Guideline on dossier requirements for Type IA and IB notifications

In accordance with Regulation (EC) No 726/2004 and Directives 2001/83/EC and 2001/82/EC, a common approach to the procedures for variations to the terms of a marketing authorisation has been adopted. These procedures facilitate the task of both industry and authorities and also guarantee that changes to the medicinal product do not give rise to public health concerns.

Commission Regulation (EC) No 1084/2003[1] concerning the examination of variations to the terms of marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State and Commission Regulation (EC) No 1085/2003[2] concerning the examination of variations to the terms of marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Regulation (EEC) No 2309/93, now reflected by Regulation (EC) No 726/2004, set out the provisions relating to variations and categorise them into Type IA, Type IB and Type II. The simplified procedures for Type IA and Type IB variations are in fact notifications, which follow two distinct timetables for validation and acceptance. Annex I of the above mentioned Regulations set out the conditions necessary for a given variation to follow either a type IA or a Type IB procedure.

For acceptance of a Type IA and IB notification, documentation in support of the notified changes must be submitted. In order to clarify what documentation should be submitted with these notifications, this guideline has been prepared. It elaborates the documentation required for both Regulation (EC) No 1084/2003 and Regulation (EC) No 1085/2003. Sometimes reference is made to specific guidelines. However, the applicant should always check whether other guidelines are also applicable for the variation concerned. Furthermore, if the change notified implies a change in the summary of product characteristics, labelling and/or package leaflet/insert, this change forms part of the notification. In such cases up-dated product literature has to be submitted as part of the documentation.

In the following table each Type I notification is defined using the terminology of Annex I to the Regulations. For each variation the conditions which apply and the relevant part of the dossier to be (re-)submitted or updated is identified, as well as any other documentation required. The appropriate fee must also be paid, in accordance with the prevailing rules at the time of submission of the notification. The notification shall be submitted simultaneously to the competent authorities of the Member States where the medicinal product has been authorised via the mutual recognition procedure or to the European Agency for the evaluation of medicinal products (EMEA) in the case of medicinal products authorised by the Community.

A variation notification normally concerns only one variation. To cover any other changes, it is necessary to submit notification for any consequential or parallel variations, which may be linked to the change applied for, at the same time and to clearly describe the relationship between these variations. Consequential variations form part of the same notification, while parallel variations do not. A consequential variation to a Type IA notification can only be another Type IA notification, while a consequential variation to a Type IB notification can be either another Type IB notification or a Type IA notification. All other consequential variations will therefore not be accepted and such changes should be submitted under a Type II variation procedure.

A consequential Type IA/IB variation is a change, which is an unavoidable and direct result of another change and not simply a change which occurs at the same time. Examples of consequential and parallel variations are listed below:

1. The replacement of a finished product manufacturing site within the EU, which is also responsible for quality control and batch release by a new site responsible for all operations. In the

[1] OJ L 159, 27.6.2003, p. 1.
[2] OJ L 159, 27.6.2003, p. 24.

case the quality control and batch release will be done at a different site, this will also be regarded as a consequential change. This would be a Type IB number 7 with consequential Type IA number 8.

2. A more complicated scenario is if the manufacturing site is outside the EU e.g. India. In this example a new manufacturing site is added but as a consequence a batch release site and possibly separate QC sites (depending upon the testing requirements) in the EU have to be replaced to reflect the need for testing and release of batches on importation. This again is a Type IB number 7 with consequential Type IA number 8.

3. The addition of one site for both the primary and secondary packaging can be considered as consequential. This variation should be submitted as the appropriate Type IA or IB number 7 notification including the consequential Type IA number 7a change.

4. An example where the variations would not be consequential and where separate applications should normally be submitted is where three different manufacturing sites are being added. In this case, three separate applications should be submitted, not one to add three sites.

5. In some cases a change in the test procedure and the specification are to be considered consequential, when it relates to a single test procedure. A change affecting a number of test procedures, even if it relates to the testing of a single substance or product, are not related and should be submitted as parallel notifications.

The Type I notification procedures are set out to provide for rapid and efficient processing of variations. Applicants should be aware that submitting redundant or irrelevant information does not facilitate rapid procedures. On the other hand deficient documentation can lead to non-validation/rejection of the notification. Acknowledgement of the validity of a Type IA notification/validation of the Type IB notification is made by the competent authority of the reference Member State /EMEA. A notification Type IB will be rejected if the applicant has not supplemented the documentation within 30 days of receipt of a notification of the competent authority stating that the original documentation is not adequate. Rejections do not prejudice the applicant's right to resubmission or, in the case of a Type IB notification, the right to refer the matter to the Agency.

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.			

Deleted: .

2	Change in the name of the medicinal product	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1, 2,3	1	IB
	Conditions			
	1. No confusion with the names of existing medicinal products or with the international non-proprietary name (INN).			
	2. For products in the centralised procedure only: The check by the EMEA on the acceptability of the new name by the Member States should be finalised before the variation application is submitted.			
	3. For products in the centralised procedure only: The change does not concern the addition of a name.			
	Documentation			
	1. For products in the centralised Procedure only: Copy of the EMEA letter of acceptance of the new invented name.			

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	Documenta-tion 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	Documenta-tion 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	Documenta-tion to be supplied	Procedure type
	a) Medicinal products for human use	**1**	**1**	**IA**
	b) Veterinary medicinal products	**2**	**2**	**IA**
	Conditions			
☐	1. Change following granting of or amendment to ATC Code by WHO.			
☐	2. Change following granting of or amendment to ATC Vet Code.			
	Documentation			
☐	1. Proof of acceptance by WHO or copy of the ATC Code list.			
☐	2. Copy of the ATC Vet 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.

