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BROMI
DOSSIER REQUIREMENTS FOR TYPE IA AND TYPE IB UK NATIONAL NOTIFICATIONS
Version 2.1

This document should be read together with the EU Guideline on Dossier Requirements for Type IA and Type IB Notifications in Volume 2C and 6C of The Rules governing Medicinal products in the European Community - Regulatory Guidelines of the Notice to Applicants

UK National Dossier requirements for Type IA and IB Notifications under the Better Regulation of Medicines Initiative (BROMI)

New European variation regulations came into force on 1 October 2003. Commission Regulations 1084/2003/EC and 1085/2003/EC concern Mutual Recognition (MR) and Centralised Procedures respectively. The texts have been published in the Official Journal of the EU (OJ L159 27.6.2003 pl and 24) and are available from the Commission website: [http:// europa.eu.int/eur-lex/en/index.html](http://europa.eu.int/eur-lex/en/index.html).

This new legislation introduced a new category of minor variation (Type IA notification) with a 14-day timescale and involving a scientific validation only. The existing Type I minor variation categories were revised and became known as Type IB notifications, with retention of a 30-day timescale.

With the introduction of new legislation the MHRA revised its procedures for processing applications to vary marketing authorisations in line with the new European legislation and has followed the principles of the Regulation 1084/2003/EC and CMD(h)/MRFG best practice guidance for both MR and National procedures.

In the light of experience gained since the introduction of the legislation in 2003 the MHRA has reviewed national procedures for minor notifications and is now offering further simplified procedures. These procedures have been agreed with industry as part of the Better Regulation of Medicines Initiative (BROMI). Further information on BROMI can be found on our website www.mhra.gov.uk. For National procedures Regulation 1084/2003/EC will continue to be followed in principle, with the introduction of simplified processing for certain categories of notifications.

Commission Regulation (EC) No 1084/2003¹ sets out the provisions relating to variations and categorises them into Type IA, Type IB and Type II. Annex I of the Regulation sets out the conditions necessary for a given variation to follow either a Type IA or a Type IB Notification procedure.

For acceptance of a Type IA or IB notification, certain conditions have to be met and documentation in support of the notified changes must be submitted. In order to clarify what documentation should be submitted with these notifications, the Notice to Applicants Group prepared a guideline entitled – “Guideline and Dossier Requirements for Type IA and IB Notifications”. The guideline document included a table defining each notification using the terminology of Annex I of the regulations. For each variation the conditions that apply, the documentation required and the relevant part of the dossier to be (re)submitted or updated was identified. The appropriate page of the guideline is required to be submitted with the notification.

This procedural document follows the format of the EU guideline and gives additional information for simplified procedures for UK Nationally authorised human medicinal products. The following has been introduced.

	A self certification procedure of some Type IA Notifications. These changes can be implemented on submission through the portal on receipt of acknowledgement. A formal letter of acknowledgement will be sent within 14 days of submission. (Self-Certification BROMI)
	A Scientific validation procedure for some current Type IB changes. Applicants will be notified of the validity of applications within 14 days of receipt. (Type IA BROMI)
	A 30-day assessment procedure for some specified changes that are considered Type II variations by virtue of their exclusion from the EU Guideline on Dossier Requirements for Type IA and IB Notifications. (TYPE IB BROMI)

¹ OJ L 159, 27.6.2003, p. 1.

Submission of UK National Notifications

Please refer to Special MAIL 5 for guidance on submission of licensing applications to the MHRA. Simplified processing procedures will be limited to Portal applicants.

All BROMI variations will be identified by the submission type selected by the applicant on the variation application form on the portal. The appropriate submission type (i.e. Self-Certification Type 1A BROMI or Type IB BROMI) would be selected from the drop down menu in Section 1.b of the application form and the fee type in Section 8.2 of the form.

Applications should be accompanied by the relevant page from the BROMI National procedures document, which will replace the checklist from the EU Guideline on Dossier Requirements for Type IA and IB Notifications.

