk management plan concerns more than one medicinal product, vaccine, tuberculin a separate summary of the risk management plan shall be provided for each medicinal product, vaccine, tuberculin.

9. The summary of the risk management plan shall be placed to the Center website.

10. When the risk management plan is updated as a result of getting new information that may have the significant impact on the benefit-risk balance or of getting important findings pertinent to pharmacovigilance or risk minimization the applicant shall submit to the Center the updated risk management plan within 30 calendar days after the updated version has been prepared. After agreement with the Center as appropriate, the applicant may submit only the modules, parts, sections concerned by the update. If necessary, the applicant shall submit an updated summary of the risk management plan upon request of the Center.

## **5. Requirements for post-registration safety and efficacy studies of medicinal product, vaccine, tuberculin to be conducted by applicant**

1. The applicant shall conduct non-interventional post-registration safety and efficacy studies of medicinal product, vaccine, tuberculin (hereinafter – safety study) voluntarily or pursuant to obligations. The safety studies involve the collection of safety data from patients or medical workers.

2. The safety studies shall not be performed where the act of conducting the study promotes the use of a medicinal product, vaccine, tuberculin on the pharmaceutical market.

3. The Center may require the applicant to submit the protocol and the progress reports on safety study.

4. While a safety study is being conducted, the applicant shall monitor the data generated and consider its implications for the benefit-risk balance of the medicinal product, vaccine, tuberculin.

The applicant shall provide the Center with any new information, which might have an impact on the benefit-risk balance of the medicinal product, vaccine, tuberculin. This obligation is without prejudice to the information on the results of safety studies that shall be made available by means of the PSUR.

5. Before a safety study is conducted, the applicant shall submit a draft protocol to the Center (this item and subsequent items of this chapter refer only to the safety studies, which are initiated, managed pursuant to obligations).

6. The Center shall provide the applicant with the following within 60 days after receipt of a draft protocol:

a letter of notification of approval or objection of the draft protocol (in the latter case the Center shall set out in detail the grounds for the objection and indicate that the conduct of the study promotes the use of a medicinal product, vaccine, tuberculin on the pharmaceutical market or does not fulfil the study objectives);

a letter of notification that the study is a clinical trial falling under the scope of Ukraine's legislation on clinical trials.

7. The applicant may commence a safety study only when the written approval from the Center has been obtained.

Where a letter of notification of approval of the protocol has been obtained, the applicant may commence the safety study according to the approved protocol. After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the Center. The Center shall assess the amendments and inform the applicant of approval or objection to their implementation.

8. Within 12 months of the end of data collection the applicant:

1) shall submit to the Center a final safety study report in Ukrainian, if the study was conducted only at the territory of Ukraine, or in English, if the study was also conducted in other countries. For the latter case, the applicant shall provide a Ukrainian translation of the title and abstract of the safety study protocol;

2) shall submit to the Center the abstract of the final study report in Ukrainian (in electronic form);

3) shall assess results of the safety study, and if necessary, shall submit an application for introduction of changes into registration materials during the validity period of registration certificate in accordance with the Procedure for conducting expert evaluation;

4) shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final safety study report are kept in electronic format and are available for auditing;

5) shall ensure that all safety study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

6) shall draw up protocols, abstract and final study reports according to the format set out in Annex 15 to this Procedure;

7) shall publish the results of the conducted safety study in specialized medical publications over the year after the end date of the safety study.

9. Based on the results of the safety study the Center may make a decision concerning the registration certificate, stating the reasons on which it is based and notifying the applicant. When a decision on the necessity to introduce changes is made the applicant shall submit to the Center an application for introduction of changes to the registration materials, including the instructions for

medical use, during the validity period of registration certificate in accordance with the Procedure for conducting expert evaluation.

10. This chapter shall apply in order to comply with the legislation for ensuring protection of the health and rights of participants in safety studies.

## **VII. PERFORMANCE OF PHARMACOVIGILANCE ACTIVITIES BY THE CENTER**

### **1. General provisions on performance of pharmacovigilance activities by the Center**

1. In order to obtain information on adverse reactions, lack of efficacy, AEFI, and any other concerns related to safety and efficacy of medicinal products, vaccines, tuberculin the Center shall use any methods for collecting information, including spontaneous reporting, active monitoring including hospital-based active monitoring, monitoring of prescriptions, meta-analysis, and involve applicants, medical workers, legal and natural persons performing an economic activity on medical practice, patients and/or their legal representatives.

