Annex 17
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 the Validity Period of Registration Certificate (item 1 of section V)

REQUIREMENTS TO DOCUMENTS
submitted for expert evaluation at introduction of changes to registration materials during the validity period of the registration certificate

A. ADMINISTRATIVE CHANGES

A.1. Change in the name and/or address of the applicant (registration certificate holder)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1,2**	**IA_{IN}**

Conditions
1. The registration certificate holder shall remain the same legal person.
Documentation
1. Document from a relevant competent authority in which the new name and/or new address of the applicant (registration certificate holder) is specified. 2. Revised summary of product characteristics, instructions for medical use and labelling text on package (if necessary).

A.2. Change in the name of the medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IB**

Conditions
1. The proposed name does not violate the rights of third parties.
Documentation
1. Grounds for change in the name of medicinal product. 2. Revised summary of product characteristics, instructions for medical use and labelling text on package (if necessary).

A.3. Change in name of the API or of an excipient	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IA_{IN}**

Conditions
API/excipient shall remain the same.
Documentation

1. Proof of the INN recommended by WHO or copy of the INN list. If applicable, proof that the change is in line with the Ph. Eur. For herbal medicinal products, declaration that the name is in accordance with valid requirements or the Note for Guidance on Quality of Herbal Medicinal Products, and with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products (current edition). 2. Revised summary of product characteristics, instructions for medical use and labelling text on package.

A.4. Change in the name and/or address where a manufacturer carries out his activity (including where relevant quality control testing sites); or an holder of API master file; or a supplier of the API/starting material/reagent/intermediate used in the manufacture of the API (where specified in the dossier for the medicinal product) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the dossier)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2, 3**	**IA**

Conditions
1. The manufacturing site and all manufacturing operations shall remain the same.
Documentation
1. Document from a relevant competent authority with indication of the new name and/or new address where a manufacturer carries out his activity. 2. Amendment of the relevant sections of materials of registration dossier. 3. In case of change in the name of the holder of the API Master File, updated consent to access to Master File from the holder.

A.5. Change in the name and/or address where a manufacturer carries out his activity/importer of the finished medicinal product (including batch release or quality control testing sites)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) The activities for which the manufacturer/importer is responsible include batch release	**1**	**1, 2**	**IA$_{IN}$**
b) The activities for which the manufacturer/importer is responsible do not include batch release	**1**	**1, 2**	**IA**

Conditions
The manufacturing site undergoing the name and/or address change and all manufacturing operations must remain the same.
Documentation

Documentation
1. Copy of the modified manufacturing license (if according to manufacturer's country legislation the license to manufacture is available in electronic form only (e.g. USA), the printout with reference to appropriate official site certified by applicant's signature/stamp should be provided) or other licensing document to manufacture the applied pharmaceutical form in manufacturer's country, where a new name and/or new address are specified. 2. Amendment of the relevant sections of materials of registration dossier, including revised summary of product characteristics, instructions for medical use and labelling text on package (if necessary).

A.6. Change in ATC Code	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IA**

Conditions
1. Assigning a new or change of ATC code by WHO.
Documentation
1. Proof of acceptance by WHO or copy of the ATC Code list. 2. Revised summary of product characteristics, instructions for medical use and labelling text on package (if necessary).

7. Deletion of any manufacturing site (including site for API, intermediate or finished medicinal product, packaging site, manufacturer responsible for batch release, site where batch control takes place) or supplier of a starting material, reagent or excipient (if mentioned in the dossier)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1, 2	**1, 2**	**IA**

Conditions
1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. Where applicable at least one manufacturer responsible for batch release that is able to certify the product testing for the purpose of batch release within the EU/EEA remains in the EU/EEA. 2. The deletion should not be due to unforeseen circumstances concerning manufacturing process.
Documentation
1. The registration form for introduction of changes shall clearly outline approved and proposed manufacturers as listed in section 2.5 of the registration form for state registration of medicinal product. 2. Changes to relevant parts of registration dossier including revised summary of product characteristics, instructions for medical use and labelling text on package (if necessary).

A.8. Changes to date of the audit to verify good manufacturing practice (GMP) compliance of the manufacturer of the API*	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			IA

Documentation

Written confirmation from the manufacturer of the finished medicinal product stating verification of compliance of the API manufacture with principles and guidelines of good manufacturing practices in respect of requirements for active substances used as starting materials.			
* This variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the 'Qualified person declaration')			
B. QUALITY CHANGES			
B.I. API			
B.I.a) Manufacture			
B.I.a.1. Change in the manufacturer of a starting material/ intermediate/reagent used in the manufacturing process of the API or change in the manufacturer (including where relevant quality control testing site(s)) of the API, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	**1, 2, 3**	**1, 2, 3, 4, 5, 6, 7**	**IA_{IN}**
b) Introduction of a new manufacturer of the API supported by an API Master File.			**II**
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the API, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties of API impacting on bioavailability			**II**
d) New manufacturer of a starting material for which an assessment is required of viral safety and/or TSE risk			**II**
e) The change relates to a biological API or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			**II**
f) Changes to quality control testing arrangements for the API replacement or addition of a site where batch control/testing takes place	**2, 4**	**1, 5**	**IA**
g) Introduction of a new manufacturer of the API that is not supported by an APIMF and requires significant update to the relevant API section of the dossier			**II**
h) Addition of an alternative sterilisation site for the API using a Ph.Eur. method		**1, 2, 4, 5, 8**	**IB**
i) Introduction of a new site of micronisation	**2, 5**	**1, 4, 5, 6**	**IA**
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological/immunological/immunochemical method takes place			**II**

k) New storage site of Master Cell Bank and/or Working Cell Banks		**1, 5**	**IB**

Conditions
1. The specifications of starting materials and reagents (including in-process controls, methods of analysis of all materials) are identical to those already approved. For intermediates and API the specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved. 2. The API is not a biological/immunobiological substance or sterile. 3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance of compliance with the current EMA *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. 4. Method transfer from the old to the new site has been successfully completed. 5. The particle size specification of the API and the corresponding analytical method remain the same.
Documentation

1. Amendments to relevant sections of materials of registration dossier (if necessary).
2. A declaration from the registration certificate holder or holder of the API Master File (if necessary) that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, source, production of herbal API and manufacturing route), quality control methods and specifications of API and of the starting material/reagent/intermediate in the manufacturing process of API (if applicable) are the same as those already approved.
3. Either a TSE European Pharmacopoeia certificate of suitability for a new source of material or, where applicable, documentary evidence that the source of the TSE risk material for API has previously been assessed by the competent authority of the manufacturing country and demonstrated to comply with the current EMA *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (2011/C 73/01)*. The information should include the following: name of the manufacturer, species and tissues from which the starting material has been obtained, country of origin of the source animals, its use and previous acceptance.
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of API from the approved and proposed manufacturers/sites.
5. The registration form for introduction of changes should clearly outline the approved and proposed manufacturers as listed in section 2.5 of the registration form for state registration of medicinal product.
6. A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where API is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the dossier as responsible for batch release. The declarations should state that API manufacturer(s) operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note of item B.II.b.1).
7. Where relevant, a commitment of the manufacturer of API to inform the registration certificate holder of any changes to the manufacturing process, specifications and test procedures of API.
8. Proof that the proposed site is appropriately authorised for the pharmaceutical form or medicinal product or manufacturing operation, namely:
For a manufacturing site within Ukraine: a copy of the current manufacturing authorisation;
For a manufacturing site outside Ukraine: a copy of the current manufacturing authorisation (if according to manufacturer's country legislation the manufacturing authorisation is available in electronic form only (e.g. USA), the printout with reference to an appropriate registration database (official site) certified by applicant's signature/stamp (if any) should be provided or other licensing document for the pharmaceutical form or medicinal product or manufacturing operation.

B.I.a.2. Changes in the manufacturing process of API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**

a) Minor change in the manufacturing process of the API	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change to the manufacturing process of the API, which may have a significant impact on the quality, safety or efficacy of the medicinal product.			**II**
c) The change refers to a biological/immunological active substance or use of a chemically derived API in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol			**II**
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production			**II**
e) Minor change to the restricted part of an API Master File		**1, 2, 3, 4**	**IB**

Conditions
1. No change in qualitative and quantitative impurity profile or in physico-chemical properties of API. 2. The method of synthesis remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In case of herbal medicinal products, the source of raw material, production of API and the manufacturing route remain the same. 3. The specifications of API or intermediates are unchanged. 4. The change is fully described in the open for applicant part of an API Master File, if applicable. 5. API is not a biological/immunological substance. 6. The change does not refer to the source and manufacturing route of a herbal medicinal product. 7. The change does not refer to the restricted part of an API Master File.
Documentation
1. Amendment of the relevant sections of registration dossier and of the approved API Master File (if applicable) as well as results of the comparison of the approved and proposed production processes. 2. Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process. 3. Copy of approved specifications of API. 4. A declaration from the registration certificate holder or the API Master File Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of API or intermediates are unchanged.
Note for B.I.a.2.b. For chemical API, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important characteristics of the API, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties of the API impacting on bioavailability

B.I.a.3. Change in batch size (including ranges) of API or intermediate used in the manufacturing process of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Up to 10-fold increase compared to the approved batch size	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**

b) Downscaling down to 10-fold	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c) The change requires assessment of the comparability of a biological/immunological active substance			**II**
d) More than 10-fold increase compared to the approved batch size		**1, 2, 3, 4**	**IB**
e) The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line)		**1, 2, 3, 4**	**IB**

Conditions
1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment. 2. Test results of at least two batches according to the specifications should be available for the proposed batch size. 3. API is not a biological/immunological substance. 4. The change does not adversely affect the reproducibility of the process. 5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 6. The specifications of API/intermediates remain the same. 7. API is not sterile. 8. The batch size is within the 10-fold range of the batch size foreseen at the registration or this batch size was not approved as a Type IA variation.
Documentation
1. Amendment of the relevant sections of registration dossier. 2. The batch numbers of the tested batches having the proposed batch size. 3. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of API or intermediate as appropriate, manufactured to both the approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported to the Center if outside specification (with proposed action). 4. Copy of approved specifications of API (and of the intermediate, if applicable). 5. A declaration from the registration certificate holder or the API Matser File holder that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of API/intermediates remain the same.