The following should also be submitted:

- All documentation as specified in the checklist. Please note that, where relevant, the appropriate headings and numbering of the EU-CTD format must be used. It should also be noted that you will need to submit the whole section or sub-section of any changed CTD depending on the changes applied for.
- In cases where the changes affect SPC, labelling and/or package leaflets (PILs), revised documents should be provided that include the proposed new wording. Clean and highlighted copies should be provided of these documents. The proposed artwork should be provided for the revised labels and PILs.
- All variation applications affecting the SPC should be accompanied by the appropriate Section(s) of the SPC submitted as individual Word fragments and using the templates found at: <http://www.mhra.gov.uk/LicenceApplicationForms>

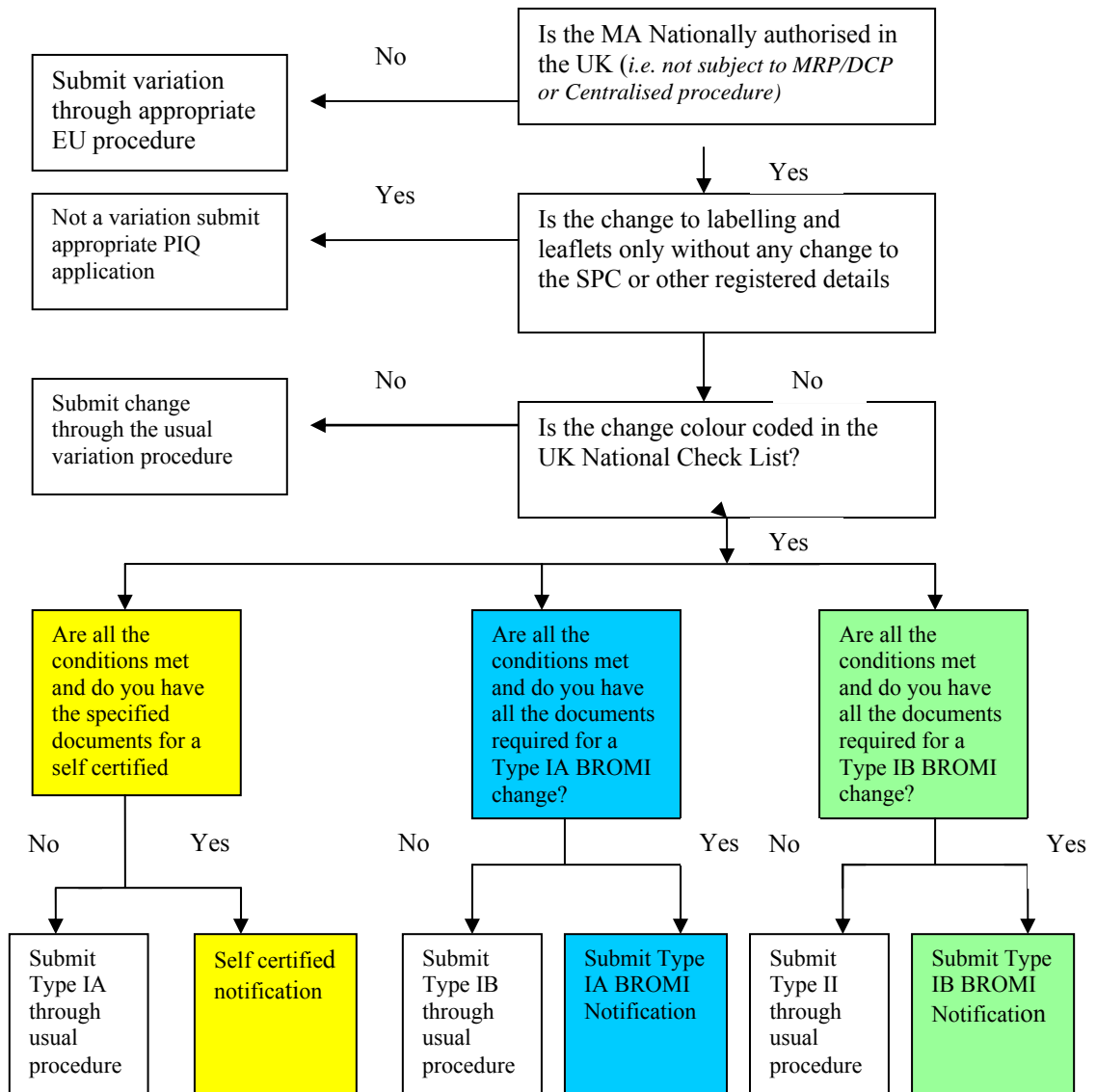
Explanatory Note:

Some categories in the document have been colour coded as follows:

