REG - 76, version 1 Variations to marketing authorisations of products authorised via the national procedure

Effective date: January 1, 2010

In compliance with Section 35 of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended (hereinafter referred to as the "Act"), the marketing authorisation holder is obliged to apply with the State Institute for Drug Control (hereinafter referred to as the "Institute") in advance of implementation of any variation for its authorisation. A variation to marketing authorisation shall be considered any change to the content of data and documentation as against its status as of the date of marketing authorisation issue or approval of the latest variation to the marketing authorisation.

The classification of variations to marketing authorisation as Type IA variations (variations to be announced), Type IB variations (notified variations) and Type II variations (variations requiring the issue of a decision) and the method of their handling are stipulated by the provisions of Section 35) of the Act and of Decree No 228/2008 Coll., on marketing authorisation of medicinal products, as amended (hereinafter referred to as the "Decree") (Section 8, Annex 7 to the Decree, which defines Type I variations).

Section 8, paragraph (9) of the Decree stipulates the cases when it is not possible to implement a variation to the marketing authorisation, and where it is necessary to apply for a new marketing authorisation instead. The European Commission has issued a guideline regarding the distinction between changes which require the submission of an application for new marketing authorisation and those which may be submitted in the form of a variation to marketing authorisation (Guideline on the categorisation of New Applications (NA) versus Variations Applications (V) - October 2003 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/v2c_ea_v__10_2003.pdf-). Pursuant to the provisions of the Act, this guideline shall be applicable also to the applications submitted to the Institute and is therefore binding. The applicant should always check whether the particular variation (Types I and II) may be also governed by other guidelines. Pursuant to the provisions of the Act, the applicants/marketing authorisation holders shall be also obliged to observe the regulatory guidance issued by the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm)) and scientific guidelines published by EMEA(http://www.emea.europa.eu/htms/human/humanguidelines/background.htm)).

Pursuant to Section 35, paragraph (12) of the Act, any proposed change to the labelling of the medicinal product or changes to the package leaflet which are not associated with the Summary of the product characteristics, shall be notified to the Institute by means of an application for variation to marketing authorisation. Pursuant to Section 8, paragraph (11) of the Decree, the notification of such changes shall be submitted together with a rationale thereof and the proposed labelling of the product or package leaflet.

The application for variation to marketing authorisation shall be submitted by the marketing authorisation holder using the form REG-77, version 3 "Application for variation to marketing authorisation of a medicinal product/national marketing authorisation". An application for variation may be filed only for previously authorised products.

Within the scope of a single application, only one variation to marketing authorisation of a product may be filed, with the exception of those cases, where such variation directly implies other changes, i.e. resulting variations. Resulting variations are those variations which are an inevitable and direct consequence of the primary variation. This is the only situation where the same form may include several variations. A variation resulting from a notified Type IA variation may be only another Type IA variation; a variation resulting from a notified Type IB variation may be either another notification of Type IB variation or Type IA variation. No other resulting variations shall be acceptable; such variations have to be submitted as part of the procedure applicable to Type II variations.

Variations, which only *happen* to occur at the same time, but are not related to the primary variation, shall be considered parallel variations and shall require the submission of separate applications. *Examples of resulting variations and parallel variations are provided below.*

For the Institute to be able to accept the application for authorisation/notification of a variation for assessment, all of the mandatory data in the application form have to be completed.

In the paragraph titled "Brief characteristics of the variation", the applicant shall provide a text specifying the concerned change. In the paragraph titled "Rationale of the variation and resulting variations" the applicant shall explain the cause which has triggered the variation, and if the primary variation implies resulting variations, the association between both variations shall be explained. The form also includes a paragraph reserved for a distinction between the "Existing" and the "Proposed". The provision of specific data about the proposed change in this part of the form (where a more extensive text is concerned, by means

of an Annex) constitutes the essential prerequisite for the acceptance of the variation. The paragraph "Other applications" shall provide a brief overview of variations submitted for the concerned product at the same time as parallel variations, as well as any variations to and renewals of marketing authorisation which are the subject of currently active procedures running in the Institute. Where a Type I variation is concerned, the relevant table provided herein, concerning only the variation in question, shall be attached to the form. In the table the applicant shall bindingly declare which conditions have been met and what documentation is being submitted. The application cannot be accepted without the full declaration of these data. The form shall also include the applicant's statement which requires special attention.

Pursuant to the effective legal regulations, relevant documentation shall be attached to each application. Ideally, only those parts of the documentation which directly pertain to the variation should be submitted. The documentation for marketing authorisation variations shall be submitted in the eCTD format, but it is not necessary to reformat the entire marketing authorisation dossier of the concerned product. Where the applicant avails of the submission of application for variation as of an opportunity to submit the entire reformatted dossier, it shall be necessary to concurrently provide a declaration to the effect that no changes other than those which are subject of the submission have been made.