B.I.a.4. Change to specification in-process tests or limits applied during the manufacture of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new test and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant test	**1, 2, 7**	**1, 2, 5**	**IA**
d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the API			**II**
e) Deletion of an in-process test which may have a significant effect on the overall quality of the API			**II**
f) Addition or replacement of an test as a result of a safety or quality studies		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any previous assessments to review specification limits (e.g. made during expert evaluation of registration materials at registration or introduction of Type II changes). 2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 3. Any change should be within the range of approved specification limits. 4. The test procedure remains the same, or changes in the test procedure are minor. 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for analysis of API of biological origin (does not include standard pharmacopoeial microbiological methods). 7. The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is not used in the manufacture of the API), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.
Documentation
1. Amendment to relevant sections of registration dossier. 2. Comparative table of approved and proposed test methods. 3. Details of any new non-pharmacopoeial test method and validation data, where relevant. 4. Batch analysis data on two production batches (three production batches for API of biological origin, unless otherwise justified) of API for all specification parameters. 5. Justification/risk-assessment from the registration certificate holder or the API Master File Holder as appropriate showing that the parameter changed is non-significant, or it is obsolete. 6. Justification from the registration certificate holder or API Matser File Holder as appropriate for the new test method and limits in specifications.

B.I.a.5. Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Replacement of the strain(s) in a seasonal, prepandemic or a pandemic vaccine against human influenza			**II**

B.1.b) Control of the API

B.I.b.1. Change in the specification parameters and/or limits of an API, or starting material/intermediate/reagent used in the manufacturing process of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of specification limits for medicinal products subject to Official Regulatory Authority Batch Release	**1, 2, 3, 4**	**1, 2**	**IA$_{IN}$**
b) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
c) Addition of a new specification quality parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. an obsolete parameter)	**1, 2, 8**	**1, 2, 6**	**IA**

e) Deletion of a specification parameter which may have a significant effect on the quality of the API and/or the finished medicinal product			**II**
f) Change outside the approved specifications limits range for the API			**II**
g) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the quality of the API and/or the finished product			**II**
h) Addition or replacement (excluding biological or immunological active substance) of a specification parameter with its corresponding test method as a result of a safety or quality studies		**1, 2, 3, 4, 5, 7**	**IB**
i) Where there is no monograph in the SPhU, the European Pharmacopoeia or national pharmacopoeia of an EU state for the API, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 7**	**IB**

Conditions
1. The change is not a consequence of any previous assessments to review specification limits (e.g. made during expert evaluation of registration materials at registration or introduction of Type II changes). 2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 3. Any change should be within the range of approved specification limits. 4. The test procedure remains the same, or changes in the test procedure are minor. 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 6. A new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for API of biological origin (does not include standard pharmacopoeia microbiological methods). 7. For any material, the change does not concern a genotoxic impurity. If it involves the final API, other than for residual solvents which must be in line with ICH limits, any new impurity control should be in line with the SPhU, Ph. Eur. or other harmonized pharmacopoeia, or National Pharmacopoeia of a EU State. 8. The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is not used in the manufacture of the API), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.
Documentation

1. Amendment of the relevant sections of the registration dossier. 2. Comparative table of approved and proposed specifications. 3. Details of any new analytical method and validation data, where relevant. 4. Batch analysis data on two production batches (3 production batches for API of biological origin, unless otherwise justified) of API for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished medicinal product on at least one pilot batch containing API complying with approved and proposed specification. For herbal medicinal products, disintegration data may be acceptable. 6. Justification/risk-assessment from the registration certificate holder or ASMF holder as appropriate showing that the parameter is non-significant. 7. Justification from the registration certificate holder or API Master File Holder as appropriate of the new specification test method and the limits.

B.I.b.2. Change in test procedure for API or starting material/ intermediate/reagent used in the manufacturing process of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure for the API or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	**7**	**1**	**IA**
c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the quality of the API	**1, 2, 3, 5, 6**	**1, 2**	**IA**
d) Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological API			**II**
e) Other changes to a test procedure (including replacement or addition) for the API or a starting material/intermediate		**1, 2**	**IB**

Conditions
1. Validation studies having been performed in accordance with the current pharmacopoeial requirements or current Note for Guidance on validation of analytical procedures confirm that the results of analysis obtained by approved or proposed method are identical. 2. There have been no changes of the total impurity limits, no new unqualified impurities are detected. 3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 4. A new test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for API of biological origin (does not include standard pharmacopoeial microbiological methods). 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 6. The API is not active substance of biological/immunological origin. 7. There is an approved test method for specification parameter and this method has not been approved through type IA variation.
Documentation

1. Amendment of the relevant sections of the registration dossier, including a description of test methods, a report of validation data, revised limits for impurities (if applicable). 2. Comparative validation data, or if justified comparative analysis results showing that the approved test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c) Container closure system

B.I.c.1. Change in immediate packaging of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Changes to qualitative and/or quantitative composition	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
b) Changes to qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			**II**
c) Liquid API (non sterile)		**1, 2, 3, 5, 6**	**IB**

Conditions
1. The proposed packaging material must be equivalent to the approved material in respect of its relevant quality properties. 2. Stability studies have been started under the EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 of at least two pilot scale or industrial scale batches of API and at least three months satisfactory stability data are at the disposal of the applicant at time of release. However, if the proposed packaging is more resistant than the approved packaging, the three months' stability data do not yet have to be available. The guarantees shall be provided that these studies will be finalised and the data of finalised studies will be provided immediately to the Center if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action). 3. Sterile API, liquid API and biological/immunological active substances are excluded.
Documentation

1. Amendment of the relevant sections of the registration dossier.
2. Appropriate data on the new packaging (e.g. comparative data on permeability e.g. for O_2, CO_2 moisture), including a confirmation that the packaging material complies with current relevant pharmacopoeial requirements or EU legislation on safety of plastic packaging materials and objects in contact with foodstuffs.
3. Proof must be provided that no interaction between the API and the packaging material occurs (e.g. no migration of components of the proposed packaging material into API and no loss of components of the product into the pack), including confirmation that the packaging material complies with current relevant pharmacopoeial requirements or EU legislation on safety of plastic material and objects in contact with foodstuffs.
4. A confirmation from the registration certificate holder or the API Master File holder as appropriate that the stability studies have been started under EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (with indication of the batch quantity and numbers of API) and that, as relevant, the required minimum stability data was submitted by the applicant at time of introduction of variation and that the available data did not indicate a problem related to stability. Assurance should also be given that the studies will be finalised and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of shelf life/retest period (with proposed action).
5. The results of stability studies that have been carried out under EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013, on the relevant parameters, on at least two pilot or industrial scale batches of API with satisfactory stability data, covering a minimum period of three months. Assurance should be given that these studies will be finalised, and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of shelf life/retest period (with proposed action).
6. Comparative table of the approved and proposed specifications, if applicable.

B.I.c.2. Change in the specification parameters and/or limits of the immediate packaging of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality study		**1, 2, 3, 4, 6**	**IB**

Conditions
1. The change is not a consequence of any previous assessments to review specification parameters (e.g. made during expert evaluation of registration materials at registration or introduction of Type II changes) unless it has been previously assessed and agreed as part of a follow-up measure. 2. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of API. 3. Any change should be within the range of approved specification. 4. The test procedure remains the same, or changes in the test procedure are minor. 5. Any new test method does not concern a non-standard technique or a standard technique used in a novel way.

Documentation
1. Amendment of the relevant sections of the registration dossier. 2. Comparative table of approved and proposed specifications. 3. Details of any new test method and validation data where relevant. 4. Batch analysis data on two batches of the immediate packaging for all specification parameters. 5. Justification/risk assessment from the registration certificate holder or the API Naster File Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete. 6. Justification from the registration certificate holder or the API Master File Holder, as appropriate, of the new specification parameter and the limits.

B.I.c.3. Change in test procedure for the immediate packaging of the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**

Conditions
1. Appropriate validation studies were performed in accordance with the current pharmacopoeial requirements or Note for Guidance on validation of analytical procedures (current edition), and their results show that the proposed test procedure is equivalent to the approved test procedure. 2. The test method should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 4. The API is not biological/immunological. 5. There is a test procedure approved for the specification parameter and this procedure has not been approved through type IA variation.
Documentation
1. Amendment to relevant sections of the registration dossier including a description of the analytical methodology and a report on validation data. 2. Comparative validation data or if justified comparative analysis results showing that the approved test and a new one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.d) Stability

B.I.d.1. Change in the re-test period/storage period or storage conditions of the API (where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Re-test period/storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**
2. Extension of the retest period based on extrapolation of stability data not in accordance with EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013*			**II**

3. Extension of storage period of a biological/ immunological active substance supported by results of the studies conducted not in accordance with an approved stability protocol			**II**
4. Extension or introduction of a re-test period/storage period supported by results of real time study		**1, 2, 3**	**IB**
b) Storage conditions			
1. More restrictive storage conditions	**1**	**1, 2, 3**	**IA**
2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with an approved protocol			**II**
3. Change in storage conditions of the API		**1, 2, 3**	**IB**
c) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**

Conditions
1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing
Documentation
1. Amendment of the relevant sections of the registration dossier must contain results of real time stability studies, conducted in accordance with the EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 on at least two (three for biological medicinal products) pilot or production scale batches of API in the approved packaging material covering the requested re-test period and requested storage conditions. 2. Confirmation that stability studies have been done according to the approved protocol. The studies must confirm that the specifications are met. 3. Copy of approved specifications of API. 4. Justification for the proposed changes.
*Retest period not applicable for biological/immunological active substance.

B.1.e) Design space and postregistration change management protocol

B.I.e.1. Introduction of a new design space or extension of an approved design space for the API, concerning:	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) One unit operation in the manufacturing process of the API including the in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for starting materials/reagents/ intermediates and/or the API		**1, 2, 3**	**II**

Documentation

1. The design space has been developed in accordance with the scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of API has been achieved. 2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges. 3. Amendment of the relevant sections of the registration dossier.

B.I.e.2. Introduction of a postregistration change management protocol related to the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
		1, 2, 3	**II**

Documentation
1. Detailed description for the proposed change. 2. Change management protocol related to API. 3. Amendment of the relevant section(s) of the dossier.

B.I.e.3. Deletion of an approved change management protocol related to the API	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IA_{IN}**

Conditions
The deletion of the approved change management protocol related to the API is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.
Documentation
1. Justification for the proposed deletion. 2. Amendment of the relevant section(s) of the dossier.

B.I.e.4. Changes to an approved change management protocol	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**
Documentation			
Declaration that any change should be within the range of currently approved limits. Declaration that an assessment of comparability is not required for biological/immunological medicinal products.			

B.I.e.5. Implementation of changes foreseen in an approved change management protocol	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IA_{IN}**

b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**

Conditions
The proposed change has been performed fully in line with the approved change management protocol.
Documentation
1. Reference to the approved change management protocol. 2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. Declaration that an assessment of comparability is not required for biological/immunological medicinal products. 3. Results of the studies performed in accordance with the approved change management protocol. 4. Amendment of the relevant section(s) of the dossier. 5. Copy of approved specifications of the API.