	Categories of notification suitable for self certification. Conditions and documentation requirements additional for National procedures may also be coded in yellow. (Self-Certification BROMI)
	Categories of notification that are considered Type IB under EU legislation but may be submitted as Type IA for national authorised products providing the specified conditions and documentation requirements presented here are met. Conditions and documentation requirements additional for National procedures may also be coded in blue. (Type IA BROMI)
	Categories of notification that are considered Type II variations under EU legislation but may be submitted as Type IB Notifications for national authorised products providing the specified conditions and documentation requirements are met. Conditions and documentation requirements additional to those of MR procedures are also coded in green. (Type IB BROMI)

UK NATIONAL NOTIFICATIONS

Decision Tree – Is my application acceptable as a BROMI Notification?



Bulk Applications for Identical Changes

A particular change may be made simultaneously to a series of products and the supporting data package for each product may be identical (e.g. change in address of MA holder). Under UK National procedures a ‘bulk discount’ would be applied to such applications. Usually the first (or lead) authorisation in the bulk is charged at the full variation fee and the second and subsequent authorisations are charged at 50%. It should be noted that applications can only be bulked for a group of licences held by the same authorisation holder.

Consequential Changes

Usually each change should be submitted as separate notifications however; in some cases there may be changes that are consequential on one another. A consequential variation is

UK NATIONAL NOTIFICATIONS

regarded as a change, which is an unavoidable, and the direct result of another change (i.e. the 'main change') and not simply a change that occurs at the same time.

Consequential variations are submitted as one notification and therefore attract only one fee.

In cases of consequential variations, the MAH must include a clear justification/explanation in the Variation application form.

Changes that cannot be considered as consequential must be submitted as separate (parallel) variation notifications.

Audit of BROMI Notifications

Self Certified applications are not assessed and Type IA notifications are validated but are not subject to a full scientific assessment. A portion of these applications will however be audited by assessors on a monthly basis to confirm whether they have been submitted under the correct category and whether the conditions and documentation requirements have been applied correctly. If any application is found to have been submitted incorrectly then it will be revoked. In such cases the applicant will be required to reapply under the correct variation category and pay the appropriate fee.

UK NATIONAL NOTIFICATIONS

1	Change in the name and/or address of the marketing authorisation holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	1, 2	Self Certification
Conditions				
<input type="checkbox"/>	1. The marketing authorisation holder shall remain the same legal entity.			
<input type="checkbox"/>	2. The change to the name and address are the only changes made to the SPC and the statutory information in the label and leaflet.			
Documentation				
<input type="checkbox"/>	1. Formal documentation from a relevant official body (e.g. Chamber of Commerce or Companies House) in which the new name or new address is mentioned.			
<input type="checkbox"/>	2. Revised SPC (Section 7) , label and leaflet Please note that if the notification is a bulk application affecting a number of licences you are only required to submit labels and leaflets for one member of the bulk, as a minimum. Revised labels and leaflets for other licences in the bulk, that have not been submitted with the variation should be submitted by the appropriate application to the Patient Information Quality (PIQ) Unit.			

2	Change in the name of the medicinal product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	Not a BROMI change			Usual Type IB route

3	Change in name of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3	1	Self Certification
Conditions				
<input type="checkbox"/>	1. The active substance shall remain the same.			
<input type="checkbox"/>	2. The change in active name is the only change made to the SPC, label and PIL.			
<input type="checkbox"/>	3. The name has been accepted by, the WHO and/or the INN list has been updated. For herbal medicinal products, the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products.			
Documentation				
<input type="checkbox"/>	1. Revised SPC, label and leaflet artwork			

UK NATIONAL NOTIFICATIONS

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	Self Certification
Conditions				
<input type="checkbox"/>	1. The manufacturing site remains the same.			
Documentation				
<input type="checkbox"/>	1. Formal documentation from a relevant official body (e.g. Chamber of Commerce or Companies House) in which the new name and/or address is mentioned.			
<input type="checkbox"/>	2. Replacement page(s) of the dossier in 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, 2	1, 2, 3	Self Certification
Conditions				
<input type="checkbox"/>	1. The manufacturing site shall remain the same i.e. the same location.			
<input type="checkbox"/>	2. If changes to the label and or leaflet are necessary, the only changes made are the name and address of the manufacturer			
Documentation				
<input type="checkbox"/>	1. Formal documentation from a relevant official body (e.g. Chamber of Commerce or Companies House) in which the new name and/or address is mentioned.			
<input type="checkbox"/>	2. Replacement page(s) of the dossier in the CTD format.			
<input type="checkbox"/>	3. Revised label and leaflet artwork (if applicable)			

6	Change in ATC Code	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	Medicinal products for human use	1	1	Self Certification
Conditions				
<input type="checkbox"/>	1. Change following granting of or amendment to ATC Code by WHO.			
Documentation				
<input type="checkbox"/>	1. Revised SPC (if applicable).			

