### GUIDANCE ON MODULE 3.2.S FOR NOSODES

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Introduction
The Homeopathic Medicinal Products Working Group (HMPWG) agreed to develop a specific guidance in the compilation of the module 3.2.S. in an application dossier for homeopathic medicinal products containing nosodes. This guidance is part of the existing guidance on module 3 (published on HMA-HMPWG website).

Scope
Nosodes are homeopathic preparations made from products of human or animal disease processes, from pathogens or their metabolic products, from the decomposition products of animal organs, or from cultured microorganisms. The information provided in this document does not replace the texts of the NTA template, it merely provides some clarification. Hence, this document should be read in conjunction with the NTA and the “Guidance on Module 3 of the Homeopathic Medicinal Products Dossier” taking into account also the “Points to consider on safety of homeopathic medicinal products of biological origin”.

The text following the section titles is intended to be explanatory and illustrative only. It is not all-inclusive and additional national requirements may apply. References to guidelines are inserted to assist applicants. However, it remains the applicant’s responsibility to ensure that all relevant legislation and guidelines are considered in the preparation of each part of the dossier.
All analytical test procedures described in the various sections must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.
The principle of GMP and the detailed guidelines are applicable to all operations which require the authorization referred to in Article 40 of Directive 2001/83/EC as amended.
3.2.5. DRUG SUBSTANCE\textsuperscript{1}

(NAME\textsuperscript{2}, MANUFACTURER)

\textsuperscript{1} For homeopathic medicinal products in part S information on raw material(s), homeopathic stock(s), intermediate dilutions and/or triturations and final dilutions should be provided.

\textsuperscript{2} For a drug product containing more than one drug substance, the information requested for part “S” should be provided in its entirety for each drug substance.

3.2.5.1 General information (name, manufacturer)

3.2.5.1.1. Nomenclature (name, manufacturer)

A definition of the homeopathic stock(s) and the homeopathic name(s) should be provided.

For homeopathic stocks of human, animal origin:

- Binominal scientific name of the pathogenic agent disease-causing, other names (synonyms)/Latin names
- Homeopathic stock (e.g. mother tincture)
- Reference of the homeopathic manufacturing procedure
- Raw material (human, animal)
- Part(s) used
- State (e.g. fresh, dried, preserved as frozen or ethanol preserved)
- Description of vehicles used

For homeopathic stocks of microbiological origin:

- Homeopathic name, binominal scientific name of the microorganism(s) (genus, species, variety and author), other names (synonyms)/Latin names
- Homeopathic stock (e.g. mother tincture)
- Reference of the homeopathic manufacturing procedure
- Part(s) used
- State (e.g. fresh, dried, preserved as frozen or ethanol preserved)
- Description of vehicles used

3.2.5.1.3 General Properties (name, manufacturer)

For homeopathic nosode stocks and final dilution, a list of physico-chemical/biological and other relevant properties should be provided.
3.2.5.2 Manufacture (name and manufacturer)

3.2.5.2.1 Manufacturer(s) (name and manufacturer)
The name, address, and responsibility of each manufacturer, including manufacturer of homeopathic stock, dilutions and/or triturations as well as, contractors, and each proposed production site or facility involved in manufacturing/collection and testing should be provided.

3.2.5.2.2 Description of Manufacturing Process and Process Controls (name and manufacturer)
The description of the homeopathic stock(s), intermediate dilutions and/or triturations and final dilution manufacturing process represents the applicant's commitment for the manufacture of the homeopathic stock(s) and final dilution.

Information should be provided to adequately describe the manufacturing process and process controls.

A flow chart of the manufacturing process should be included.

Raw materials
For raw materials of human, animal or microbiological origin, due to the variability of the sources, a detailed description of the manufacturing process in order to ensure a consistent and reproducible quality should be provided:

- Information on the origin (e.g. animal/human donors, microbial strains)
- Condition of the production of microorganism (e.g. cell culture, growth condition, antigen production, etc.)
- Production of immune sera in animals
- Collection of sample
- Storage time and conditions
- Transport conditions
- Batch size

Homeopathic Stock
Adequate description of the manufacturing process and IPC should be provided taking into account each phase of the preparation of the homeopathic stock:

- Treatment of raw material
- Details of each phase (e.g. heat treatments, lysis, filtration, etc.)
- Details of each in process control (IPC)
- Holding time (if applicable) and storage conditions

Reference should be made to the appropriate section of the European Pharmacopoeia, or in absence thereof, to a homeopathic manufacturing procedure described in an official Pharmacopoeia of a Member State of the European Union.
**Dilution**

The manufacturing process of each intermediate dilution/trituration up to the final dilution should be clearly described:

- Details of each manufacturing step
- Details of each IPC
- Storage time and conditions (if applicable)

Reference should be made to the appropriate section of the European Pharmacopoeia, or in absence thereof, to a homeopathic manufacturing procedure described in an official Pharmacopoeia of a Member State of the European Union.

For raw materials and homeopathic stocks not described in an official pharmacopoeia, an in-house monograph, should be provided.