B.II. FINISHED MEDICINAL PRODUCT

B.II.a) Description and composition

B.II.a.1. Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for medicinal product marking	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Changes in imprints, bossing or other markings	**1, 2, 3, 4**	**1, 2**	**IA$_{IN}$**
b) Changes in scoring/break lines intended to divide tablets into equal doses		**1, 2, 3**	**IB**
Conditions			
1. Finished medicinal product release and end of shelf life specifications have not been changed (except for appearance). 2. Any new ink must comply with the requirements for pharmaceutical products. 3. The scoring/break lines are not intended to divide into equal doses. 4. Any medicinal product markings used to differentiate strengths should not be completely deleted			
Documentation			
1. Amendment of the relevant sections of the registration dossier, including a detailed drawing or written description of the approved and proposed appearance of medicinal product, and including revised summary of product characteristics as appropriate. 2. Samples of the finished medicinal product, where applicable. 3. Results of the pharmacopoeial tests demonstrating equivalence in characteristics/correct dosing of medicinal product.			

B.II.a.2. Change in the shape or dimensions of the pharmaceutical form	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Immediate release tablets, capsules, suppositories and pessaries	**1, 2, 3, 4**	**1, 4**	**IA$_{IN}$**

b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses		**1, 2, 3, 4, 5**	**IB**
c) Addition of a new kit for a radiopharmaceutical preparation with another fill volume			**II**
Conditions			
1. If appropriate, the comparison of dissolution profile of the medicinal product with new and approved shape or dimensions. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration data shall be provided. 2. Release and end of shelf-life specifications of medicinal product have not been changed (except for dimensions). 3. The qualitative or quantitative composition and mean mass of medicinal product remain unchanged. 4. The change does not relate to a scored tablet that is intended to be divided into equal doses.			
Documentation			
1. Amendment of the relevant sections of the registration dossier, including a detailed drawing of the approved and proposed shape and dimensions, and including revised summary of product characteristics as appropriate. 2. Comparative data on at least one pilot batch of medicinal product confirming no differences in dissolution profile for new and approved shape or dimensions. For herbal medicinal product disintegration data may be acceptable. 3. Justification for not conducting a new bioequivalence study according to the EMA Guideline on the investigation of bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1 or MoH Ukraine document 42-7.1:2014. 4. Samples of the finished medicinal product with new shape or dimensions (if necessary). 5. Results of the pharmacopoeial tests demonstrating equivalence in characteristics/correct dosing of medicinal product.			
Note for B.II.a.2.c): any change to the strength of the medicinal product requires a new registration.			

B.II.a.3. Changes in the composition (excipients) of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Flavouring or colouring system			
1. Addition, deletion or replacement	**1, 2, 3, 4, 5, 6, 7, 9**	**1, 2, 4, 5, 6**	**IA$_{IN}$**
2. Increase or reduction	**1, 2, 3, 4**	**1, 2, 4**	**IA**
b) Other excipients			
1. Any minor change to the quantitative composition of the finished medicinal product with respect to excipients	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**IA**
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the finished medicinal product			**II**
3. Change that relates to a biological/immunological medicinal product			**II**

4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			**II**
5. Change that is supported by a bioequivalence study			**II**
6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**

Conditions
1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile. 2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which makes up a major part of the finished medicinal product formulation. 3. The finished medicinal product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test, if necessary. 4. Stability studies have been started under the EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (with indication of batch numbers) for at least two pilot scale or industrial scale batches with satisfactory stability data during three months (at the time of application for Type IA or Type IB variation) showing similar stability profile to the approved one. Applicant ensures that these studies will be finalised and that data will be provided after study termination immediately to the Center if outside specifications or potentially outside specification at the end of the shelf life (with proposed action). In addition, where relevant, photostability testing of the finished medicinal product should be performed. 5. Any new components must comply with the established requirements. 6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk. 7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations. 8. The dissolution profile of at least two pilot scale batches of proposed and approved composition of medicinal product shows no differences. For herbal medicinal products where dissolution testing may not be feasible, the disintegration data shall be provided. 9. The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths. 10. The medicinal product is not a biological/immunological product.
Documentation

1. Amendment of the relevant sections of the registration dossier, including identification method for any new colorant, where relevant, and including revised summary of product characteristics, instructions for medical use and and labelling text on package (if necessary).
2. A declaration that the stability studies have been started under the EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (with indication of the batch numbers) and that, as relevant, the required minimum stability data were submitted by by the applicant at time of introduction of variation and that the available data did not indicate a stability problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the Center after the study termination if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action).
3. The results of stability studies that have been carried out under the EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013, on the relevant parameters, on at least two pilot or industrial scale batches of API with satisfactory stability data, covering a minimum period of three months. An assurance is given that these studies will be finalised, and that data will be provided after study termination immediately to the Center if outside specifications or potentially outside specifications at the end of shelf life (with proposed action).
4. Sample of the new medicinal product with new composition (if necessary).
5. Either a Ph. Eur. Certificate of Suitability for any new starting material of animal origin susceptible to TSE risk or where applicable, documentary evidence that the source of the TSE risk excipient has been previously assessed by the competent authorities of country manufacturer and shown to comply with the current EMA *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (2011/C 73/01)*. The information should include: name of manufacturer, species and tissues from which the starting material is a derivative, country of origin of the source animals and its use.
6. Data to demonstrate that the new excipient does not interfere with the finished medicinal product specification test methods, if appropriate.
7. Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
8. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of medicinal product in the new and approved composition. For herbal medicinal products, disintegration data may be acceptable.
9. Justification for not submitting a new bioequivalence study according to the EMA *Guideline on the investigation of bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1* or MoH Ukraine document 42-7.1:2014 (current edition).

B.II.a.4. Change in coating weight of oral dosage forms or change in weight of capsule shells	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Solid oral pharmaceutical forms	**1, 2, 3, 4**	**1, 2**	**IA**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism			**II**

Conditions

1. No changes in dissolution profile of at least two pilot scale batches of the medicinal product with proposed and approved composition. For herbal medicinal products where dissolution testing may not be feasible, the disintegration data may be acceptable. 2. The coating is not a critical factor for the release mechanism. 3. The finished medicinal product specification has only been updated in respect of weight and dimensions, if applicable. 4. Stability studies in accordance with the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) have been started with at least two pilot scale or industrial scale batches, and at least three months' satisfactory stability data are available. Applicant ensures that these studies will be finalised and that data will be provided after study termination immediately to the Center if outside specifications or potentially outside specification at the end of the shelf life (with proposed action).
Documentation
1. Amendment of the relevant sections of the registration dossier. 2. A declaration that the stability studies have been started under the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) (with indication of the batch numbers) and that, as relevant, the required minimum stability data were submitted by the applicant at time of implementation of variation. Assurance should also be given that the studies will be finalised and that data will be provided after study termination immediately to the Center if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action). In addition, where relevant, photostability testing of the finished medicinal product should be performed.

B.II.a.5. Change in concentration of a single-dose, total use parenteral medicinal product, where the amount of API per unit dose (i.e. the strength) remains the same	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II

B.II.a.6. Deletion of the solvent/diluent container from the pack	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
		1, 2	**IB**

Documentation
1. Justification for the deletion, including a statement regarding alternative means to obtain the solvent/diluent as required for the safe and effective use of the medicinal product. 2. Revised summary of product characteristics, instructions for medical use and labelling text on package.

B.II.b. Manufacture

B.II.b.1. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Secondary packaging site	**1, 2**	**1, 3, 8**	**IA IN**
b) Primary packaging site	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IA IN**

c) Site where any manufacturing operation(s) take place, except batch release, quality control, and secondary packaging, for biological/ immunological medicinal products or for pharmaceutical forms manufactured by complex manufacturing processes			**II**
d) Site which requires an initial or product specific inspection			**II**
□ e) Site where any manufacturing operation(s) take place, except batch release, quality control, primary and secondary packaging, for non-sterile medicinal products		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
□ f) Site where any manufacturing operation(s) take place, except batch release, quality control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products		**1, 2, 3, 4, 5, 6, 7, 8**	**IB**

Conditions
1. Satisfactory inspection of manufacture in the last three years by competent authorities of PIC/S countries, WHO inspectors, Ukraine's competent authority. 2. Site appropriately authorised to manufacture the pharmaceutical form or medicinal product. 3. Medicinal product is not a sterile product. 4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the approved protocol with at least three production scale batches. 5. The medicinal product is not a biological/immunological medicinal product.
Documentation

1. For a manufacturing site within Ukraine - a copy of the current manufacturing authorisation;
For a manufacturing site outside Ukraine - a copy of the current manufacturing authorisation (if according to manufacturer's country legislation the manufacturing authorisation is available in electronic form only (e.g. USA), the printout with reference to an appropriate registration database (official site) certified by applicant's signature/stamp (if any) or other licensing document for the pharmaceutical form or medicinal product or manufacturing operation;
Certified copy of the document confirming the compliance of manufacture of the medicinal product with Good Manufacturing Practice requirements issued by the State Administration of Ukraine on Medicinal Products according to provisions of the Procedure for confirming compliance of manufacture of medicinal products with GMP approved by MoH Ukraine Order of December 27, 2012 № 1130 registered with the Ministry of Justice of Ukraine of January 21, 2013 №133/22665 (as amended) or applicant's letter of guarantee to submit such document during specialized expert evaluation.
If applicable conclusions of other inspections performed. Copies of documents shall be certified by signature/stamp of the applicant's/applicant' representative in Ukraine (if any).
2. Where relevant, the batch quantity (≥ 3), batch numbers, batch size and the manufacturing date of batches used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3. The registration form for introduction of variation should clearly outline the 'approved' and 'proposed' finished medicinal product manufacturers as listed in section 2.5 of the registration form for state registration.
4. Copy of approved release and end-of-shelf life specifications if relevant.
5. Comparative batch analysis data on one production batch and two pilot-scale batches (or two production batches) manufactured at proposed site and on the three batches from the approved site; batch data on the next two production batches should be available on request or reported to the Center if outside specifications (with proposed action).
6. For semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique should be provided.
7. If the new manufacturing site uses API as a starting material – A declaration by the Qualified Person (QP) that API is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.
8. Amendment of the relevant sections of the materials of registration dossier.
9. If the manufacturing site and the primary packaging site of the finished medicinal product are different, conditions of transport and storage of the finished medicinal product in bulk should be specified and validated.

Note.
In case of no GMP certificate recognized in Ukraine, registration certificate holders are advised to consult the relevant competent authorities first before making the submission of the application and to provide information about any previous manufacturing inspection in the last 2- 3 years and/or any planned inspection(s) including inspection dates, medicinal product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a good manufacturing practice inspection if needed.