This guideline provides tables for all announced and notified Type IA and Type IB variations. The tables are based upon Annex 7 to the Decree which defines Type I variations. For each variation, the preconditions which are necessary for the variation to be classified as a Type IA or Type IB variation are specified; furthermore, the part of documentation to be submitted or updated as well as any other requirements, where applicable, are described (e.g. submission of a product sample or immediate packaging).

Type II variations include such changes to the marketing authorisation which cannot be classified as Type IA or IB variations. Where an application for Type II variation is concerned, relevant parts of the marketing authorisation dossier which have been affected by the proposed change shall be submitted. With respect to the broad range of these variations it is impossible to list the requirements governing the documentation to be submitted. An amendment of the Quality Overall Summary, Module 2 of the documentation in CTD format which shall evaluate the concerned change has to be submitted with any application for Type II variation. Where the Type II variation implies a change to the product presentation or to the immediate packaging of the product, a sample of the product or the packaging shall be provided.

Where the proposed variation (IA, IB and II) is reflected also in the Summary of the product characteristics, in the product labelling and/or package leaflet, proposals concerning these parts of the marketing authorisation dossier shall be also presented together with the notification of the variation. Any proposed changes shall be highlighted with regard to the original wording in these proposals.

The applicant should always check whether the variation presented thereby results in a change concerning the product safety in terms of a TSE risk. Variations involving the securing of raw materials with respect to the risk of TSE may be notified via the procedure intended for Type I variations only in the case of such changes which are listed in the tables below. In practice this means only such cases where a TSE certificate of conformity with the European Pharmacopoeia is available for the concerned raw material or where a raw material involving a TSE risk is being replaced with a raw material of vegetable or synthetic origin. In any other cases which require the assessment of expert data regarding the safety of a raw material of animal origin (not only in terms of TSE but also with respect to viral safety), shall be submitted as Type II variations.

Examples of resulting and parallel variations:

1. Addition of one manufacturing site where the bulk is manufactured, primary and secondary packaging and batch quality control and release are performed, may be submitted on a single form where the primary variation shall be indicated as the IB7c Type and resulting variations as IA7a + IA/B7b + IA8b2 Types. Type 7c variation is, in the guideline, considered a change of the manufacturing site for any other manufacturing operations except for batch release, secondary and primary packaging.

2. Where in the new manufacturing site of the finished product a minor change to the manufacturing process or change to the production batch size occurs at the same time, these shall be considered parallel variations and have to be submitted on separate forms.

3. An example of a situation which would not involve resulting variations and for which separate notifications should be submitted, is the addition of three various manufacturing sites. In this case three separate notifications of the additions of the concerned three sites should be submitted using three forms.

4. In some cases a change to the control method and a change to the specification may be considered resulting variations if they concern the same test (e.g. a change to the control method which allows for a more accurate distinction of individual impurities and resulting change to the limits for these impurities). The changes which concern several tests shall not be considered resulting variations, and hence shall require

the submission of separate notifications for the individual variations (e.g. a replacement of a test for the presence of pyrogenic substances with a test for bacterial endotoxins and addition of a second method for the test for the identity of the active substance into the specification).

5. Where an application for Type IA15b variation is concerned, i.e. the submission of a new or updated Ph.Eur. Certificate of Suitability for the active substance from a new manufacturer, where the certificate of suitability does not specify the retest period and the applicant wishes to provide data evidencing the retest period, i.e. a stability study of the substance of the new manufacturer, this has to be made prior to the submission of the parallel application for Type IB17a variation. A Type IB variation cannot be a variation resulting from a Type IA variation. The relation between both variations has to be reflected in the application form.

1	Change in the name and/or address of the marketing authorisation holder	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1	1	IA
	Conditions			
	1. The marketing authorisation holder shall remain the same legal entity.			
	Documentation			
	1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

2	Change in the name of the medicinal product	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1	none	IB
	Conditions			
	1. No confusion with the names of existing medicinal products or with the international non-proprietary name (INN).			

3	Change in name of the active substance	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1	1	IA
	Conditions			
	1. The active substance shall remain the same.			
	Documentation			
	1. Proof of acceptance by WHO or copy of the INN list. For herbal medicinal product, declaration that the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products.			

4	Change in the name and/or address of a manufacturer of the active substance where no European Pharmacopoeia certificate of suitability is available	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	1, 2	IA
	Conditions			
	1. The manufacturing site shall remain the same.			
	Documentation			
	1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned.			
	2. Replacement page(s) of Part IIC or equivalent in the CTD format.			