### 3.2.5.2.3 Control of Materials (name, manufacture)

The information on the raw material(s) and the solvents/reagents or vehicles used for the Homeopathic Stock(s) and final dilution preparation should be presented.

**Nomenclature of the raw materials**

For raw materials of human, animal or microbiological origin, the scientific name(s), genus, species, tissue(s), fluid(s), parts of organ(s) or organ(s) used and other necessary information should be provided.

**Description of the raw materials**

For raw materials of human, animal or microbiological origin, information on the physical and/or anatomical and histological state (where applicable) should be provided.

A macroscopic and microscopic description of the raw material should be provided.

The donor (human/animal) needs to be identified and coded for traceability in accordance with Article 8 (1) of the Directive 2004/23/EC. The raw material should comply with current Ph. Eur. Monographs (0853- *Human plasma for fractionation*, 1483- *Products with risk of transmitting agents of animal spongiform encephalopathies*) and the requirements on tissue(s) should follow the Directive 2004/23/EC.

Human material may contain blood or may have been exposed to it during the extraction process, so the transmission of viruses is of particular concern, therefore the selection of the donors must follow the Commission Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council.
**Supportive Data**

For example, the following data should be presented:

- Name and address of the supplier and supplier commitment and/or manufacturer and manufacturer’s commitment, if different from the applicant
- Data on the origin/source of the material
- Production

**For raw materials of animal origin including cell cultures:**

- Age of the animal, culture history
- Health status, method of breeding and feeding of animals, immunization techniques (immune sera) with description of antigens, cell culture origin, culture media
- Conditions of slaughtering and dissection of the animals, culture conditions
- Size of organ, tissue, fluid pools
- Method of acquisition, treatments, transport conditions and storage conditions of the organ or pool of organs or microbial cultures or immune sera
- Provisions made for tracing the origin of the raw material(s)
- Assessment of the risk of infectivity

**For raw materials of human origin:**

- Origin of donation;
- Clinical data (e.g. clinical diagnosis confirmed by biological tests, medical questionnaire, etc.)
- Identification of raw material biological fluid description, tissue description, cells nature, origin name, reference, volume of sample, method of collection, transport, storage conditions pool
- Assessment of the risk of infectivity

The microorganism (bacteria/virus/ fungi) contained in the material of human /animal origin needs to be identified and characterized with appropriate methods (e.g. macroscopic and microscopic methods, biochemical tests)

**For raw materials constituted by microorganism:**

The microorganism (bacteria/virus/ fungi) needs to be identified and characterized at strain level.

Characterization includes determination of the phenotype and genotype of the strain, using microbiological macroscopic and microscopic methods, biochemical tests, immunological methods, molecular genetic tests (sequencing) as well as antimicrobial resistance determination.

Information should be provided on culture media (bacterial strains/fungi), cell culture origin and media for viral propagation.

The presence of the microorganism in the source raw material must be demonstrated and quantified (CFU/titer- e.g. TCID50, etc).
3.2.5.2.4 Control of Critical Steps and Intermediates (name, manufacture)

Critical steps should be highlighted (for instance cell culture, harvesting, purification, thermal inactivation, lysis, filtration, sterilization, succussion, standing time) and the specific IPC should be described in this section.

3.2.5.2.5 Process validation and/or Evaluation (name, manufacture)

For raw material(s), homeopathic stock(s) and dilutions of biological origin (human/animal/ microbiological) sufficient information should be provided on validation to demonstrate that the manufacturing process is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2.5.2.6 Manufacturing Process Development (name, manufacture)

Reference shall be made to a manufacturing procedure described in the European Pharmacopoeia, or in absence thereof, to a homeopathic manufacturing procedure described in an official Pharmacopoeia of a Member State of the European Union, The process development needs to be described in detail, where necessary.

3.2.5.3 Characterisation (name, manufacturer)

3.2.5.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

Information on the composition and the biochemical and physical-chemical characterization of the stock should be provided:

- Molecules of microbial origin (e.g. DNA, RNA, proteins, lipids, endotoxins)
- Molecules deriving from the human serous fluid or tissue (e.g. the protein /lipid content, identification of the immune cells present)

3.2.5.3.2 Impurities (name, manufacturer)

Information on impurities originating from the raw material(s) or arising from the manufacturing process should be provided.

Raw material

- Microbial contamination
- Viral contamination

Homeopathic stock

- Microbial contamination
- Specification related to the vehicle
This section, for materials of animal, human, cell culture origin, is in part covered by adventitious virus, see 3.2.A.2.3.

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specifications (name, manufacturer)

The specifications for raw material(s), the homeopathic stock(s) and the final dilutions should be provided. Information provided should comply with relevant CHMP quality guidelines.

If the raw material is described in a Pharmacopoeia, the reference to the monograph should be stated and, where applicable, supplementary tests should be described. If the raw material(s) is (are) not described in a Pharmacopoeia, the monograph should be compiled based on scientific data.