QP Declarations in relation to API

Manufacturers are obliged to only use as starting materials API that have been manufactured in accordance with good manufacturing practice. So an appropriate declaration should be submitted by each of the manufacturing authorisation holders that use the API as a starting material. In addition, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification should be submitted when the batch release site is a different site from the above.
In many cases only one manufacturing authorisation holder is involved and therefore only one QP declaration will be required. However, when more than one manufacturing authorisation holder is

involved rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP provided: the declaration makes it clear that it is drawn up on behalf of all the involved QPs. Manufacturing and analysis is performed under an agreement between applicant and manufacturer as described in Chapter 7 of the GMP Guide where the responsibilities of each party are stated and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the API manufacturer(s). **Note.** Manufacturing and analysis under the agreement are subject to inspection by the competent authorities. Applicants shall take into consideration that a Qualified Person of a manufacturing authorisation holder is located in the EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within mutual recognision agreement partner countries are not acceptable. According to Article 46a(1) of Directive 2001/83/EC, manufacture of API as starting materials includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or relabeling as carried out by a distributor of starting materials. A declaration is not required for blood or blood components which are subject to the requirements of Directive 2002/98/EC of the European Parliament and of the Council.

B.II.b.2. Change to importer/batch release arrangements and quality control testing of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Replacement or addition of a site where batch control/testing takes place	**2, 3, 4, 5**	**1, 2, 5**	**IA**
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological medicinal product and any of the test methods performed at the site is a biological/immunological method			**II**
c) Replacement or addition of a manufacturer responsible for importation and/or batch release			
1. Not including batch control/testing	**1, 2, 5**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
2. Including batch control/testing	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
3. Including batch control/testing for a biological/immunological medicinal product and any of the test methods performed at that site is a biological/immunological/immunochemical method			**II**

Conditions
1. The manufacturer responsible for batch release must be located within the EEA. 2. The site is appropriately authorised. 3. The medicinal product is not a biological/immunological medicinal product. 4. Transfer from the approved to the new site or new test laboratory has been successfully completed. 5. At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement exists between the country concerned and the EU, that is able to carry out medicinal product testing for the purpose of batch release within the EU/EEA.
Documentation

1. For a manufacturing site within Ukraine - a copy of the current manufacturing authorisation;
For a manufacturing site outside Ukraine - a copy of the current manufacturing authorisation (if according to manufacturer's country legislation the manufacturing authorisation is available in electronic form only (e.g. USA), the printout with reference to an appropriate registration database (official site) certified by applicant's signature/stamp (if any) or other licensing document for the pharmaceutical form or medicinal product or manufacturing operation;
Certified copy of the document confirming the compliance of manufacture of the medicinal product with Good Manufacturing Practice requirements issued by the State Administration of Ukraine on Medicinal Products according to provisions of the Procedure for confirming compliance of manufacture of medicinal products with GMP approved by MoH Ukraine Order of December 27, 2012 № 1130 registered with the Ministry of Justice of Ukraine of January 21, 2013 №133/22665 (as amended) or applicant's letter of guarantee to submit such document during specialized expert evaluation.
If applicable conclusions of other inspections performed. Copies of documents shall be certified by signature/stamp of the applicant's/applicant' representative in Ukraine (if any).
2. The variation registration form shall clearly outline "approved" and "proposed" finished product manufacturers as listed in section 2.5 of the registration form for state registration.
3. For centralised procedure only: contact details of new contact person in the EEA for product defects and recalls, if applicable.
4. A declaration by the Qualified Person (QP) responsible for batch quality control stating that the API is manufactured in compliance with the guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note to item B.II.b.1).
5. Amendment of the relevant section(s) of the registration dossier including revised summary of product characteristics, instructions for medical use and and labelling text on package (if necessary).

B.II.b.3. Change in the manufacturing process of the finished medicinal product, including an intermediate used in the manufacture of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor change in the manufacturing process	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 6, 7, 8**	**IA**
b) Substantial change to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			**II**
c) The medicinal product is a biological/immunological medicinal product and the change requires a comparative study			**II**
d) Introduction of a non-standard terminal sterilisation method			**II**
e) Introduction or increase in the overage that is used for the API			**II**
f) Minor change in the manufacturing process of an aqueous oral suspension		**1, 2, 4, 6, 7, 8**	**IB**

Conditions

1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.
2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product is not a biological/immunological or herbal medicinal product;
or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished medicinal product (regardless of the type of medicinal product and/or dosage form).
3. The manufacturing process including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any solvent used in the manufacturing process.
4. The approved manufacturing process has to be controlled by relevant controls and no changes (widening or deletion of limits) are required to these controls.
5. The specifications of the finished medicinal product or intermediates are unchanged.
6. The new manufacturing process must ensure production of a medicinal product identical to previous one regarding all aspects of quality, safety and efficacy.
7. Stability studies in accordance with the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) have been started with at least one pilot scale or industrial scale batch and at least 3 months satisfactory stability data. Assurance is given by the applicant that these studies will be finalised and that after completion of studies the data will be provided immediately to the Center if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action).

Documentation

1. Amendment of the relevant sections of the registration dossier including a comparison of the approved and proposed manufacturing process.
2. For semi-solid and liquid dosage forms in which the API is present in non-dissolved form: appropriate data on validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.
3. For solid dosage forms: data confirming lack of change in dissolution profile of one production batch manufactured by changed process comparing with the last three batches from the approved process. Data on the next two full production batches should be available on request or reported to the Center if outside specification (with proposed action). For herbal medicinal products, disintegration data may be acceptable
4. Justification for not conducting a bioequivalence study according to the EMA Guideline on the investigation of bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1 or MoH Ukraine document 42-7.1:2014 (current edition).
5. For changes to process parameter(s) that have been considered to have no impact on the quality of the finished medicinal product, declaration that a lack of such impact was confirmed in the context of the previously approved risk assessment.
6. Copy of approved release and end-of-shelf life specifications.
7. Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the approved and the proposed process. Data on the next two full production batches should be made available upon request and reported to the center if outside specification (with proposed action).
8. Confirmation that stability studies have been started under EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) (with indication of the batch numbers concerned) with at least two pilot scale or industrial scale batches, and with at least three months satisfactory stability data, and that the stability profile is similar to one of the medicinal product manufactured with the approved process. Assurance is given that these studies will be finalised and that after the completion of studies the data will be provided immediately to the Center if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.b.4. Change in the batch size (including batch size ranges) of the finished medicinal product	Conditions to be met	Documents to be submitted	Type of variation
a) Up to 10-fold compared to the approved batch size	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c) The change requires assessment of the comparability (comparative studies) of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study			**II**
d) The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes			**II**
e) More than 10-fold increase compared to the approved batch size for immediate release solid oral pharmaceutical forms		**1, 2, 3, 4, 5, 6**	**IB**
f) The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)		**1, 2, 3, 4, 5, 6**	**IB**
Conditions			
1. The change does not affect the reproducibility and/or consistency of the medicinal product. 2. The change relates only to immediate release solid oral pharmaceutical forms and non-sterile liquid pharmaceutical forms. 3. Any changes to the manufacturing method and/or to the in-process controls are those necessitated by the change in batch size, e.g. use of different-sized equipment. 4. Validation scheme is available or validation of the manufacture has been successfully carried out according to the approved protocol with at least three batches of the medicinal product at the new batch size in accordance with the EMA Guidance on validation of analytical procedures or MoH Ukraine document 42-3.5:2004 (current edition) . 5. The medicinal product is not a biological/immunological medicinal product. 6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 7. The batch size is within the 10-fold range of the batch size foreseen at the registration or this batch size is not approved as a Type IA variation			
Documentation			

1. Amendment of relevant sections of the registration dossier.
2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the approved and the proposed sizes. Data on the next two full production batches should be made available upon request and reported to the Center if outside specifications (with proposed action).
3. Copy of approved release and end-of-shelf life specifications.
4. Information on batch quantity (≥3), batch numbers, batch size of medicinal products and the manufacturing date of batches used in the validation study should be indicated or validation scheme be submitted.
5. The validation results.
6. The confirmation that stability studies have been started under EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) (with indication of batch quantity and batch numbers), for at least one pilot or industrial scale batch, with satisfactory stability data covering a minimum period of three months. An assurance is given that these studies will be finalised, and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action). For biologicals/immunological medicinal products: a confirmation that an assessment of comparability is not required.

B.II.b.5. Change to specification tests or limits applied during the manufacture of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new test(s) and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c) Deletion of a non-significant in-process test	**1, 2, 7**	**1, 2, 6**	**IA**
d) Deletion of an in-process test which may have a significant effect on the overall quality of the finished medicinal product			**II**
e) Widening of the approved limits for parameters, which may have a significant effect on overall quality of the finished medicinal product			**II**
f) Addition or replacement of an in-process test as a result of a safety or quality study		**1, 2, 3, 4, 5, 7**	**IB**

Conditions
1. The change is not a consequence of previous assessments to review specification limits (e.g. made during expert evaluation of registration materials for the registration or introduction of a type II variation). 2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 3. Any change should be within the range of the approved specification limits. 4. The test procedure remains the same, or changes in the test procedure are minor. 5. Any new test method does not concern a novel non-standard technique or standard technique used in a novel way. 6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological API (does not include standard pharmacopoeial microbiological methods). 7. The in-process test does not concern the control of a critical parameter, e.g.: assay; impurities (unless a particular solvent is not used in the manufacture); any critical physical characteristics (particle size, bulk, tapped density, etc.); identity test (unless there is a suitable alternative control already present); microbiological control (unless not required for the particular dosage form)
Documentation
1. Amendment of relevant sections of the registration dossier. 2. Comparative table of approved and proposed tests and limits. 3. Details of any new analytical method and validation data where relevant. 4. Batch analysis data on two production batches (3 production batches for biological medicinal products, unless otherwise justified) of the finished medicinal product for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished medicinal product on at least one pilot batch manufactured using the approved and proposed conditions. For herbal medicinal products, disintegration data may be acceptable. 6. Justification/risk-assessment showing that the parameter changed is non-significant. 7. Justification of the new in-process test and limits.

B.II.c) Control of excipients

B.II.c.1. Change in the specification parameters and/or limits of an excipient	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 7**	**IA**
d) Change outside the approved specifications limits range			**II**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished medicinal product			**II**

f) Addition or replacement (excluding biological or immunological medicinal product) of a specification parameter with its corresponding test method, as a result of a safety or quality study		**1, 2, 3, 4, 5, 6, 8**	**IB**
g) Where there is no monograph in the SPhU, European Pharmacopoeia or national pharmacopoeia of an EU state for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 6, 8**	**IB**

Conditions
1. The change is not a consequence of previous assessments to review specification limits (e.g. made during expert evaluation of registration materials for the registration or introduction of a type II variation). 2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 3. Any change should be within the range of approved specification limits. 4. The test procedure remains the same, or changes in the test procedure are minor. 5. Any new test methods do not concern a novel non-standard technique or standard technique used in a novel way. 6. A new test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). 7. The change does not concern a genotoxic impurity. 8. The in-process test does not concern the control of a critical parameter, e.g.: impurities (unless a particular solvent is not used in the manufacture); any critical physical characteristics (particle size, bulk, tapped density, etc.); identity test (unless there is a suitable alternative control already present); microbiological control (unless not required for the particular dosage form).
Documentation
1. Amendment of relevant sections of the registration dossier. 2. Comparative table of approved and proposed specifications. 3. Details of any new analytical method and validation data where relevant. 4. Batch analysis data on two production batches (3 production batches for biological medicinal products unless otherwise justified) of the finished medicinal product for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished medicinal product on at least one pilot batch containing the excipient complying with the approved and proposed specification. For herbal medicinal products disintegration data may be acceptable. 6. Justification of a lack of new bioequivalence data according to the EMA Guideline on the investigation of bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1 or MoH Ukraine document 42-7.1:2014 (current edition) (if applicable). 7. Justification/risk assessment showing that the parameter changed is non-significant or that the specification parameter is obsolete. 8. Justification of the new specification parameter and the limits.

