

Annex 10  
to the Procedure for Conducting Expert  
Evaluation of Registration Materials Pertinent  
to Medicinal Products Submitted for the State  
Registration (Re-registration) and for Expert  
Evaluation of Materials about Introduction of  
Changes to Registration Materials during  
Validity Period of Registration Certificate  
(item 4 of section IV)

## **PARTICULAR MEDICINAL PRODUCTS**

### **and special requirements related to their registration dossier**

#### 1. Biological medicinal products

##### 1.1. Plasma-derived medicinal product

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the registration dossier drawn up according to the requirements mentioned in item 3.2 of CTD for starting materials made of human blood/plasma may be replaced by a Plasma Master File (hereinafter – PMF) drawn up in accordance with this Part.

#### Principles

PMF shall mean a stand-alone documentation, which is separate from the registration dossier, which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substances, which are part of medicinal products.

Every centre or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in PMF.

The applicant of medicinal product derived from human blood or plasma shall provide PMF to the competent authority. Where the applicant differs from the PMF holder, the latter shall make PMF available to the applicant for submission to the competent authority. In any case, the applicant shall take responsibility for the medicinal product.

The competent authority that is evaluating the registration dossier shall await for the Agency to issue the certificate for PMF before deciding on the medicinal product.

Any registration dossier for medicinal product containing a human plasma-derived constituent shall refer to the PMF corresponding to the plasma used as a starting/raw material.

#### Content

PMF shall include information on the plasma used as starting/raw material, in particular:

1) Plasma origin:

information on centres or establishments in which blood/ plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections;

information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status;

selection/exclusion criteria for blood/plasma donors;

system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished medicinal products and vice versa;

2) Plasma quality and safety:

compliance with European Pharmacopoeia or SPhU Monographs;

testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used;

technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used;

conditions of storage and transport of plasma;

procedures for any inventory hold and/or quarantine period;

characterisation of the plasma pool;

3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the PMF shall provide a list of the medicinal products derived from this plasma, whether the medicinal products have been registered or are in the process of being registered, including medicinal products produced for clinical trials.

#### Evaluation and Certification

For medicinal products not yet registered, the applicant shall submit a full registration dossier to a competent authority, which shall be accompanied by a separate PMF where one does not already exist.

PMF is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of compliance for PMF, which shall be accompanied by the evaluation report.

PMF shall be updated and re-certified on an annual basis.

Changes introduced to the PMF must follow evaluation according to provisions of section VI of the Procedure. Conditions for introducing these changes are laid down by section B.V.a) Annex 17 of the Procedure.

The competent authority that will decide on registration of medicinal product shall take into account the certification, re-certification or variation of PMF on the concerned medicinal product.

## 1.2. Vaccines

For vaccines for human use if the Vaccine Antigen Master File (hereinafter – VAMF) system is used, the provisions of Module 3 may be derogated when the registration dossier is drawn up according to the requirements of item 3.2 of CTD for starting materials.

The registration dossier of any vaccine other than human influenza vaccine, shall be required to include a VAMF for every vaccine antigen that is an active substance of this vaccine.

### Principles

VAMF shall mean a stand-alone part of the registration dossier, which contains all relevant detailed information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant/registration certificate holder.

A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

### Content

VAMF shall contain the following information related to the quality of active substance:

#### Active Substance

- 1) General Information, including compliance with the relevant monographs of the European Pharmacopoeia, SPhU;
- 2) Information on the manufacture of the active substance including data on the manufacturing process, starting and raw materials, specific measures on assessment of TSEs risk, adventitious agents safety evaluation, facilities and equipment;
- 3) Characterisation of the active substance;
- 4) Quality control of the active substance;
- 5) Reference standard and materials;
- 6) Container and closure system of the active substance;
- 7) Stability of the active substance.

### Evaluation and Certification

For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit a full registration dossier including all VAMF corresponding to each single vaccine antigen that is part of the novel vaccine where no VAMF already exists for the single vaccine antigen.

A scientific and technical evaluation of each VAMF shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance for each VAMF, which shall be accompanied by the evaluation report.

The provisions of the first indent of this subitem shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of already registered vaccines.

Changes to VAMF shall be subject to evaluation carried out in accordance with the provisions of section VI of the Procedure. The conditions of such changes are stated in section B.V.a) of Annex 17 of the Procedure.

The competent authority that will grant the registration certificate shall take into account the certification, re-certification or variation of the VAMF on the concerned vaccines.