5	Change in the name and/or address of a manufacturer of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	1,2	IA
	Conditions			
	1. The manufacturing site shall remain the same.			
	Documentation			
	1. Copy of the modified manufacturing authorisation, if available; or a formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned.			
	2. If applicable, replacement page(s) of Part IIB or equivalent in the CTD format.			

6	Change in ATC Code	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	1	IA
	Conditions			
	1. Change following granting of or amendment to ATC Code by WHO.			
	Documentation			
	1. Proof of acceptance by WHO or copy of the ATC Code list.			

7	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Secondary packaging for all types of pharmaceutical forms**	**1, 2**	**1, 2, 5**	**IA**
b)	**Primary packaging site**			
	1. Solid pharmaceutical forms, e.g. tablets and capsules	**1, 2, 3, 5**	**1, 2, 5**	**IA**
	2. Semi-solid or liquid pharmaceutical forms	**1, 2, 3, 5**	**1, 2, 5**	**IB**
	3. Liquid pharmaceutical forms (suspensions, emulsions)	**1, 2, 3, 4, 5**	**1, 2, 4, 5**	**IB**
c)	**All other manufacturing operations except batch release**	**1, 2, 4, 5**	**1, 3, 4, 5, 6, 7, 8, 9**	**IB**

Conditions

1. Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EEA or of a country where an operational good manufacturing practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).
3. Product concerned is not a sterile product.
4. Validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.
5. Product concerned is not a biological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.:
   - For a manufacturing site within the EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice once this is operational;
   - For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a copy of the current manufacturing authorisation equivalent, a GMP certificate or equivalent document issued by the relevant competent authority;
   - For a manufacturing site outside the EEA where no such mutual recognition agreement exists: a Statement of GMP compliance, or when available, GMP certificate issued by an inspection service of one of the Member States of the EEA. A reference to the EudraGMP database will suffice once this is operational.
2. Date of the last satisfactory inspection concerning the packaging facilities by an inspection service of one of the Member States, or of the country where a GMP MRA with the EU is in operation, in the last three years.
3. Date and scope (indicate if product specific, if related to a specific pharmaceutical form, etc.) of the last satisfactory inspection by an inspection service of one of the Member States, or of the country where a GMP MRA with the EU is in operation, in the last 3 years.
4. The batch numbers of batches (≥ 3) used in the validation study should be indicated or validation protocol (scheme) to be submitted.
5. The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in section 2.5 of the (Part IA) application form.
6. Copy of approved release and end-of-shelf life specifications.
7. Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site;
   batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).
8. For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
9. i) If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Community.

   ii) In addition, if the new manufacturing site is located within the EEA and uses the active substance as a starting material – A declaration by the Qualified Person (QP) of the new manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Community.

8	Change to batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Replacement or addition of a site where batch control/testing takes place**	**2, 3, 4**	**1, 2,**	**IA**
b)	**Replacement or addition of a manufacturer responsible for batch release**			
	1. Not including batch control/testing	**1, 2**	**1, 2, 3**	**IA**
	2. Including batch control/testing	**1, 2, 3, 4**	**1, 2, 3**	**IA**

Conditions

1. The manufacturer responsible for batch release must be located within the EEA.
2. The site is appropriately authorised.
3. The product is not a biological medicinal product.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.

Documentation

1. For a manufacturing site within the EEA: a copy of the current manufacturing authorisation or formal accreditation as test laboratory or equivalent document.

   For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a copy of the current manufacturing authorisation, a GMP certificate, or formal accreditation as test laboratory or equivalent document issued by the relevant competent authority.
2. The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in section 2.5 of the (Part IA) application form.
3. A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorisation 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 change no. 7 above.

9	Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		None	**1**	**IA**

Conditions: None

Documentation

1. The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the (Part IA) application form.

10	Minor change in the manufacturing process of the active substance	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1, 2, 3	**1, 2, 3**	**IB**
	Conditions			
1.	No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2.	The active substance is not a biological substance.			
3.	The synthetic route remains the same, i.e. intermediates remain the same. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.			
	Documentation			
1.	Amendment to relevant sections Part IIC or equivalent in the CTD format and of the approved Drug Master File (where applicable), including a direct comparison of the present process and the new process.			
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 the active substance.			

11	Change in batch size of active substance or intermediate	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
a)	**Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Downscaling**	**1, 2, 3, 4, 5**	**1, 2**	**IA**
c)	**More than 10-fold compared to the original batch size approved at the grant of the marketing authorisation**	**1, 2, 3, 4**	**1, 3, 4**	**IB**

Conditions

1. Any changes to the manufacturing methods are only those necessitated by scale-up, 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. The active substance is not a biological substance.
4. The change does not 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.

Documentation

1. Amended section Part IIC or equivalent in the CTD format.
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 manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
4. Copy of approved specifications of the active substance (and of the intermediate, if applicable).