B.II.c.2. Change in test procedure for an excipient	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor changes to the approved test procedures	**1, 2, 3, 4**	**1, 2**	**IA**

b) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
c) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**

Conditions
1. Validation studies have been performed in accordance with the the current pharmacopoeial requirements or the EMA Guidance on validation of analytical procedures (current edition), and study results show that new test procedure is equivalent to the approved one. 2. There have been no changes of the total impurity limits; no new unqualified impurities are detected. 3. The method of analysis should remain the same (e.g., a change in column length or temperature, but not a different type of column or method). 4. A new test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). 5. A test procedure is already approved for the specification parameter and this procedure has not been approved through Type IA variation.
Documentation
1. Amendment of relevant sections of the registration dossier including a description of the analytical methodology, a report on validation data, revised specifications for impurities (if applicable). 2. Comparative validation results or if justified comparative analysis results showing that the approved test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.c.3. Change in source of an excipient or reagent with TSE risk	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) From TSE risk material to vegetable or synthetic origin			
1. For excipients or reagents not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product	**1**	**1**	**IA**
2. For excipients or reagents used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product		**1, 2**	**IB**
b) Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability			**II**

Conditions
1. Excipient and finished medicinal product release and end-of-shelf life specifications remain the same.

Documentation
1. Declaration from the manufacturer or applicant confirming that excipient is purely of vegetable or synthetic origin. 2. Results of equivalence study of the materials and the impact on production of the final material and impact on behaviour (e.g. Dissolution characteristics) of the finished medicinal product.

B.II.b.4. Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished medicinal product.			**II**
c) The excipient is a biological/immunological substance			**II**

Conditions
1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are in accordance with the EMA guidelines), or in physico-chemical properties. 2. Vaccine adjuvants are excluded.
Documentation
1. Amendment of relevant sections of the registration dossier. 2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the approved and the new process. 3. Where appropriate, comparative dissolution profile data for the finished medicinal product of at least two batches (minimum pilot scale) using excipient manufactured by approved and new process (if necessary). For herbal medicinal products, disintegration data may be acceptable. 4. Copy of approved and new (if applicable) specifications of the excipient.

B.II.d) Control of the finished medicinal product

B.II.d.1. Change in the specification parameters and/or limits of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening of specification limits for medicinal products subject to batch release approval by an official regulatory authority	**1, 2, 3, 4**	**1, 2**	**IA$_{IN}$**
c) Addition of a new parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	**1, 2**	**1, 2, 6**	**IA**
e) Change outside the approved specifications limits range			**II**

f) Deletion of a parameter which may have a significant effect on the quality of the finished medicinal product			**II**
g) Addition or replacement (excluding biological or immunological medicinal product) of a specification parameter as a result of a safety or quality study		**1, 2, 3, 4, 5, 7**	**IB**
h) Update of the dossier to comply with the provisions of an updated general monograph of the SPhU/Ph. Eur for the finished dosage form*	**1, 2, 3, 4, 7, 8**	**1, 2**	**IA_{IN}**
i) Changes to the dossier to comply with the introduced SPhU/Ph. Eur. General Chapter 2.9.40 Uniformity of dosage units to replace the approved, either Ph. Eur. 2.9.5 (Uniformity of mass). or Ph. Eur. 2.9.6 (Uniformity of content)	**1, 2, 10**	**1, 2, 4**	**IA**

Conditions

1. The change is not a consequence of any previous assessments to review specification limits (e.g. made during expert evaluation of registration materials at registration or introduction of Type II changes).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of approved specification limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.
7. The change does not concern any impurities (including genotoxic) or dissolution.
8. The updating of the "Microbiological purity" test (the microbial control limits) to be in line with the current Pharmacopoeia, and the approved test are in line with the pre January 2008 (non-harmonised test) and does not include any additional specified controls for the particular dosage form and the proposed controls are in line with the harmonised pharmacipoeial monograph.
9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example:
assay;
impurities (unless a particular solvent is not used in the manufacture);
any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.);
a test that is not required for the particular dosage form in accordance with the general notices of the SPhU or Ph. Eur.;
any request for skip testing.
10. The proposed test (control) is fully in line with the Table 2.9.40.-1 of the SPhU/Ph. Eur. 2.9.40 monograph, and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.

Documentation

1. Amendment of relevant sections of the registration dossier. 2. Comparative table of approved and proposed specifications. 3. Details of any new analytical method and validation data, where relevant. 4. Batch analysis data on two production batches (3 production batches for biological medicinal products, unless otherwise justified) of the finished medicinal product for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished medicinal product on at least one pilot batch complying with the approved and proposed specification. For herbal medicinal products, disintegration data may be acceptable. 6 Justification/risk assessment showing that the parameter changed is non-significant or that this parameter is obsolete. 7. Justification of the new parameter and the limits
*There is no need to notify the competent authorities of a change to comply with an updated monograph of the SPhU, European pharmacopoeia or a national pharmacopoeia of an EU state in the case that reference is made to the 'current edition' in the dossier of an registered medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the dossier and the variation is made to comply with the updated version.

B.II.d.2. Change in test procedure for the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure if an alternative method is already authorised	**4**	**1**	**IA**
c) Substantial change to, or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
e) Update of the test procedure to comply with the updated general monograph in the SPhU or Ph. Eur.	**2, 3, 4, 5**	**1**	**IA**
f) To reflect compliance with the SPhU or Ph.Eur. and remove reference to the outdated internal test method and its number*	**2, 3, 4, 5**	**1**	**IA**

Conditions
1. Validation studies have been performed in accordance with the current pharmacopoeial requirements or the EMA Guidance on validation of analytical procedures (current edition), and conducted studies show that the new test procedure is equivalent to the approved test procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities are detected. 3. The method of analysis should remain the same (e.g. change in column length or temperature, but not a different type of column or method). 4. A new test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). 5. The approved test procedure already refers to the general monograph of the SPhU or Ph. Eur. and any changes are minor in nature and require update of the dossier.
Documentation

1. Amendment of appropriate sections of the registration dossier, including a description of the analytical methodology, a report of validation data, revised specifications for impurities (if applicable. 2. Comparative validation results or if justified comparative analysis results showing that the approved test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.
* There is no need to notify the competent authorities of a change to comply with an updated monograph of the SPhU, European pharmacopoeia or a national pharmacopoeia of an EU state in the case that reference is made to the 'current edition' in the dossier of an registered medicinal product.

B.II.d.3. Variations related to the introduction of real-time release or parametric release in the manufacture of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II

B.II.e) Container closure system

B.II.e.1. Change in immediate packaging of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
2. Semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological/ immunological medicinal products			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life			**II**
b) Type of container or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological/ immunological medicinal products			**II**
3. Deletion of an immediate packaging container that does not lead to the complete deletion of a specific strength or specific pharmaceutical form of the medicinal product	**4**	**1, 8**	**IA**

Conditions

1. The change only concerns the same packaging/container type (e.g. blister to blister). 2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. 3. Stability studies have been started under the EMA guidelines on stability testing (current edition) or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 of at least two pilot scale or industrial scale batches of API with at least three months satisfactory stability data. However, if the proposed packaging is more resistant than the approved packaging, the three months stability data do not yet have to be available. The guarantees shall be provided that these studies will be finalised and the data of finalised studies will be provided immediately to the Center if outside specifications or potentially outside specifications at the end of the shelf-life (with proposed action). 4. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics and instructions for medical use of the medicinal product.
Documentation
1. Amendment of relevant sections of the registration dossier including revised summary of product characteristics, instructions for medical use and labelling text on packaging (if appropriate). 2. Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture). 3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed packaging material into the medicinal product and and vice versa), including confirmation that the packaging material complies with current pharmacopoeial requirements for packaging material or EU legislation on safety of plastic material and objects in contact with foodstuffs. 4. A declaration that the stability studies have been started under the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) (with indication of the batch numbers) and that, as relevant, the required minimum stability data were submitted by the applicant at time of variation implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action). 5. The results of stability studies that have been started under the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition), on the relevant stability parameters, on at least two pilot or industrial scale batches of medicinal product, covering a minimum period of three months satisfactory stability data. An assurance is given that these studies will be finalised, and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of shelf life (with proposed action). 6. Comparative table of the approved and proposed specifications, if applicable. 7. Samples of the new container/closure where applicable. 8. Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment recommended in the approved summary of product characteristics and instructions for medical use of the medicinal product.
Note for B.II.e.1.b. Any change which results in a new pharmaceutical form requires a new registration.

B.II.e.2. Change in the specification parameters and/or limits of the immediate packaging of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**

c) Deletion of a non-significant parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a parameter as a result of a safety or quality studies		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any previous assessments to review specification limits (e.g. made during expert evaluation of registration materials at registration or introduction of Type II changes).
2. The change does not result from unexpected events arising during manufacture.
3. Any change should be within the range of approved specification limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant sections of the registration dossier.
2. Comparative table of approved and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.
5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
6. Justification of the new quality parameter and the limits

B.II.e.3. Change in test procedure for the immediate packaging of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the current pharmacopoeial requirements or the EMA Guidance on validation of analytical procedures (current edition), and studies show that the new test procedure is equivalent to the approved test procedure.
2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3. Any new method does not concern a novel non-standard technique or a standard technique used in a novel way.
4. The API/finished medicinal product is not biological/immunological.
5. The test procedure is already approved for the specification parameter and this procedure has not been approved through Type IA variation.