## 2. Radio-pharmaceuticals and precursors

### 2.1. Radio-pharmaceuticals

For radio-pharmaceuticals registration a full registration dossier shall be submitted in which the following specific details shall be included.

#### Module 3

1) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia or SPhU. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

For radio-nuclides, the nuclear reactions involved shall be discussed.

In a generator, both mother and daughter radio-nuclides shall be considered as active substances;

2) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided;

3) Starting materials include irradiation target materials;

4) Considerations on chemical/radiochemical purity of medicinal product and its relationship to bio-distribution shall be provided;

5) Radio-nuclide purity, radiochemical purity and specific activity shall be described;

6) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided;

7) The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated;

8) For kits, the specifications of the finished medicinal product shall include tests on performance of medicinal products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed;

9) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled medicinal products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

#### Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

#### Module 5

The results of clinical trials or data justified in the clinical overviews shall be provided.

#### 2.2. Radio-pharmaceutical precursors used for radio-labelled medicinal products manufacturing

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.

In particular, the following information shall be provided:

#### Module 3

The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as defined in indents 1-9 of subitem 2.1 of this item, where applicable.

#### Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice shall be provided, unless otherwise justified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant 'cold' (not containing radioactive substances) nuclide shall be presented.

#### Module 5

Clinical information generated from clinical studies on using the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

### 3. Homeopathic medicinal products

(except for medicinal products described in Annex 7 of the Procedure)

This section sets out specific provisions on the registration dossier of Modules 3 and 4 to homeopathic medicinal products.

### Module 3

The provisions of Module 3 shall apply to homeopathic medicinal products specified in Annex 7 of the Procedure as well as to homeopathic medicinal products registered through other procedures with the following modifications:

#### 1) Terminology.

The Latin name of the homeopathic stock described in the registration dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by other national pharmacopoeia. Where relevant the traditional name used in other countries shall be provided;

#### 2) Control of starting materials.

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediates up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described.

In case dilutions are involved, these dilution steps should be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by other national pharmacopoeia;

#### 3) Control tests on the finished medicinal product.

The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality of medicinal product shall be demonstrated by complete validation of the manufacturing and dilution process;

#### 4) Stability tests.

The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the medicinal product may be considered.

### Module 4

The provisions of Module 4 shall apply to homeopathic medicinal products specified in Annex 7 of the Procedure as well as to homeopathic medicinal products registered through other procedures.

The provisions of Module 4 shall apply to the registration of homeopathic medicinal products specified in Annex 7 of the Procedure with the following specifications.

Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking;

Homeopathic nature of all homeopathic medicinal products shall be justified.

#### 4. Herbal medicinal products

For registration of herbal medicinal products a full registration dossier shall be provided in which the following specific details shall be included.

##### Module 3

The provisions of Module 3, including compliance with monograph of the European Pharmacopoeia or SPhU, shall apply to the registration of herbal medicinal products. The state of scientific knowledge at the time when the registration dossier is lodged shall be taken into account.

The following aspects specific to herbal medicinal products shall be considered:

##### 1) Herbal substances and herbal preparations.

For the purposes of this chapter the terms ‘herbal substance’ and ‘herbal preparation’ shall be considered equivalent to the terms ‘herbal drug’ and ‘herbal drug preparation’, as defined in the European Pharmacopoeia

With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

To document the section of the structure for herbal substance and herbal preparation where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry) as well as other constituents shall be provided.

To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier of raw material, including contractors, and each proposed manufacturing site or facility involved in production/collection and testing of the herbal substance shall be provided.

To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

With respect to the description of manufacturing process for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance and herbal preparation where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance and herbal preparation where applicable used in supporting bibliographic data and the herbal substance and herbal preparation, where applicable, contained as active substance in the herbal medicinal product submitted for registration shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.

The specifications for the herbal substance and herbal preparation where applicable shall be provided.

The analytical procedures used for testing the herbal substance and herbal preparation where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance and herbal preparation where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substances and herbal preparations where applicable shall be provided, including those for pharmacopoeial substances.

Justification for the specifications of the herbal substances and herbal preparations shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance and herbal preparation where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant may submit a certificate of suitability to monograph of European Pharmacopoeia;

## 2) Herbal medicinal products.

A brief summary of the formulation development of medicinal product should include information on the development of herbal medicinal product, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the medicinal product used in supporting bibliographic data and the medicinal product submitted for registration shall be discussed, where appropriate.

{ Annex 10 in wording of MoH Ukraine Order №460 as of 23.07.2015 }