12	Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
a)	**Tightening of specification limits**	**1, 2, 3**	**1, 2**	**IA**
		2, 3	**1, 2**	**IB**
b)	**Addition of a new test parameter to the specification of**			
	1. an active substance	**2, 4, 5**	**1, 2, 3, 4, 5, 6**	**IB**
	2. a starting material/intermediate/reagent used in the manufacturing process of the active substance	**2, 4**	**1, 2, 3, 4**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The active substance is not a biological substance.

Documentation

1. Amendment to relevant section of Part IIC or equivalent in the CTD format.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data.
4. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6. Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*, if relevant.

13	Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
a)	**Minor changes to an approved test procedure**	**1, 2, 3, 5**	**1**	**IA**
b)	**Other changes to a test procedure, including replacement or addition of a test procedure**	**2, 3, 4, 5**	**1, 2**	**IB**

Conditions

1. 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); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The active substance, starting material, intermediate or reagent is not a biological substance.

Documentation

1. Amendment to relevant sections of Part IIC or equivalent in the CTD format, which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable); amendment to relevant sections of Part IIG (old Part IIF) or equivalent in the CTD format (if applicable).
2. Comparative validation results showing that the current test and the proposed one are equivalent.

14	Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no European Pharmacopoeia certificate of suitability is available	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Change in site of the already approved manufacturer (replacement or addition)**	**1, 2, 4**	**1, 2, 3, 4, 5, 6**	**IB**
b)	**New manufacturer (replacement or addition)**	**1, 2, 3, 4**	**1, 2, 3, 4, 5, 6**	**IB**

Conditions

1.	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.	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 with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.
3.	The current or new active substance manufacturer does not use a drug master file.
4.	The change does not concern a medicinal product containing a biological active substance.

Documentation

1.	Amended page(s) of Part IIC and IIG (old Part IIF) or equivalent in the CTD format, if applicable.
2.	A declaration from the marketing authorisation holder that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.
3.	Either a TSE European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to comply with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant). For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5.	The variation application form should clearly outline the “present” and “proposed” manufacturers as listed in section 2.5 of the (Part IA) application form.
6.	A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application 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 change no. 7 above.

15	Submission of a new or updated European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**From a manufacturer currently approved**	**1, 2, 4**	**1, 2, 3, 4**	**IA**
b)	**From a new manufacturer (replacement or addition)**			
	1. Sterile substance	**1, 2, 3, 4**	**1, 2, 3, 4, 5**	**IB**
	2. Other substances	**1, 2, 3, 4**	**1, 2, 3, 4, 5**	**IA**

Conditions

1.	The finished product release and end of shelf life specifications remain the same.
2.	Unchanged additional (to European Pharmacopoeia) specifications for impurities and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The active substance will be tested immediately prior to use if no retest period is included in the European Pharmacopoeia certificate of suitability or if data to support a retest period is not provided.
4.	The manufacturing process of the active substance, 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 required.

Documentation

1.	Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2.	Amended page(s) of Part IIC and IIF (old Part IIE) or equivalent in the CTD format, if applicable
3.	Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant). For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.
4.	The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the (Part IA) application form.
5.	A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application 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 change no. 7 above.

Note

The reference to unchanged specifications for impurities, if applicable, in condition no. 2 should refer to new additional impurities. In notification no. 10 on minor change in the manufacturing process of the active substance, condition no. 1 stipulates that there is no change in the qualitative and quantitative impurity profile or in the physio-chemical properties. In notification no. 12 on change in specification of active substance tightening of specification limits or addition of new test parameters are allowed. One of the conditions for these changes to qualify as a type I notification is that the change should not be the result of unexpected events during manufacture. The conditions of these notifications should be borne in mind in the fulfilment of the conditions of notification no. 15.

16	Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance for a currently approved manufacturer and currently approved manufacturing process	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		None	**1, 2, 3**	**IA**
	Conditions: None			
	Documentation			
☐	1. Copy of the current (updated) European Pharmacopoeia TSE certificate of suitability.			
☐	2. Amended page(s) of Part IIC or equivalent in the CTD format.			
☐	3. A document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant). For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.			

17	Change in:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	a) the re-test period of the active substance	**1, 2, 3**	**1, 2**	**IB**
	b) the storage conditions for the active substance	**1, 2**	**1, 2**	**IB**
	Conditions			
☐	1. Stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.			
☐	2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
☐	3. The active substance is not a biological substance.			
	Documentation			
☐	1. Amendment to relevant sections of Part IIF (old Part IIE) or equivalent in the CTD format must contain results of appropriate real time stability studies; conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorised packaging material and covering the duration of the requested re-test period or requested storage conditions.			
☐	2. Copy of approved specifications of the active substance.			