Documentation

1. Amendment of relevant sections of the registration dossier which including a description of the analytical methodology and report on validation data.
2. Comparative validation results or if justified comparative analysis results showing that the approved test and the new one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.e.4. Change in shape or dimensions of the container or closure (immediate packaging)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**

a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished medicinal product			**II**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**
Conditions			
1. No change in qualitative or quantitative composition of the packaging material. 2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished medicinal product. 3. In case of a change in the headspace of medicinal product or a change in the surface/volume ratio, stability studies in accordance with the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) have been started for at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and with at least three months (six months for biological/immunological medicinal products) satisfactory stability data. Assurance is given that these studies will be finalised and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action).			
Documentation			
1. Amendment to relevant sections of the registration dossier including description, detailed drawing and composition of the container or closure material, and, if necessary, revised summary of product characteristics and instructions for medical use. 2. Samples of the new container/closure where applicable. 3. Re-validation studies have been performed in case of sterile medicinal products terminally sterilised. The batch numbers of medicinal product used in the re-validation studies should be indicated, where applicable. 4. In case of a change in the headspace of medicinal product or a change in the surface/volume ratio, a confirmation that the stability studies in accordance with the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) have been started (with indication of the batch numbers of medicinal product) and that, as relevant, the required minimum stability data were at the disposal of the applicant at time of submission of Type IA or Type IB application, and that the available data did not indicate a stability problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately after study termination to the Center if outside specifications or potentially outside specifications at the end of the shelf life (with proposed action).			

B.II.e.5. Change in pack size of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the approved pack sizes	**1, 2**	**1, 3**	**IAIN**
2. Change outside the range of the approved pack sizes		**1, 2, 3**	**IB**
b) Deletion of pack size(s)	**3**	**1, 2**	**IA**

c) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products.			**II**
d) Change in the fill weight/fill volume of non-parenteral multidose (or single-dose, partial use) medicinal products		**1, 2, 3**	**IB**

Conditions
1. New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics and instructions for medical use of the medicinal product. 2. The primary packaging material remains the same. 3. The remaining product pack size (s) must be adequate for the dosing instructions and treatment duration specified in the approved Summary of Product Characteristics and instructions for medical use of the medicinal product.
Documentation
1. Amendment of the relevant sections of the registration dossier including revised summary of product characteristics where appropriate. 2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of use as approved in the summary of product characteristics. 3. Declaration that stability studies will be conducted in accordance with the EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) where stability parameters could be affected. Data to be reported to the Center only if outside specifications (with proposed action).
Note for B.II.e.5 c) and d). Any changes to the strength of the medicinal product require a new registration of medicinal product.

B.II.e.6. Change in any part of the primary packaging material not in contact with the finished medicinal product (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Change that affects the summary of product characteristics	**1**	**1**	**IA$_{IN}$**
b) Change that does not affect the summary of product characteristics	**1**	**1**	**IA**

Conditions
1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished medicinal product.
Documentation
1. Amendment of the relevant section of the registration dossier including revised summary of product characteristics as appropriate.

B.II.e.7. Change in supplier of packaging components or devices (when mentioned in the dossier)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Deletion of a supplier	**1**	**1**	**IA**
b) Replacement or addition of a supplier	**1, 2, 3, 4**	**1, 2, 3**	**IA**

c) Any change to suppliers of spacer devices for metered dose inhalers			**II**

Conditions
1. No deletion of packaging component or device. 2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same. 3. The specifications and quality control method are at least equivalent. 4. The sterilization method and conditions remain the same, if applicable.
Documentation
1. Amendment of relevant sections of the registration dossier. 2. For devices for medicinal products, proof of CE marking (CE certificate) or a conclusion on device safety issued by MoH. 3. Comparative table of approved and proposed specifications, if applicable.
Note. CE- marking is an abbreviation of Conformité Européenne ("European Conformity"), a special mark affixed on a product indicating that the product meets the essential requirements of the applicable EC directives and has undergone the assessment procedure of conformity to European directives. CE marking indicates that the product is safe for human health and environment.

B.II.f) Stability			
B.II.f.1. Change in the shelf life or storage conditions of the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Reduction of the shelf life of the finished medicinal product			
1. As packaged for sale	**1**	**1, 2, 3**	**IA_{IN}**
2. After first opening	**1**	**1, 2, 3**	**IA_{IN}**
3. After dilution or reconstitution	**1**	**1, 2, 3**	**IA_{IN}**
b) Extension of the shelf life of the finished medicinal product			
1. As packaged for sale (supported by real time data)		**1, 2, 3**	**IB**
2. After first opening (supported by real time data)		**1, 2, 3**	**IB**
3. After dilution or reconstitution (supported by real time data)		**1, 2, 3**	**IB**
4. Extension of the shelf life based on extrapolation of stability data not in accordance with EMA guidelines on stability testing of medicinal products or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013*			**II**
5. Extension of the shelf life of a biological/ immunological medicinal product based on results of the stability studies performed in accordance with an approved stability protocol		**1, 2, 3**	**IB**
c) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved protocol			**II**

d) Change in storage conditions of the finished medicinal product or the diluted/reconstituted product		**1, 2, 3**	**IB**
e) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**

Conditions
1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 2. The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.
Documentation
1. Amendment of the relevant sections of the registration dossier must contain results of real time stability studies (covering the entire shelf life) conducted in accordance with EMA guidelines on stability testing or MoH Ukraine documents 42-3.3:2004 and 42-8.2:2013 (current edition) on at least two pilot scale batches[1] of the finished medicinal product in the approved packaging and/or after first opening or reconstitution, as appropriate. Where applicable, results of microbiological testing should be included. 2. Revised summary of product characteristics, instructions for medical use and labelling text on packaging. 3. Copy of approved end of shelf life finished product specification and where applicable, medicinal product specifications after dilution/reconstitution or first opening. _____ [1] Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.
* Extrapolation not applicable to biological/immunological medicinal product.

B.II.g) Design space and postregistration change management protocol

B.II.g.1. Introduction of a new design space or extension of an approved design space for the finished medicinal product (except for the biological medicinal products), concerning:	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) One or more unit operations in the manufacturing process of the finished medicinal product including the in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for excipients/intermediates and/or the finished medicinal product.		**1, 2, 3**	**II**

Documentation
1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved. 2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges. 3. Amendment of the relevant sections of the registration dossier.

B.II.g.2. Introduction of a post approval change management protocol related to the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**

		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change. 2. Change management protocol related to the finished medicinal product. 3. Amendment of the relevant section(s) of the registration dossier.			

B.II.g.3. Deletion of an approved change management protocol related to the finished medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IA IN**
Conditions			
The deletion is not a result of unexpected events or out of specification results during the introduction of the change(s) described in the protocol and does not have any effect on information in the registration dossier.			
Documentation			
1. Justification for the proposed deletion. 2. Amendment of the relevant section(s) of the registration dossier.			

B.II.g.4. Changes to an approved change management protocol	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**
Documentation			
Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			

B.II.g.5. Introduction of changes foreseen in an approved change management protocol	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Introduction of the change requires no further supportive data	**1**	**1, 2, 4**	**IA IN**
b) Introduction of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Introduction of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**
Conditions			
The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.			
Documentation			

1. Reference to the approved change management protocol. 2. Declaration that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products. 3. Results of the studies performed in accordance with the approved change management protocol. 4. Amendment of the relevant section(s) of the dossier. 5. Copy of approved specifications of the finished medicinal product.

B.II.h. Adventitious agents safety			
B.II.h.1. Update to the "Adventitious agents safety evaluation" information (section 3.2.A.2)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Manufacturing steps investigated for the first time for one or more adventitious agents			**II**
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			**II**
2) without modification of risk assessment		**1, 2, 3**	**IB**
Documentation			
1. Amendment of the relevant section(s) of the registration dossier including the new studies to investigate the capability of manufacturing steps to inactivate adventitious agents. 2. Justification that the studies do not modify the risk assessment. 3. Revised summary of product characteristics, instructions for medical use and labelling text on packaging (if applicable).			

B.III. Certificate of Suitability /TSE Certificate of Suitability to the European Pharmacopeia/Monograph			
B.III.1. Submission of a new or updated certificate of suitability or deletion of certificate of suitability to the European Pharmacopeia: **For an API;** **For a starting material/reagent/intermediate used in the manufacturing process of the API;** **For an excipient**	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Certificate of Suitability to the European Pharmacopoeia			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 6, 9**	**1, 2, 3, 4, 5**	**IAIN**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 6**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 6, 9**	**1, 2, 3, 4, 5**	**IAIN**
4. Deletion of certificates (in case multiple certificates exist per material)	**8**	**3**	**IA**

5. New certificate for a non-sterile API that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be bacterial endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**
b) European Pharmacopoeial TSE Certificate of suitability for an API/starting material/reagent/ intermediate/or excipient			
1. New certificate for an API from a new or an already approved manufacturer	**3, 5, 9**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	**3, 7**	**1, 2, 3, 4,5**	**IA**
3. Updated certificate from an already approved manufacturer	**9**	**1, 2, 3, 4, 5**	**IA**
4. Deletion of certificates (in case multiple certificates exist per material)	**8**	**3**	**IA**
5. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			**II**
Conditions			
1. The finished medicinal product release and end-of-shelf life specifications remain the same. 2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with EMA guidelines) and medicinal product specific requirements (e.g. particle size profiles, polymorphic form), if applicable. 3. The manufacturing process of API, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is performed. 4. For API only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier 5. The API/starting material/reagent/intermediate/excipient is not sterile. 6. For herbal API: the manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same. 7. If gelatine of animal origin is to be used in a medicinal product for parenteral use, it should only be manufactured in compliance with the relevant requirements of a country of origin. 8. At least one manufacturer for the same API remains in the dossier. 9. If a non-sterile API is to be used in manufacture of a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the API must also be claimed to be free from bacterial endotoxins.			
Documentation			

1. Copy of the approved (updated) CEP.
2. In case of an addition of a manufacturing site, the registration form should clearly outline the 'approved' and 'proposed' manufacturers as listed in section 2.5 of the registration form for state registration of medicinal product.
3. Amendment of the relevant sections of the registration dossier.
4. Where applicable, a document providing information of any materials subject to viral safety assessment falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human Medicinal Products* including those which are used in the manufacture of API/excipient. The information should include: name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use and preliminary permit.
5. For API, if applicable, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the variation application where API is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the dossier as responsible for batch release. These declarations should confirm that the API manufacturer(s) referred to in the dossier operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note under item B.II.b.1). The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for API and intermediates are concerned, a QP declaration is only required if, compared to the current certificate, there is a change to the approved list of manufacturing sites.
6. Cofirmation of compliance of the water used in the final steps of the synthesis of the API with the requirements on quality of water for pharmaceutical use.