UK NATIONAL NOTIFICATIONS

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
<input type="checkbox"/> a) Secondary packaging for all types of pharmaceutical forms	1, 2, 8	1, 2, 5, 10	Self Certification
<input type="checkbox"/> b) Primary packaging site			
<input type="checkbox"/> 1. Solid pharmaceutical forms, e.g. tablets and capsules	Not a BROMI change. Submit by usual route		
<input type="checkbox"/> 2. Semi-solid or liquid pharmaceutical forms	”		
<input type="checkbox"/> 3. Liquid pharmaceutical forms (suspensions, emulsions)	”		
<input type="checkbox"/> c) All other manufacturing operations except batch release	”		
<input type="checkbox"/> d) Additional Distributor or Own Label Supplier	1, 5, 6, 7	1, 2, 10	IA
<input type="checkbox"/> e) Replacement or addition of a manufacturing site for part or all of the manufacturing process of a sterile finished product.	1, 2, 3, 4,	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	IB
Conditions			
<input type="checkbox"/> 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.		
<input type="checkbox"/> 2.	Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).		
<input type="checkbox"/> 3.	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.		
<input type="checkbox"/> 4.	Product concerned is not a biological medicinal product.		
<input type="checkbox"/> 5.	The addition of the new distributor or own label supplier is not associated with a change of the product name.		
<input type="checkbox"/> 6.	The only changes made to the label and leaflet concern the company logo and name and address of the distributor/ supplier Or: <input type="checkbox"/> Additional changes have been made to the label and leaflet and it is confirmed that a parallel application has been submitted to the Patient Information and Quality Unit.		
<input type="checkbox"/> 7.	The distributor has been appropriately authorised for wholesale dealing, where relevant Or <input type="checkbox"/> The proposed distributor is a retail outlet and the product concerned has GSL status.		
<input type="checkbox"/> 8.	Confirmation that the only operation to be undertaken will be the placing of finished product into secondary packaging (e.g. cartons) that is not in contact with the finished product.		
Documentation			
<input type="checkbox"/> 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. ▪ 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		

UK NATIONAL NOTIFICATIONS

	one of the Member States of the EEA. A reference to the EudraGMP database will suffice once this is operational.
<input type="checkbox"/>	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.
<input type="checkbox"/>	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.
<input type="checkbox"/>	4. The batch numbers of batches (≥ 3) used in the validation study should be indicated or validation protocol (scheme) to be submitted.
<input type="checkbox"/>	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.
<input type="checkbox"/>	6. Copy of approved release and end-of-shelf life specifications.
<input type="checkbox"/>	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).
<input type="checkbox"/>	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.
<input type="checkbox"/>	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.
<input type="checkbox"/>	10. Copy of revised label and PIL artwork (if applicable).

UK NATIONAL NOTIFICATIONS

8	Change to batch release arrangements and quality control testing of the finished product NOT A BROMI CHANGE- SUBMIT TYPE 1A BY USUAL PROCEDURE	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	a) Replacement or addition of a site where batch control/testing takes place			
<input type="checkbox"/>	b) Replacement or addition of a manufacturer responsible for batch release			
<input type="checkbox"/>	1. Not including batch control/testing			
<input type="checkbox"/>	2. Including batch control/testing			

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
<input type="checkbox"/>	a)	1	1	Self Certification
<input type="checkbox"/>	b) Deletion of a UK distributor	None	1	Self Certification
Conditions				
<input type="checkbox"/>	1. An appropriately authorised site remains registered on the authorisation to undertake the manufacturing operation concerned.			
Documentation				
<input type="checkbox"/>	1. The “present” and “proposed” manufacturers should be clearly stated on the variation application form.			