18	Replacement of an excipient with a comparable excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3, 4, 5	**1, 2, 3, 4, 5, 6, 7**	**IB**

Conditions

1.	Same functional characteristics of the excipient.
2.	The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability cf Note for Guidance on Bio-availability and Bio-equivalence, Annex II; the principles contained in this note for guidance for medicinal products for human use should still be taken into account for veterinary medicinal products, if relevant). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
3.	Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. For excipients in a veterinary medicinal product for use in animal species susceptible to TSE, a risk assessment has been carried out by the competent authority.
4.	It does not concern a medicinal product containing a biological active substance.
5.	Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

Documentation

1.	Amended pages of Part IIA, IIB, IIC2, IIF1 (old IIE1) and IIG2 (old IIF2) or equivalent in the CTD format.
2.	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
3.	For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.
4.	Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence.*
5.	Either a European Pharmacopoeia certificate of suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The information should include the following information: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and evidence of its previous acceptance. For the Centralised Procedure this information should be included in an updated TSE table A (and B, if relevant). For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.
6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test method (if appropriate).
7.	The batch numbers of the batches used in the stability studies should be given.

19	Change in specification of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Tightening of specification limits**	**1, 2, 3**	**1, 2**	**IA**
		2, 3	**1, 2**	**IB**
b)	**Addition of a new test parameter to the specification**	**2, 4, 5**	**1, 2, 3, 4, 5, 6**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The change does not concern adjuvant for vaccines or a biological excipient.

Documentation

1. Amendment of relevant section of Part IIC or equivalent in the CTD format.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and summary of validation data.
4. Batch analysis data on two production batches for all tests in the new specification.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6. Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*, if relevant.

20	Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Minor changes to an approved test procedure**	**1, 2, 3, 5**	**1**	**IA**
b)	**Minor changes to an approved test procedure for a biological excipient**	**1, 2, 3**	**1, 2**	**IB**
c)	**Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure**	**2, 3, 4, 5**	**1, 2**	**IB**

Conditions

1. 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); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The substance is not a biological excipient.

Documentation

1. Amendment to relevant sections of Part IIC or equivalent in the CTD format which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable); amendment to relevant sections of Part IIG (old Part IIF) or equivalent in the CTD format, if applicable.
2. Comparative validation results showing that the current test and the proposed one are equivalent.

21	Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**From a manufacturer currently approved**	**1, 2, 3**	**1, 2, 3**	**IA**
b)	**From a new manufacturer (replacement or addition)**			
	1. Sterile substance	**1, 2, 3**	**1, 2, 3**	**IB**
	2. Other substances	**1, 2, 3**	**1, 2, 3**	**IA**

Conditions

1. The finished product release and end of shelf life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the excipient does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Amended page(s) of Part IIC or equivalent in the CTD format.
3. Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
   For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
   For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.

22	Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		None	1, 2, 3	IA
	Conditions: None			
	Documentation			
☐	1. Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.			
☐	2. Amended page(s) of Part IIC or equivalent in the CTD format.			
☐	3. A document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant). For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.			

23	Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Excipient or reagent used in manufacture of biological active substance or manufacture of a finished product containing biological active substance**	1	1, 2	IB
b)	**Other cases**	1	1	IA
	Conditions			
☐	1. Excipient and finished product release and end of shelf life specifications remain the same.			
	Documentation			
☐	1. Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin.			
☐	2. Study of equivalence of the materials and the impact on production of the final material.			

24	Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier)	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1, 2	1, 2, 3, 4	IB
	Conditions			
☐	1. Specifications are not adversely affected; no change in qualitative and quantitative impurity profile or in physico-chemical properties.			
☐	2. The excipient is not a biological substance.			
	Documentation			
☐	1. Amendment to relevant sections of Part IIC or equivalent in the CTD format.			
☐	2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.			
☐	3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.			
☐	4. Copy of approved and new (if applicable) specifications of the excipient.			

25	Change to comply with European Pharmacopoeia or with the national pharmacopoeia of a Member State	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Change of specification(s) of a former non-European pharmacopoeial substance to comply with European Pharmacopoeia or with the national pharmacopoeia of a Member State**			
	1. Active substance	**1, 2**	**1, 2, 3, 4, 5, 6**	**IB**
	2. Excipient	**1, 2**	**1, 2, 3, 4, 5, 6**	**IB**
b)	**Change to comply with an update of the relevant monograph of the European Pharmacopoeia or national pharmacopoeia of a Member State**			
	1. Active substance	**1, 2**	**1, 2**	**IA**
	2. Excipient	**1, 2**	**1, 2**	**IA**

Conditions

1. The change is made exclusively to comply with the pharmacopoeia.
2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.