Release and shelf life specification

Raw material of human/animal origin:

- Appearance
- Identification
- Sterility/microbial quality

Raw material of microbiological origin:

- Appearance
- Identification
- Quantification
- Sterility/microbial quality

Homeopathic stock:

- Appearance
- Identification and quantification of nosode, if possible
- Sterility/microbial quality

Dilution:

- Appearance
- Microbial quality

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Analytical procedures used for testing the raw material(s), the homeopathic stock(s) and final dilution should be provided. For raw material of human origin, information on analytical kits can be provided.

All analytical test procedures must be described in sufficient detail to enable the procedures to be repeated if necessary, e.g. by an official laboratory.

The analytical controls should provide sufficient data on the quality and the consistency of the product.
Raw materials of human, animal or microbiological origin:

- Tests for appearance (if applicable)
- Tests for identification and quantification (if applicable)
- Tests for sterility/microbial quality

Homeopathic Stock:

- Tests for appearance (e.g. clarity and degree of the opalescence of liquids, degree of coloration of liquids etc.)
- Tests for identification of the nosode (e.g.: PCR, ELISA, HPLC, SDS-PAGE, ect.)
- Microbial quality, where applicable

Dilution:

- Tests of appearance (e.g. clarity and degree of the opalescence of liquids, degree of coloration of liquids)
- Tests for microbial quality, where applicable

3.2.S.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the raw material(s), homeopathic stock(s) and final dilution should be provided.

For Pharmacopoeial methods validation is not always required, but in some cases, at least, the suitability for the intended use should be verified.

3.2.S.4.4 Batch Analyses (name, manufacturer)

Information provided in the batch analysis:

- Name of the raw material/homeopathic stock/dilution or trituration
- Batch number
- Batch size
- Manufacturing date
- Batch number supplier
- Supplier
- Testing date
- Specification
- Acceptance criteria
- Results
If possible, quantitative results should be presented numerically and not in general terms such as “complies”, “meets limit” etc.

a. Raw material

Results of batch analysis of at least two batches of raw material should be provided, unless otherwise justified. In case of more than one supplier, the results of at least one batch for each supplier should be provided.

b. Homeopathic stock

Results of batch analysis of at least two batches should be provided, unless otherwise justified. In case of more than one supplier/manufacturer, the results of at least one batch for each supplier/manufacturer should be provided.

c. Dilutions

Results of batch analysis of at least two batches of intermediate dilutions (if stored or purchased) should be provided. In case of more than one manufacturer, the results of at least one batch for each supplier/manufacturer should be provided, unless otherwise justified.

In case of several manufacturing sites, results of batch analysis from each manufacturing site should be provided.

In any cases, the certificates should not be older than three years, unless appropriately justified.

3.2.S.4.5 Justification of Specifications (name, manufacturer)

Justification for the raw material(s), homeopathic stock(s) and final dilution specifications should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or reference materials used for testing raw material(s), homeopathic stock(s) and final dilution should be provided.

If reference standards or reference materials are not available, an appropriate in-house reference preparation should be selected, characterized and used to verify batch-to-batch consistency.

3.2.S.6 Container Closure System (name, manufacturer)

Descriptions of container closure system(s) used for storage of the homeopathic stock(s), final dilution, intermediate dilution/trituration and raw materials (if stored) should be provided. The combination of the container closure specifications and the homeopathic stock stability data may be sufficient to demonstrate suitability of the container closure system for storage and shipping of the homeopathic stock.
3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

Stability data may also be required for raw materials that are not processed immediately after testing. Stability data of the homeopathic stock(s) and intermediate or final dilution(s) should be provided. Stability data or re-testing may also be required for homeopathic stocks that are not processed immediately after testing. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof, if the expiry date of the dilutions/triturations does not exceed the expiry date of the homeopathic stock.

A stability protocol, covering the proposed shelf-life should be provided, including specification, analytical methods and test intervals.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided (where applicable).

3.2.S.7.3 Stability Data

Stability data may also be required for dilutions or triturations, if the stability is not linked to the expiry date of the homeopathic stock and they are not processed immediately after testing.

3.2.A APPENDICES

3.2.A.1. Facilities and Equipment (name, manufacturer)

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

For human donors: Compliance with Ph. Eur. monographs 0853- *Human plasma for fractionation* and 1483- *Products with risk of transmitting agents of animal spongiform encephalopathies* as well as European Directives 2004/23/EC and 2004/33/EC should be demonstrated.

Any deviation from the requirements for selection of donors should be reported and fully justified.

Results of the donor testing, and medical history and evaluation of the donor should be provided.

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., TSE, bacteria, mycoplasma, fungi). Relevant certification should be provided.

For viral adventitious agents detailed information from viral safety validation studies should be provided, such as:

- Manufacturing steps claimed to inactivate/remove virus should be clearly identified
- Choice of relevant and model viruses
- Cytotoxicity and interference data
- Removal/inactivation data
- Kinetic of inactivation

A risk assessment in accordance with the principles outlined in the European Pharmacopoeia General Chapter (5.1.7) should be presented.