2. The Center shall analyze information on adverse reactions, lack of efficacy, AEFI, and any other concerns relating to safety and efficacy of medicinal products, vaccines, tuberculin, obtained from any available sources and by any means used in pharmacovigilance.

3. The Center, while analyzing information specified in a report form to verify whether data on adverse reactions, lack of efficacy, AEFI, and any other concerns relating to safety and efficacy of medicinal products, vaccines, tuberculin are reliable, has a right to request and obtain copies of documents including primary medical records from medical workers, health facilities, applicants, organizations, legal and natural persons performing an economic activity on medical practice, patients and/or their legal representatives that have provided such information.

4. The Center shall raise awareness about pharmacovigilance among medical workers, patients and/or their legal representatives, and applicants with enrollment of the Center's representatives for pharmacovigilance in administrative territorial units.

5. The Center shall authorize the Center's representatives for pharmacovigilance in administrative territorial units for providing and supervising pharmacovigilance in Ukraine at the appropriate administrative territorial level with a support of heads of all healthcare structural units, medical workers, persons performing an economic activity on medical practice, applicants, heads and workers of the State Service of Ukraine for Medicinal Products and Narcotics Control;

6. The Center shall perform a regular audit of its pharmacovigilance system and audit of the applicant's pharmacovigilance system, and publish their results.

7. The Center shall publish the List of safety studies of medicinal product/vaccines, tuberculin at its website.

### **2. Procedure for auditing applicant's pharmacovigilance system by the Center**

1. The Center shall perform an audit of applicant's pharmacovigilance system to clarify issues relating to its existence and functioning.

2. Audits may be:

1) routine:

if the audit of the applicant's pharmacovigilance system has not been conducted for 5 years after placing the first medicinal product, vaccine, tuberculin of the applicant on the pharmaceutical market of Ukraine;

according to the schedule of routine audits;

2) triggered:

because of safety concerns related to medicinal products, vaccines, tuberculin, or because of failure to follow the established requirements (changes in organizational and legal form of entities), substantial change in his own pharmacovigilance system, etc.);

because of safety concerns of medicinal products, vaccines, tuberculin, or because of failure to follow the established requirements (untimely submission of reports on adverse reactions to medicinal product, vaccine, tuberculin and/or lack of efficacy, submission of reports with incomplete information, submission of poor quality addendum to the clinical overview, submission of poor quality PSURs, submission of poor quality risks management plans, non-correspondence of data specified in reports to data from other information sources, changes in benefit-risk balance, results of previous audits, publication of pharmacovigilance information, which is biased or misleading).

3. The audit envisages:

1) the beginning not earlier than 7 weeks after sending a previous notification-request and agreeing upon with the applicant its conduct except for cases, where there is a need to conduct the audit without the announcement, or when the audit is announced in a timeframe less than 7 weeks. The applicant shall provide the Center with the documents requested according to the previous notification-request not later than 14 calendar days before the beginning of the audit;

2) the conduct of the audit by the Center's pharmacovigilance specialists with relevant experience and whose activity does not result in the conflict of interest. If applicable, other specialists (depending on the peculiarities of use and safety of the medicinal product, vaccine, tuberculin) may be involved in the audit by arrangement. During the audit the presence of the applicant's QPPV/CPV is obligatory, if appropriate, other applicant's legal representatives may also be present by arrangement.