Documentation

1. Amendment to relevant section of Part IIC or equivalent in the CTD format.
2. Comparative table of current and proposed specifications.
3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.
4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.
5. Where appropriate, batch analysis data (in a comparative tabulated format) on two production batches of the finished product containing the substance complying with the current and proposed 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.
6. For biological medicinal products, demonstration that consistency of quality and of the production process is maintained.

26	Change in the specifications of the immediate packaging of the finished product	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
a)	**Tightening of specification limits**	**1, 2, 3**	**1, 2**	**IA**
		2, 3	**1, 2**	**IB**
b)	**Addition of a new test parameter**	**2, 4**	**1, 2, 3, 4**	**IB**

Conditions

1. The change is not a consequence of any commitments from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment to relevant section of Part IIC or equivalent in the CTD format.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data.
4. Batch analysis data on two batches for all tests in the new specification.

27	Change to a test procedure of the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Minor change to an approved test procedure**	**1, 2, 3**	**1**	**IA**
b)	**Other changes to a test procedure, including replacement or addition of a test procedure**	**2, 3, 4**	**1, 2**	**IB**

Conditions

1. 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).
2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way

Documentation

1. Amendment to relevant sections of Part IIC or equivalent in the CTD format which includes a description of the analytical methodology and a summary of validation data.
2. Comparative validation results showing that the current test and the proposed one are equivalent.

28	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	**1**	**IA**

Conditions

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

Documentation

1. Amendment to the relevant section of Part IIC or equivalent in the CTD format.

29	Change in the qualitative and/or quantitative composition of the immediate packaging material	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
a)	**Semi-solid and liquid pharmaceutical forms**	**1, 2, 3, 4**	**1, 2, 3, 4, 5**	**IB**
b)	**All other pharmaceutical forms**	**1, 2, 3, 4**	**1, 4, 5**	**IA**
		1, 3, 4	**1, 2, 3, 4, 5**	**IB**

Conditions

1.	The product concerned is not a biological or sterile product.
2.	The change only concerns the same packaging type and material (e.g. blister to blister).
3.	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
4.	Relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1.	Amendment to relevant sections of Part IIA, IIC and IIG (old Part II F) or equivalent in the CTD format.
2.	Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture).
3.	Proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack).
4.	The batch numbers of batches used in the stability studies should be indicated.
5.	Comparative of the current and proposed specifications, if applicable.
6.	Samples of the new container/closure where applicable.

30	Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Deletion of a supplier**	**1**	**1**	**IA**
b)	**Replacement or addition of a supplier**	**1, 2, 3, 4**	**1, 2, 3**	**IB**

Conditions

1. No deletion of packaging component or device.
2. The qualitative and quantitative composition of the packaging components/device remain the same.
3. The specifications and quality control method are at least equivalent.
4. The sterilisation method and conditions remain the same, if applicable.

Documentation

1. Amended section Part IIC or equivalent in the CTD format.
2. For devices for medicinal products for human use, proof of CE marking.
3. Comparative table of current and proposed specifications, if applicable.

31	Change to in-process tests or limits applied during the manufacture of the product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Tightening of in-process limits**	**1, 2, 3**	**1, 2**	**IA**
		2, 3	**1, 2**	**IB**
b)	**Addition of new tests and limits**	**2, 4**	**1, 2, 3, 4**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. Any change should be within the range of the currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amended section Part IIB or equivalent in the CTD format, and IIE (old Part IID) or equivalent in the CTD format, where relevant.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data.
4. Batch analysis data on two (three for biological medicinal products) production batches of the finished product for all tests in the new specification.

32	Change in the batch size of the finished product	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
a)	**Up to10-fold compared to the original batch size approved at the grant of the marketing authorisation**	**1, 2, 3, 4, 5**	**1, 4**	**IA**
b)	**Downscaling down to 10-fold**	**1, 2, 3, 4, 5, 6,**	**1, 4**	**IA**
c)	**Other situations**	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5**	**IB**

Conditions

1.	The change does not affect reproducibility and/or consistency of the product.
2.	The change relates only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms.
3.	Any changes to the manufacturing method and/or to the in-process controls are only 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 current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.
5.	It does not concern a medicinal product containing a biological active substance.
6.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
7.	Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1.	Amended section Part IIB or equivalent in the CTD format.
2.	Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specifications (with proposed action).
3.	Copy of approved release and end-of-shelf life specifications.
4.	The batch numbers (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5.	The batch numbers of batches used in the stability studies should be indicated.

33	Minor change in the manufacture of the finished product	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1, 2, 3, 4, 5	**1, 2, 3, 4, 5, 6, 7, 8**	**IB**

Conditions

1.	The overall manufacturing principle remains the same.
2.	The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3.	The medicinal product does not contain a biological active substance.
4.	In case of a change in the sterilisation process, the change is to a standard pharmacopoeial cycle only.
5.	Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1.	Amended section Part IIB or equivalent in the CTD format.
2.	For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate 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: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.
4.	Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*.
5.	In case of a change to the sterilisation process, validation data should be provided.
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 currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
8.	The batch numbers of batches used in the stability studies should be indicated.