10	Minor change in the manufacturing process of the active substance with no changes to reagents or solvents used in the process	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	(b)	1, 2, 3, 4, 5	1, 2, 3	IA
Conditions				
<input type="checkbox"/>	1. No change in qualitative and quantitative impurity profile or in physico-chemical properties, including residual solvent levels.			
<input type="checkbox"/>	2. The active substance is not a biological substance.			
<input type="checkbox"/>	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.			
<input type="checkbox"/>	4. There are no changes to the reagents or solvents used in the process			
<input type="checkbox"/>	5. The specifications of the active substance are unchanged			
Documentation				
<input type="checkbox"/>	1. Amendment to relevant sections of the dossier 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.			
<input type="checkbox"/>	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.			
<input type="checkbox"/>	3. Copies of the approved specifications of the active substance			
Other changes to active ingredient manufacture: Not a BROMI change – submit through usual Type IB (i.e. change code 10a) or Type II route, as appropriate				

UK NATIONAL NOTIFICATIONS

11 Change in batch size of active substance or intermediate	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> Downscaling	1, 2, 3, 4, 5, 6	1, 2, 3	Self Certification
Other changes to batch sizes – Not a BROMI change			Submit through usual Type IA or IB procedures
Conditions			
<input type="checkbox"/> 1. Any changes to the manufacturing methods are only those necessitated by the change in scale, e.g. use of different-sized equipment.			
<input type="checkbox"/> 2. Test results of at least two batches according to the specifications are available for the proposed batch size.			
<input type="checkbox"/> 3. The active substance is not a biological substance.			
<input type="checkbox"/> 4. The change does not affect the reproducibility of the process.			
<input type="checkbox"/> 5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
<input type="checkbox"/> 6. The specifications of the active substance (and/or intermediate if applicable) are unchanged.			
Documentation			
<input type="checkbox"/> 1. Amended section of the dossier in the CTD format.			
<input type="checkbox"/> 2. The batch numbers of the tested batches having the proposed batch size.			
<input type="checkbox"/> 3. Copies of the specifications of the active substance and/or intermediate as applicable			

UK NATIONAL NOTIFICATIONS

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	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Tightening of specification limits	1, 2, 3	1, 2	Self Certification
b) Addition of a new test parameter to the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active – Not a BROMI change			Submit through usual Type IB procedures
<input type="checkbox"/> c) Addition of a new test parameter to the specification of an active, starting material, intermediate or reagent used in the manufacturing process, without a change to the overall impurity limits.	1, 2, 4, 5, 6, 7, 8, 9	1, 2, 3, 4, 5	IA
Conditions			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 2. The change should not be the result of unexpected events arising during manufacture.			
<input type="checkbox"/> 3. The change is within the range of currently approved limits.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/> 5. The active substance is not a biological substance.			
<input type="checkbox"/> 6. The change does not concern a new unqualified impurity.			
<input type="checkbox"/> 7. The new method has been adequately validated in line with current guidance.			
<input type="checkbox"/> 8. There have been no changes to the total impurity limits			
<input type="checkbox"/> 9. There have been no changes to the technical characteristics of an active that would affect the manufacture of the finished product e.g. particle size.			
Documentation			
<input type="checkbox"/> 1. Amendment to relevant section of the dossier in the CTD format.			
<input type="checkbox"/> 2. Comparative table of current and proposed specifications.			
<input type="checkbox"/> 3. Details of any new analytical method and validation data.			
<input type="checkbox"/> 4. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.			
<input type="checkbox"/> 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.			

UK NATIONAL NOTIFICATIONS

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	Documentation to be supplied	Procedure type
a)	Minor changes to an approved test procedure – Not a BROMI change			Submit through usual Type IA procedure
b)	Other changes to a test procedure, including replacement or addition of a test procedure – if does not meet conditions below for (c) Not a BROMI change			Submit through usual Type IB procedure
<input type="checkbox"/>	c) Addition of a new test procedure or replacement of a test with no change in total impurity limits	1, 2, 3, 4, 5, 6, 7	1, 2	IA
Conditions				
<input type="checkbox"/>	1. Appropriate validation studies have been performed in accordance with relevant guidelines.			
<input type="checkbox"/>	2. Results of method validation show the new test procedure to be at least equivalent to the former procedure.			
<input type="checkbox"/>	3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/>	4. The active substance, starting material, intermediate or reagent is not a biological substance.			
<input type="checkbox"/>	5. The change does not concern a new unqualified impurity.			
<input type="checkbox"/>	6. There have been no changes to the total impurity limits			
<input type="checkbox"/>	7. There have been no changes to the technical characteristics of the active ingredient that would affect the manufacture of the finished product e.g. particle size			
Documentation				
<input type="checkbox"/>	1. Amendment to relevant sections of the dossier in CTD format, which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).			
<input type="checkbox"/>	2. Comparative validation results showing that the current test and the proposed one are equivalent.			