3) that specialists, who conduct the audit, shall not disclose confidential data they obtain during its conduct according to the current legislation;

4) detection of the following non-compliances, if any;

critical – non-compliances that make impossible the assessment of safety and benefit-risk balance of medicinal products, vaccines, tuberculin resulting in negative consequences for public health. The critical non-compliances include the absence of the pharmacovigilance system or one or more elements of the pharmacovigilance system;

essential - non-compliances that may have a negative impact on the assessment of safety and benefit-risk balance of medicinal products, vaccines, tuberculin resulting in negative consequences for public health. The essential non-compliances include (but not limited to) a failure to observe requirements for qualification, education, QPPV/CPV duties, shortcomings detected in documented processes relating to pharmacovigilance, shortcomings of maintaining pharmacovigilance databases, shortcomings of running a risk management system, shortcomings of document management with regard to pharmacovigilance;

non-essential - non-compliances that have no negative impact on the assessment of safety and benefit-risk balance of medicinal products, vaccines, tuberculin, and negative consequence for public health;

5) preparation of the report, based on the results of the audit, confirming the fact of the audit, including the remarks made concerning the pharmacovigilance system (if any), revealed violations (shortcomings), non-compliances;

6) sending the report to the applicant within 30 calendar days after the full termination of the audit;

7) sending information to the Center by the applicant for agreeing upon the timelines of corrective and preventive measures to eliminate critical and essential non-compliances and violations (shortcomings) revealed during the audit (non-essential violations should be eliminated as one goes).

4. The Center may perform the triggered audit to verify the elimination of non-compliances.

5. If within the period specified for eliminating shortcomings the applicant fails to eliminate the critical non-compliances the Center shall forward to the MoH Ukraine proposals on the temporary prohibition of using the medicinal product, vaccine, tuberculin through suspension of the applicant registration certificate because the applicant has no pharmacovigilance system or its components in place.

### **3. Requirements for analyzing information on safety and efficacy of medicinal products, vaccines, tuberculin**

1. The Center shall arrange and analyze:

1) the obtained information on adverse reactions and/or lack of efficacy, and/or AEFI any other problems relating to the use of medicinal product, vaccine, tuberculin;

2) the obtained information on recorded cases of infectious diseases controlled by specific immunoprophylaxis in vaccinated persons;

3) periodic safety reports;

4) risk management plans.

2. The Center shall perform:

1) assessment of quality of data on safety and efficacy of medicinal products, vaccines, tuberculin;

2) retention of data on safety and efficacy of medicinal products, vaccines, tuberculin;

3) analysis of data on safety and efficacy of medicinal products, vaccines, tuberculin;

4) assessment of causal association, expectedness/non-expectedness, severity;

5) analysis of information on registered cases of infectious diseases controlled by specific immunoprophylaxis in vaccinated persons;

6) signal detection/management;

7) assessment of benefit-risk balance;

8) assessments of the effectiveness of risk minimization/elimination measures taken by the applicant;

9) training in relation to pharmacovigilance issues;

10) post-registration non-interventional safety and efficacy study of medicinal product, vaccine, tuberculin (if necessary).

3. During the analysis of data on safety and efficacy of medicinal products, vaccines, tuberculin, assessment of causal association of clinical manifestations of any adverse reaction and use of medicinal product, vaccine, tuberculin, assessment of causal association of lack of efficacy and use of medicinal product, expectedness/non-expectedness, severity, information on registered cases of infectious diseases controlled by specific immunoprophylaxis in vaccinated persons, and assessment of benefit-risk balance, the Center may involve independent experts and other specialists (by arrangement), if applicable.

4. Based on the results of analysis of safety and efficacy data on medicinal products, vaccines, tuberculin the Center shall make proposals to the Ministry of Health of Ukraine concerning decisions:

1) about full or temporary prohibition of medical use:

In case of detection of previously unknown unsafe properties of the medicinal product, vaccine, tuberculin resulted in or capable to cause serious sequela for public health;

In the case, where risk of the use of medicinal product, vaccine, tuberculin outweighs the benefit.

In the case, where the applicant fails to observe the conditions for issuing registration certificate

In the case, where the applicant fails to fulfil his obligations;

2) on restriction of use of medicinal product, vaccine, tuberculin.

5. Based on the results of analysis of safety and efficacy data on medicinal products, vaccines, tuberculin the Center shall recommend the applicant to:

1) clarify, amend or change instructions for medical use of medicinal product/summary of product characteristics of medicinal product, vaccine, tuberculin with motivated conclusions and recommendations;

2) perform safety and efficacy studies;

3) draw up the risk management plan.

10.5. The Center's conclusions on further medical use of medicinal product(s), vaccine(s), tuberculin may be contested according to current legislation of Ukraine.

**T. Liaskovskyi**

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