34	Change in the colouring system or the flavouring system currently used in the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Reduction or deletion of one or more components of the**			
	1. colouring system	**1, 2, 3, 4**	**1, 2, 3**	**IA**
	2. flavouring system	**1, 2, 3, 4**	**1, 2, 3**	**IA**
b)	**Increase, addition or replacement of one or more components of**			
	1. colouring system	**1, 2, 3, 4, 5, 6**	**1, 2, 3, 4, 5**	**IB**
	2. flavouring system	**1, 2, 3, 4, 5, 6**	**1, 2, 3, 4, 5**	**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 currently makes up a major part of the finished product formulation.
3.	The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of an identification test.
4.	Stability studies (long-term and accelerated) in accordance with relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data shall be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.
5.	Any new proposed components must comply with the relevant Directives (e.g. Council Directive 78/25/EEC (OJ L 229, 15.8.1978, p. 63) as amended for colourants and Directive 88/388/EEC for flavours).
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 compliance with the current Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

Documentation

1.	Amended pages of Part II A, II B, II C2, II E1 or equivalent in the CTD format (including identification method for any new colorant, where relevant) and IIG (old Part IIF) or equivalent in the CTD format (if appropriate, where the end of shelf life specifications have been updated).
2.	The batch numbers of the batches used in the stability studies should be indicated.
3.	Sample of the new product, where applicable (see Notice to Applicants Requirements for samples in the Member States).
4.	Either a European Pharmacopoeia certificate of suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant). For Veterinary Medicinal Products an additional risk assessment is required for products intended for use in TSE-susceptible species.
5.	Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

35	Change in coating weight of tablets or change in weight of capsule shells	Conditions to be fulfilled	Documentation to be	Procedure type

			supplied	
a)	**Immediate release oral pharmaceutical forms**	**1, 3, 4**	**1, 4**	**IA**
b)	**Gastro-resistant, modified or prolonged release pharmaceutical forms**	**1, 2, 3, 4**	**1, 2, 3, 4**	**IB**

Conditions

1.	The dissolution profile of the new product determined on a minimum of two pilot scale batches, is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
2.	The coating is not a critical factor for the release mechanism.
3.	The finished product specification has only been updated in respect of weight and dimensions, if applicable.
4.	Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1.	Amended pages of Part IIA, IIB and IIF1 (old Part IIE1) or equivalent in the CTD format.
2.	Comparative dissolution profile data of at least two pilot scale batches of the new formulation and two production batches of the current formulation (no significant differences regarding comparability cf *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*, Annex II; the principles contained in this note for guidance for medicinal products for human use should still be taken into account for veterinary medicinal products if relevant). For herbal medicinal products, comparative disintegration data may be acceptable.
3.	Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*.
4.	The batch numbers of the batches used in the stability studies should be indicated.

36	**Change in shape or dimensions of the container or closure**	**Conditions to be fulfilled**	**Documenta-tion to be**	**Procedure type**

			supplied	
a)	**Sterile pharmaceutical forms and biological medicinal products**	**1, 2, 3**	**1, 2, 3**	**IB**
b)	**Other pharmaceutical forms**	**1, 2, 3**	**1, 2, 3**	**IA**

Conditions

1.	No change in the qualitative or quantitative composition of the container.
2.	The change does not concern a fundamental part of the packaging material, which affect the delivery**,** use, safety or stability of the finished product.
3.	In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started with at least two pilot scale (three for biological medicinal products) or industrial scale batches and at least three months' (six months for biological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1.	Amended section of Part IIC or equivalent in the CTD format (including description, detailed drawing and composition of the container or closure material).
2.	The batch numbers of the batches used in the stability studies should be indicated, where applicable.
3.	Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States).

37	Change in the specification of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	a) Tightening of specification limits	**1, 2, 3**	**1, 2**	**IA**
		2, 3	**1, 2**	**IB**
	b) Addition of a new test parameter	**2, 4, 5**	**1, 2, 3, 4**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.

Documentation

1. Amendment to relevant section of Part IIF (old Part IIE) or equivalent in the CTD format.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data.
4. Batch analysis data on two production batches of the finished product for all tests in the new specification.

38	Change in test procedure of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Minor change to an approved test procedure**	**1, 2, 3, 4, 5**	**1**	**IA**
b)	**Minor change to an approved test procedure for biological active substance or biological excipient**	**1, 2, 3, 4**	**1, 2**	**IB**
b)	**Other changes to a test procedure, including replacement or addition of a test procedure**	**2, 3, 4, 5**	**1, 2**	**IB**

Conditions

1.	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).
2.	Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.
3.	Results of method validation show new test procedure to be at least equivalent to the former procedure.
4.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5.	The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.