UK NATIONAL NOTIFICATIONS

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
<input type="checkbox"/>	Not a BROMI change submit by usual Type 1B route			

15	Submission of a new or updated European Pharmacopoeia certificate of suitability (CEP) 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
<input type="checkbox"/>	a) 2. From a manufacturer currently approved (Updated CEP)	1, 2, 3, 4	1, 2, 3	Self Certification
	b) From a new manufacturer (replacement or addition) Not a BROMI change			Submit through usual 1A or 1B route
Conditions				
<input type="checkbox"/>	1. The finished product release and end of shelf life specifications remain the same.			
<input type="checkbox"/>	2. Supplementary tests and limits listed on the CEP are unchanged – including residual solvents, particle size profile and polymorphic form			
<input type="checkbox"/>	3. This notification concerns an update to only one certificate of suitability			
<input type="checkbox"/>	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				
<input type="checkbox"/>	1. A copy of the current (updated) CEP			
<input type="checkbox"/>	2. Amended page(s) of the dossier in CTD format.			
<input type="checkbox"/>	3. If the revision to the CEP concerns a change in name or address of the manufacturer the “present” and “proposed” manufacturers should be clearly stated on the variation application form.			

UK NATIONAL NOTIFICATIONS

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
<input type="checkbox"/>	b) Human Medicinal Products	None	1, 2, 3	Self Certification
Conditions: None				
Documentation				
<input type="checkbox"/>	1. Copy of the current (or updated) European Pharmacopoeia TSE certificate of suitability.			
<input type="checkbox"/>	2. Amended page(s) of the dossier in CTD format.			
<input type="checkbox"/>	3. If there is a change in manufacturers the “present” and “proposed” manufacturers should be listed on the variation application form.			

17	Change in:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	a) the re-test period of the active substance	1, 2, 3	1, 2	IA
<input type="checkbox"/>	b) the storage conditions for the active substance – Not a BROMI change – Submit through usual Type IB route			
<input type="checkbox"/>	c) the reduction in the re-test period of the active substance	1, 3, 4	1, 2	IB
Conditions				
<input type="checkbox"/>	1. Stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.			
<input type="checkbox"/>	2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
<input type="checkbox"/>	3. The active substance is not a biological substance.			
<input type="checkbox"/>	4. The change should not be the result of unexpected events arising during manufacture.			
Documentation				
<input type="checkbox"/>	1. Amendment to relevant sections of the dossier in CTD format including results of appropriate real time stability studies; conducted in accordance with the relevant stability guidelines on at least two 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.			
<input type="checkbox"/>	2. Copy of approved specifications of the active substance.			

UK NATIONAL NOTIFICATIONS

18 Replacement of an excipient with a comparable excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) The replacement leads to a change in the summary of product characteristics – Not a BROMI change submit by usual Type IB route			
<input type="checkbox"/> b) The replacement does not lead to a change in the Summary or Product Characteristics, label or leaflet	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6, 7,	IA
Conditions			
<input type="checkbox"/> 1.	Same functional characteristics of the excipient.		
<input type="checkbox"/> 2.	Where applicable the dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (i.e no significant differences regarding comparability c.f. <i>Note for Guidance on Bioavailability and Bioequivalence</i> , Annex II). For herbal medicinal products (where dissolution testing may not be feasible), the disintegration time of the new product is comparable to the old one.		
<input type="checkbox"/> 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.		
<input type="checkbox"/> 4.	The product is not a biological medicinal product.		
<input type="checkbox"/> 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 is given 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).		
<input type="checkbox"/> 6.	The only quantitative changes to the excipients are minor adjustments to accommodate the new excipient.		
Documentation			
<input type="checkbox"/> 1.	Amended pages of the relevant sections of the dossier in CTD format.		
<input type="checkbox"/> 2.	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceuticals (including stability aspects and antimicrobial preservation where appropriate).		
<input type="checkbox"/> 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.		
<input type="checkbox"/> 4.	Justification for not submitting a new bioequivalence study according to the current <i>Note for Guidance on The Investigation of Bioavailability and Bioequivalence</i> .		
<input type="checkbox"/> 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 <i>Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products</i> . 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.		
<input type="checkbox"/> 6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test method (if appropriate).		
<input type="checkbox"/> 7.	The batch numbers of the batches used in the stability studies should be given.		