B.III.2. Change to comply with the SPhU or Ph. Eur. Monograph or with a national pharmacopoeia of an EU state	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Change of specification(s) of a non-pharmacopoeial API to comply with the SPhU or Ph. Eur. monograph or with a national pharmacopoeia of an EU state			
1. API	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA$_{IN}$**
2. Excipient/API starting material	**1, 2, 4**	**1, 2, 3,4**	**IA**
b) Change in specifications to comply with an update of the SPhU or European Pharmacopoeia or with a national pharmacopoeia of an EU state	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c) Change in specifications from requirements of the relevant monograph of the SPhU or national pharmacopoeia of an EU state to requirements of the Ph. Eur. monograph	**1, 4, 5**	**1, 2, 3, 4**	**IA**
Conditions			
1. The change is made exclusively to comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests. 2. Additional specifications to the pharmacopoeia in respect of product characteristics are unchanged (e.g. particle size profiles, polymorphic form or e.g. bioassays, aggregates). 3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened. 4. Additional validation of a new or changed pharmacopoeial method is not required. 5. For herbal API: the manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same.			
Documentation			

1. Amendment of the relevant sections of the registration dossier. 2. Comparative table of approved and updated specifications. 3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant API for all parameters (tests) in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable. 4. Data to demonstrate the suitability of the monograph to control API, e.g. a comparison of the potential impurities with the mentioned in note of the monograph. 5. Batch analysis data (in a comparative tabulated format) on two production batches of the finished medicinal product containing active substance complying with the approved and updated specification and comparative dissolution profile data for the finished medicinal product on at least one pilot batch. For herbal medicinal products, disintegration data may be acceptable.
Note: there is no need to notify the competent authorities of a change to comply with an updated monograph of the SPhU, European pharmacopoeia or a national pharmacopoeia of an EU State in the case that reference is made to the 'current edition' in the dossier of an registered medicinal product.

B.IV. MEDICAL DEVICES

B.IV.1. Change of a device for dose measuring or administration of the medicinal product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	**1, 2, 3, 5, 6**	**1, 2, 4**	**IA_{IN}**
2. Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the API in the dosage form (e.g. nebuliser)			**II**
b) Deletion of a device	**4**	**1, 5**	**IA_{IN}**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**
Conditions			
1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology. Results of appropriate studies should be submitted. 2. The new device is compatible with the medicinal product. 3. The change should not lead to substantial amendments of the summary of product characteristics, instructions for medical use and labelling text. 4. The device can still demonstrate dose reproducibility of the medicinal product. 5. The medical device is not used as a solvent of the medicinal product. 6. If a measuring function is intended the CE marking should cover the measuring function.			
Documentation			

1. Amendment of the relevant sections of the registration dossier, including description, detailed drawing and composition of the device material and supplier where appropriate, and revised summary of product characteristics, instructions for medical use and labelling text on packaging (if necessary). 2. Proof of CE marking and if a measuring function is intended the proof of CE marking should also include the 4 digit notified body number, or appropriate MoH conclusion on safety of device to be used with the medicinal product. 3. Data to demonstrate safety, precision and compatibility of the device material and medicinal product. 4. Samples of the new device where applicable. 5. Justification for the deletion of the device.
Note for B.IV.1.c. Any change which results in a new pharmaceutical form requires a new registration.

B.V. CHANGES TO REGISTRATION CERTIFICATE AS A RESULT OF OTHER REGULATORY PROCEDURES

B.V.a) PMF/VAMF (Plasma master file /Vaccine antigen master file)

B.V.a.1. Inclusion of a new, updated or amended Plasma Master File in the registration dossier of a medicinal product (PMF 2nd step procedure)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) First-time inclusion of a new Plasma Master File affecting the properties of the finished medicinal product			**II**
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished medicinal product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished medicinal product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished medicinal product	**1**	**1, 2, 3, 4**	**IA$_{IN}$**

Conditions
The updated or amended PMF has been granted a certificate of compliance.
Documentation
1. Declaration that the PMF Certificate and Evaluation Report are fully applicable for the registration of medicinal product, PMF holder has provided the PMF Certificate, Evaluation report and PMF to the applicant (where the applicant is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this registration certificate. 2. PMF Certificate and Evaluation Report. 3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished medicinal product including product specific risk assessments. 4. The variation registration form should clearly outline the ‘approved’ and ‘proposed’ PMF Certificate (code number) in the registration dossier for the finished medicinal product. When applicable, the variation registration form should clearly list also all the other PMFs to which the applicant refers even if they are not specified in the dossier.

B.V.a.2. Inclusion of a new, updated or amended Vaccine Antigen Master File in the registration dossier of a finished medicinal product (VAMF 2nd step procedure)	Conditions to be met	Documents to be submitted	Type of variation
a) First-time inclusion of a new Vaccine Antigen Master File			**II**
b) Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished medicinal product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished medicinal product	**1**	**1, 2, 3, 4**	**IA$_{IN}$**

Conditions
The updated or amended Vaccine Antigen Master File has been granted a certificate of compliance.
Documentation
1. Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the registration of medicinal product, VAMF holder has provided the VAMF Certificate, Evaluation report and VAMF to the applicant (where the applicant is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this registration dossier. 2. VAMF Certificate and Evaluation Report. 3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished medicinal products including product specific risk assessments. 4. The variation registration form should clearly outline the 'approved' and 'proposed' VAMF Certificate (code number) in the registration dossier. When applicable, the variation registration form should clearly list also all the other VAMFs to which the applicant refers even if they are not specified in the dossier.

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I.1. Change(s) in the summary of product characteristics, labelling text or instructions for medical use of a medicinal product authorized in EU according to a referral procedure	Conditions to be met	Documents to be submitted	Type of variation
a) The medicinal product is covered by the defined scope of the referral procedure	**1**	**1, 2, 3**	**IA$_{IN}$**
b) The medicinal product is not covered by the defined scope of the referral procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the marketing authorization holder		**1, 2, 3**	**IB**
c) The medicinal product is not covered by the defined scope of the referral procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the marketing authorization holder		**1, 3**	**II**
Conditions			

The variation introduction is requested by the regulatory authority and it does not require the submission of additional information and/or further assessment.
Documentation
1. A reference to the regulatory authority decision concerned, and the summary of product characteristics; proposed labelling text and instructions for medical use. 2. A declaration that the proposed summary of product characteristics, instructions for medical use and labelling text is identical for all concerned sections to that annexed to the regulatory authority decision. 3. Revised summary of product characteristics, instructions for medical use and labelling text.

C.I.2. Change(s) in the summary of product characteristics, labelling text or instructions for medical use of a generic/hybrid/biosimilar medicinal products following introduction of the same change for the reference product	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Change for which no new additional data is required		**1, 2**	**IB**
b) Change(s) which require to be further substantiated by new additional data (e.g. comparability of biological medicinal products)			**II**
Documentation			
1. National competent authority request and/or MoH decision (if applicable). 2. Revised summary of product characteristics, instructions for medical use and labelling text.			

C.I.3. Change(s) in the summary of product characteristics, labelling text or instructions for medical use based on the periodic safety update report for the medicinal product or postregistration safety study, or the outcome of the assessment of the study report in compliance with the pediatric investigation plan (PIP)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Change agreed by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Change which require to be further substantiated by new additional data		**2**	**II**
Conditions			
The variation introduction is requested by the regulatory authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. A reference to the regulatory authority decision concerned. 2. Revised summary of product characteristics, instructions for medical use and labelling text.			

C.I.4. Changes in the summary of product characteristics, labelling text or instructions for medical use due to new quality, preclinical, clinical or pharmacovigilance data	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II
Note. This variation does not apply when the new data has been submitted at introduction of changes specified in item C.I.13. In such cases, the change(s) in the summary of product characteristics, labelling text and instructions for medical use are introduced according to item C.I.13.			

C.I.5. Change in the legal status of a medicinal product	Conditions to be met	Documents to be submitted	Type of variation
a) For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product		**1, 2**	**IB**
b) All other legal status changes			**II**
Documentation			
1. Variation justification with a submission of the documentation confirming the legal status change of the reference medicinal product (e.g. reference to the Commission Decision concerned). 2. Revised summary of product characteristics, instructions for medical use and labelling text.			

C.I.6. Changes to therapeutic indications	Conditions to be met	Documents to be submitted	Type of variation
a) Addition of a new therapeutic indication or modification of an approved one			**II**
b) Deletion of a therapeutic indication			**IB**

Note: Where the addition or modification of a therapeutic indication takes place in the context of the implementation of the outcome of a referral procedure, or — for a generic/hybrid/biosimilar medicinal product — when the same change has been done for the reference medicinal product, variations C.I.1 and C.I.2 apply, respectively.

C.I.7. Deletion	Conditions to be met	Documents to be submitted	Type of variation
a) a pharmaceutical form		**1, 2**	**IB**
b) a strength		**1, 2**	**IB**

Documentation
1. Declaration that the remaining pharmaceutical form (s) and strength (s) of the medicinal product is (are) adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics and instructions for medical use. 2. Revised summary of product characteristics, instructions for medical use and labelling text.
Note. In cases where a given pharmaceutical form or strength has received a registration certificate which is separate to the registration certificate for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the registration certificate.

C.I.8. Introduction of, or changes to, a summary of pharmacovigilance system	Conditions to be met	Documents to be submitted	Type of variation

a) Introduction of a summary of pharmacovigilance system, changes in qualified person responsible for pharmacovigilance; the applicant's contact person for pharmacovigilance in Ukraine if not the same as the qualified person responsible for pharmacovigilance (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location		**1, 2**	**IA$_{IN}$**
Documentation			
1. Summary of the pharmacovigilance system, or update of the relevant elements (as applicable): Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and/or the applicant's contact person for pharmacovigilance in Ukraine if not the same as the qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that he has the necessary means to fulfil the tasks and responsibilities with regard to pharmacovigilance in Ukraine in compliance with the legislation; Contact details of the qualified person responsible for pharmacovigilance and/or the applicant's contact person for pharmacovigilance in Ukraine if not the same as the qualified person responsible for pharmacovigilance, and address at which the pharmacovigilance activities are carried out; PSMF location (where PSMF is stored). 2. PSMF number (if available).			
Note. This variation relates to the introduction of a PSMF irrespective of whether or not the registration materials contain a detailed description of the pharmacovigilance system (DDPS).			