Notes

In case of a change in or a new manufacturing site in a country outside the EEA without an operational GMP mutual recognition agreement with the EU, marketing authorisation holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous EEA inspection in the last 2-3 years and/or any planned EEA inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a GMP inspection by an inspection service of one of the Member States if needed.

QP Declarations in relation to active substances

Manufacturing authorisation holders are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP so a declaration is expected from each of the manufacturing authorisation holders that use the active substance 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 is expected 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 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. This will be accepted provided that:

- The declaration makes it clear that it is signed on behalf of all the involved QPs.
- The arrangements are underpinned by a technical agreement as described in Chapter 7 of the GMP Guide and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the active substance manufacturer(s). Note: These arrangements are subject to inspection by the competent authorities.

Applicants are reminded that a Qualified Person is at the disposal of a manufacturing authorisation holder according to Art. 41of Directive 2001/83/EC and Article 45 of Directive 2001/82/EC and located in the EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within MRA partner countries are not acceptable.

According to Article 46a (1) of Directive 2001/83/EC and Article 50a (1) of Directive 2001/82/EC, manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including re-packaging or re-labelling as carried out by a distributor.

A declaration is not required for blood or blood components they are subject to the requirements of Directive 2002/98/EC.

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, 4**	**IA**
	2. Including batch control/testing	**1, 2, 3, 4**	**1, 2, 3, 4**	**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. 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 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	Documenta-tion 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**
	c) Substance in veterinary medicinal products for use in animal species susceptible to TSE	**1, 2, 3, 4**	**1, 2, 3, 4, 5**	**IB**

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
	a) Substance in veterinary medicinal product for use in animal species susceptible to TSE	**None**	**1, 2, 3**	**IB**
	b) Other substance	**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	Documenta-tion to be supplied	Procedure type
		1, 2, 3, 4, 5	1, 2, 3, 4, 5, 6, 7, 8	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.
8.	For veterinary medicines intended for use in food producing animal species, proof that the excipient is included in Annex II of Council Regulation (EEC) No 2377/90 or, if not, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal.

19	Change in specification of an excipient	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**	**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	Documenta-tion 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	Documenta-tion 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**
c)	**Substance in veterinary medicinal product for use in animal species susceptible to TSE**	**1, 2, 3**	**1, 2, 3**	**IB**

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
a)	From a manufacturer currently approved or a new manufacturer (replacement or addition)	None	1, 2, 3	IA
b)	Substance in veterinary medicinal product for use in animal species susceptible to TSE	None	1, 2, 3	IB

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	Documenta-tion 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.

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	Documenta-tion 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	Documenta-tion 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	Documenta-tion to be supplied	Procedure type
a)	**Reduction or deletion of one or more components of the**			
	1. colouring system	**1, 2, 3, 4, 7**	**1, 2, 3**	**IA**
	2. flavouring system	**1, 2, 3, 4, 7**	**1, 2, 3**	**IA**
b)	**Increase, addition or replacement of one or more components of**			
	1. colouring system	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5**	**IB**
	2. flavouring system	**1, 2, 3, 4, 5, 6, 7**	**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.
7. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species are excluded.

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	Documenta-tion to be supplied	Procedure type
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 supplied	Procedure type
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	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, 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	Documenta-tion 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	Documenta-tion 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	Documenta-tion 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
a)	**Medicinal products for human use**			
	1. Addition or replacement	**1, 2**	**1, 2, 4**	**IA**
	2. Deletion	**3**		**IB**
b)	**Veterinary medicinal products**	**1, 2**	**1, 3, 4**	**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.	Reference to CE marking for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device if no CE marking is available.
4.	Samples of the new device where applicable (see NTA, Requirements for samples in the Member States).

44	Change in specification of a measuring or administration device for veterinary medicinal products	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 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.

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.

45	Change in test procedure of a measuring or administration device for veterinary medicinal products	Conditions to be fulfilled	Documenta-tion 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 of approved test procedure by new test procedure**	**2, 3, 4**	**1, 2**	**IB**

Conditions

1. The new or updated test procedure is demonstrated to be at least equivalent to the former test procedure.
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.

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.

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			
☐	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.			
☐	2. The application is submitted within 90 days after the publication of the Commission Decision.			
	Documentation			
☐	1. A copy of the summary of product characteristics attached to the Commission Decision on the relevant referral procedure.			

46	Change in the summary of product characteristics, labelling and package leaflet/insert as a consequence of a final opinion in the context of a referral procedure in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC (for Centralised Procedure only, Regulation 1085/2003)	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
		1	1, 2	IB
	Conditions			
☐	1. The variation only concerns the introduction of changes to the summary of product characteristics, labelling and package leaflet/insert in order to take account of a scientific opinion delivered in the context of a referral in accordance with Articles 31 and 32 of Directive 2001/83/EC or Articles 35 and 36 of Directive 2001/82/EC.			
	Documentation			
☐	1. Copy of the letter from EMEA/CXMP informing the marketing authorisation holder about the scientific opinion of CXMP and requesting specific changes to the summary of product characteristics, labelling and package leaflet/insert resulting from the opinion.			
☐	2. Letter of undertaking, if requested by EMEA/CXMP.			

47	Deletion of: (for Centralised Procedure only, Regulation 1085/2003)	Conditions to be fulfilled	Documenta-tion to be supplied	Procedure type
	a) a pharmaceutical form	1	1,2	IA
	b) a strength	1	1,2	IA
	c) a pack-size(s)	1	1,2	IA
	Conditions			
☐	1. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			
	Documentation			
☐	1. Reason for deletion of the pharmaceutical form, strength and/or pack-size(s) and declaration that no safety concerns exist for the product.			
☐	2. Declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			