Documentation

1.	Amended section Part IIF (old Part IIE) or equivalent in the CTD format, which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable); amendment to relevant sections of Part IIG (old Part IIF) or equivalent in the CTD format (if applicable).
2.	Comparative validation results showing that the current test and the proposed one are equivalent.

39	Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	1, 2	IA
	Conditions			
1.	Finished product release and end of shelf life specifications have not been changed (except for appearance).			
2.	Any ink must comply with the relevant pharmaceutical legislation.			
	Documentation			
1.	Amendment to relevant sections of Part IIA, IIC (in case of new ink), IID and IIF (old Part IIE) or equivalent in the CTD format (including a detailed drawing or written description of the current and new appearance).			
2.	Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).			

40	Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets**	1, 2	1, 2, 3, 4, 5	IB
b)	**All other tablets, capsules, suppositories and pessaries**	1, 2	1, 4	IA
	Conditions			
1.	The dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one.			
2.	Release and end of shelf-life specifications of the product have not been changed (except for dimensions).			
	Documentation			
1.	Amendments to the relevant sections of parts IIB and IIF1 (old Part IIE1) (including a detailed drawing of the current and proposed situation).			
2.	Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability cf *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*, Annex II; the principles contained in this note for guidance for medicinal products for human use should still be taken into account for veterinary medicinal products, if relevant). For herbal medicinal product comparative disintegration data may be acceptable.			
3.	Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence.*			
4.	Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).			
5.	Where applicable, data on breakability test of tablets at release must be given and commitment to submit data on breakability at the end of shelf life.			

41	Change in pack size of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Change in the number of units (e.g. tablets, ampoules, etc.) in a pack**			
1.	**Change within the range of the currently approved pack sizes**	**1, 2**	**1, 3**	**IA**
2.	**Change outside the range of the currently approved pack sizes**	**1, 2**	**1, 2, 3**	**IB**
b)	**Change in the fill weight/fill volume of non-parenteral multi-dose products**	**1, 2**	**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.
2. The primary packaging material remains the same.

Documentation

1. Amendments to the relevant sections of parts IIA, IIC and IIF (old Part IIE).
2. Justification for the new pack-size, showing that the new size is 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 relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).

42	Change in:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**the shelf life of the finished product**			
1.	**As packaged for sale**	**1, 2, 3**	**1, 2**	**IB**
2.	**After first opening**	**1, 2**	**1, 2**	**IB**
3.	**After dilution or reconstitution**	**1, 2**	**1, 2**	**IB**
b)	**the storage conditions of the finished product or the diluted/reconstituted product**	**1, 2, 4**	**1, 2**	**IB**

Conditions

1. Stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The shelf life does not exceed five years.
4. The product is not a biological medicinal product.

Documentation

1. Amendment to relevant sections of Part IIG (old Part IIF) or equivalent in the CTD format must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two production scale batches[1] of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included.
   [1] Pilot scale batches can be accepted with a commitment to verify the shelflife of production scale batches.
2. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

43	Addition or replacement or deletion of a measuring or administration device not being an integrated part of the primary packaging (spacer devices for metered dose inhalers are excluded)	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
	1. Addition or replacement	**1, 2**	**1, 2, 3**	**IA**
	2. Deletion	**3**		**IB**
	Conditions			
	1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.			
	2. The new device is compatible with the medicinal product.			
	3. The medicinal product can still be accurately delivered.			
	Documentation			
	1. Amended sections of Part IIA and Part IIC or equivalent in the CTD format (including description, detailed drawing and composition of the device material and supplier where appropriate).			
	2. Proof of CE marking.			
	3. Samples of the new device where applicable (see NTA, Requirements for samples in the Member States).			

46	Change in the summary of product characteristics of an essentially similar product following a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC or Article 34 of Directive 2001/82/EC (for Mutual Recognition Procedure only, Regulation 1084/2003)	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1, 2	1	IB
	Conditions			
ĵ	1. The proposed summary of product characteristics is identical for the concerned sections to that annexed to the Commission Decision on the referral procedure for the original product.			
ĵ	2. The application is submitted within 90 days after the publication of the Commission Decision.			
	Documentation			
ĵ	1. A copy of the summary of product characteristics attached to the Commission Decision on the relevant referral procedure.			

47	Submission of a medicinal product between products not subject to medical prescription, supply through non-pharmacy outlet	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1	1	IB
	Conditions: none			
	Documentation			
ĵ	1. Amendment of relevant documentation accordance with REG-75, version 1.			