C.I.9. Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Change in qualified person responsible for pharmacovigilance and/or the applicant's contact person for pharmacovigilance in Ukraine if not the same as the qualified person responsible for pharmacovigilance, and/or contact details and/or and/or back-up procedure	**1**	**1**	**IA$_{IN}$**
b) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and /or change of the site undergoing pharmacovigilance activities	**1, 2, 3**	**1**	**IA$_{IN}$**
c) Other change(s) to the detailed description of the pharmacovigilance system that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes)	**1**	**1**	**IA**
d) Change(s) to a detailed description of the pharmacovigilance system following the assessment of the same DDPS in relation to another medicinal product of the same registration certificate holder	**4**	**1, 2**	**IA$_{IN}$**

Conditions
1. The pharmacovigilance system remains unchanged. 2. The database system has been validated (when applicable). 3. Transfer of data from other database systems has been validated (when applicable). 4. The same changes to the pharmacovigilance system are introduced for all medicinal products of the same applicant (same final DDPS version).
Documentation
1. Latest version of the DDPS and, where applicable, latest version of the product specific addendum, which should include for changes to the QPPV and/or the applicant's contact person for pharmacovigilance in Ukraine if not the same as the QPPV: a) CV of the new QPPV and/or the applicant's contact person for pharmacovigilance in Ukraine if not the same as the QPPV; b) proof of QPPV EudraVigilance registration, if available; c) a new statement of the registration certificate holder and the QPPV and/or the applicant's contact person for pharmacovigilance in Ukraine if not the same as the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and/or the new applicant's contact person for pharmacovigilance in Ukraine if not the same as the new QPPV and the registration certificate holder, and reflecting any other consequential changes, e.g. to the organisation chart. When the QPPV, the applicant's contact person for pharmacovigilance in Ukraine if not the same as the QPPV, and/or his/their contact details are not included in a DDPS or no DDPS exists, the submission of a revised DDPS version is not required and the application form is to be provided. 2. Reference of the application/procedure and medicinal product in which the changes were accepted.
Note to item C.I.9. Covers changes to an existing pharmacovigilance system for medicinal products that have not yet introduced a PSMF. **Note to item B.I.9.d).** The assessment of a DDPS submitted as part of a new registration/extension/variation may give rise to changes at the request of the national competent authority in this DDPS. Where this occurs, the same change(s) can be introduced to the DDPS in other registration certificates of the same registration certificate holder by submitting a (grouped) application for Type IA variation.

C.1.10. Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for medicinal products	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IA IN**
Conditions			
The change in the frequency and/or date of submission of the PSUR has been agreed by the national competent authority.			
Documentation			
1. A reference to the agreement of the the national competent authority to make the change in the frequency and/or date of submission of the PSUR for medicinal products. 2. Revised frequency and/or date of submission of the PSUR for medicinal products.			
Note. This variation applies only when the frequency of submission of the PSUR is different from the frequency of submission envisaged by legislation of Ukraine.			

C.I.11. Introduction of, or change(s) to, the obligations and conditions of issuing registration certificate, including the risk management plan	**Conditions to be met**	**Documents to be submitted**	**Type of variation**

a) Implementation of wording agreed by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted to the competent authority where significant assessment by the competent authority* is required			**II**
Conditions			
The variation implements the action requested by the competent authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. A reference to the relevant decision of the competent authority. 2. Update of the relevant section of the registration dossier.			
Note. This variation concerns the conditions and/or obligations at issuing the registration certificate, and the risk management plan and the conditions and/or obligations at issuing registration certificates under exceptional circumstances.			
* The introduction of a risk management plan requested by the competent authority always requires significant assessment.			

C.1.12. Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1	**1, 2**	**IA_{IN}**
Conditions			
The medicinal product is included or removed from the list of medicinal products that are subject to additional monitoring (as applicable).			
Documentation			
1. Attached to the variation registration form: a reference to the list of medicinal products that are subject to additional monitoring. 2. Revised product information.			
Note. This variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal (re-registration) or variation procedure affecting the product information).			

C.1.13. Other variations not covered in this section which involve the submission of study results to the competent authority*	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II
Note. In cases where the assessment by the competent authority of the data submitted requires a change of the instructions for medical use, summary of product characteristics or labelling, the relevant amendment to the instructions for medical use, summary of product characteristics or labelling is covered by the variation procedure.			
* This variation does not apply to variations that can be considered as Type IB under any section of this annex.			

D. PMF/VAMF (Plasma master file /Vaccine antigen master file)

D.1. Change in the name and/or address of the VAMF holder	Conditions to be met	Documents to be submitted	Type of variation
	1	1	IA IN
Conditions			
The VAMF holder shall remain the same legal entity. .			
Documentation			
A formal document from a relevant competent authority in which the new name and/or new address of VAMF holder is specified.			

D.2. Change in the name and/or address of the PMF holder	Conditions to be met	Documents to be submitted	Type of variation
	1	1	IA IN
Conditions			
The PMF holder shall remain the same legal entity.			
Documentation			
A formal document from a relevant competent authority in which the new name and/or new address of PMF holder is specified.			

D.3. Change or transfer of the approved PMF holder to a new PMF holder (i.e. different legal entity)	Conditions to be met	Documents to be submitted	Type of variation
		1, 2, 3, 4, 5, 6	IA IN
Documentation			
1. A document including the identification (name and address) of the approved PMF holder and the identification of the person to whom the PMF transfer is to be granted together with the proposed implementation date – signed by both companies/parties. 2. Copy of the latest PMF Certificate page (EMA Plasma Master File Certificate of compliance). 3. Proof of establishment of the new holder (Excerpt of the commercial register and the English and Ukrainian translation of it) – signed by both companies/parties. 4. Confirmation of the transfer of the complete PMF documentation since its initial assessment to the transferee - signed by both companies/parties. 5. Letter of Authorisation including contact details of the person responsible for communication between the competent authorities and the PMF holder - signed by the transferee (new holder). 6. Letter of Undertaking to fulfil all remaining commitments of previous PMF holder (transferor) (if any) - signed by the transferee (new holder).			

D.4. Change in the name and/or address of a blood establishment including blood/plasma collection centers	Conditions to be met	Documents to be submitted	Type of variation
	1, 2	1, 2, 3	IA
Conditions			
1. The blood establishment (center) shall remain the same legal entity. 2. The change shall be administrative (e.g. merger, take over); change in the name of the blood/plasma establishment/collection center provided the establishment/collection center shall remain the same.			
Documentation			

1. Signed declaration that the change does not involve a change of the quality system within the blood establishment (center). 2. Declaration that there is no change in the list of the blood collection establishments (centers). 3. Updated relevant sections and annexes of the PMF.

D.5. Replacement or addition of a blood/plasma collection center within those included in the PMF	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
		1, 2, 3	**IB**

Documentation
1. Epidemiological data for viral markers related to the blood/plasma collection center covering the last 3 years. For newly opened center(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s). 2. Statement that the center (establishement) is working under the same conditions as specified in the standard contract between blood center and PMF holder. 3. Updated relevant sections and annexes of the PMF dossier.

D.6. Deletion or change of status (operational/non-operational) of establishment(s)/center(s) used for blood/plasma collection or in the testing of blood donations and plasma pools	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
	1,2	**1**	**IA**
Conditions			
1. The reason for deletion or change of status of establishment/center should not be related to a GMP issue. 2. The establishments/centers should comply with the legislation related to checkups in case of change of status from operational to non-operational.			
Documentation			
Updated relevant sections and annexes of the PMF.			

D.7. Addition of a new establishment for the collection of blood not included in the PMF	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II

D.8. Replacement or addition of a blood center for testing of blood donations and/or plasma pools within an establishment included in the PMF	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
		1, 2	**IB**
Documentation			
1. Statement that the testing is performed following the same SOPs and/or test methods as already approved. 2. Updated relevant sections and annexes of the PMF dossier.			

D.9. Addition of a new blood establishment for testing of blood donations and/or plasma pool not included in the PMF	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II

D.10. Replacement or addition of a new blood establishment or center(s) in which storage of plasma is carried out	Conditions to be met	Documents to be submitted	Type of variation
		1, 2	IB
Documentation			
1. Statement that storage of plasma is carried out following the same SOPs as the already approved. 2. Updated relevant sections and annexes of the PMF.			

D.11. Deletion of a blood establishment or center(s) in which storage of plasma is carried out	Conditions to be met	Documents to be submitted	Type of variation
	1	1	IA

Conditions
The reason for deletion of establishment (center) should not be related to a GMP issues.
Documentation
Updated relevant sections and annexes of the PMF.

D.12. Replacement or addition of an organisation involved in the transport of plasma	Conditions to be met	Documents to be submitted	Type of variation
		1	IB

Documentation
Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.

D.13. Deletion of an organisation involved in the transport of plasma	Conditions to be met	Documents to be submitted	Type of variation
	1	1	IA

Conditions
The reason for deletion should not be related to GMP issues.
Documentation
1. Updated relevant sections and annexes of the PMF.

D.14. Addition of a CE-marked test kit to test individual blood donations as a new test kit or as a replacement of one included in the PMF	Conditions to be met	Documents to be submitted	Type of variation
	1	1, 2	IA
Conditions			
1. The new test kit is CE-marked.			
Documentation			
1. List of testing center(s) where the kit is used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the 'Guideline on the scientific data requirements for a PMF'.			

D.15. Addition of a non-CE marked test kit to test individual blood donations as a new test kit or as a replacement of one included in the PMF	Conditions to be met	Documents to be submitted	Type of variation
a) The new test kit has not previously been approved in the PMF for any blood center for testing of blood donations			**II**
b) The new test kit has been approved in the PMF for other blood center (s) for testing of blood donations		**1, 2**	**IA**

Documentation
1. List of testing center(s) where the kit is currently used and a list of testing center(s) where the kit will be used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the 'Guideline on the scientific data requirements for a PMF'.

D.16. Change of kit/method used to test plasma pools (antibody or antigen or NAT test (nucleic acid amplification technology))	Conditions to be met	Documents to be submitted	Type of variation
			II

D.17. Introduction or extension of blood donation inventory hold period	Conditions to be met	Documents to be submitted	Type of variation
	1	**1**	**IA**
Conditions			
The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation			
Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.			

D.18. Removal of blood donation inventory hold period or reduction in its length	Conditions to be met	Documents to be submitted	Type of variation
		1	**IB**
Documentation			
Updated relevant sections of the PMF.			

D.19. Replacement or addition of blood containers (e.g. bottles, bags)	Conditions to be met	Documents to be submitted	Type of variation
a) The new blood containers are CE-marked	**1, 2**	**1**	**IA**
b) The new blood containers are not CE-marked			**II**
Conditions			
1. The container is CE-marked. 2. The quality criteria of the blood in the container remain unchanged.			
Documentation			

Updated relevant sections and annexes of the PMF, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.

D.20. Change in storage/transport	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
a) Storage and/or transport conditions	**1**	**1**	**IA**
b) Maximum storage time for the plasma	**1, 2**	**1**	**IA**

Conditions
1. The change should tighten the storage conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation. 2. The maximum storage time is shorter than previously.
Documentation
Updated relevant sections and annexes of the PMF, including detailed description of the new storage conditions, validation data of storage/transport conditions and the name of the blood establishment where the change takes place (if relevant).

D.21. Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II

D.22. Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
		1	**IB**
Documentation			
1. Updated relevant sections of the PMF.			

D.23. Change in the steps that would be taken if it is found retrospectively that blood donation(s) should have been excluded from processing (retrospective studies)	**Conditions to be met**	**Documents to be submitted**	**Type of variation**
			II

{Annex 17 in wording of MoH Ukraine Order №460 as of 23.07.2015}