UK NATIONAL NOTIFICATIONS

19 Change in specification of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Tightening of specification limits	1, 2, 3	1, 2	Self certification
<input type="checkbox"/> b) Addition of new test parameter to the specification- Not a BROMI change – submit by usual Type IB route			
<input type="checkbox"/> c) Addition of a new test parameter to the specification with no change to impurity limits	1, 2, 4, 5, 6, 7, 8, 9	1, 2, 3, 4, 5	IA
Conditions			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 2. The change should not be the result of unexpected events arising during manufacture.			
<input type="checkbox"/> 3. Any change should be within the range of currently approved limits.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/> 5. The change does not concern adjuvant for vaccines or a biological excipient.			
<input type="checkbox"/> 6. The change does not concern a new unqualified impurity.			
<input type="checkbox"/> 7. The new method has been adequately validated in line with current guidance.			
<input type="checkbox"/> 8. There have been no changes to the limit for total impurities in the specification.			
<input type="checkbox"/> 9. The change does not require a new bioequivalence study to be conducted (according to the current <i>Note for Guidance on The Investigation of Bioavailability and Bioequivalence</i>).			
Documentation			
<input type="checkbox"/> 1. Amendment of the relevant section of the dossier in CTD format.			
<input type="checkbox"/> 2. Comparative table of current and proposed specifications for the excipient affected by this specific change.			
<input type="checkbox"/> 3. Details of any new analytical method and summary of validation data.			
<input type="checkbox"/> 4. Batch analysis data on two production batches for all tests in the new specification.			
<input type="checkbox"/> 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.			

UK NATIONAL NOTIFICATIONS

20 Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Minor changes to an approved test procedure	1, 2, 3, 5	1	Self Certification
b) Minor changes to an approved test procedure for a biological excipient – Not a BROMI change			Submit through usual Type 1B procedure
c) Other changes to a test procedure including replacement or addition that does not meet the conditions in (d) below – Not a BROMI change			Submit through usual Type 1B procedure
<input type="checkbox"/> d) Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure	2, 3, 4, 5, 6	1, 2	IA
Conditions			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.			
<input type="checkbox"/> 3. Results of method validation show new test procedure to be at least equivalent to the former procedure.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/> 5. The substance is not a biological excipient.			
<input type="checkbox"/> 6. There are no changes to limits for total impurities.			
Documentation			
<input type="checkbox"/> 1. Amendment to relevant sections of the dossier in CTD format including a description of the analytical methodology, a summary of validation data.			
<input type="checkbox"/> 2. Comparative validation results showing that the current test and the proposed one are equivalent.			

UK NATIONAL NOTIFICATIONS

21	Submission of a new or updated European Pharmacopoeia certificate of suitability (CEP) for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
(a) & (b)	Changes to European Pharmacopoeia certificates of suitability for an excipient – that does not meet the conditions given for (c) – Not a BROMI change			Submit through usual Type 1A or 1B routes
<input type="checkbox"/>	(c) An updated CEP from a manufacturer currently approved	1, 2, 3	1, 2	Self Certification
Conditions				
<input type="checkbox"/>	1.	The finished product release and end of shelf life specifications remain the same.		
<input type="checkbox"/>	2.	The supplementary tests listed on the CEP are unchanged (including residual solvents and any product specific requirements e.g. particle size profiles, polymorphic form).		
<input type="checkbox"/>	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				
<input type="checkbox"/>	1.	Copy of the updated CEP (i.e. current version)		
<input type="checkbox"/>	2.	Amended page(s) of the dossier in CTD format.		

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
<input type="checkbox"/>	a) From a manufacturer currently approved or a new manufacturer (replacement or addition)	None	1, 2	Self Certification
Conditions: None				
Documentation				
<input type="checkbox"/>	1.	Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.		
<input type="checkbox"/>	2.	Amended page(s) of the dossier in CTD format.		

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
<input type="checkbox"/>	Not a BROMI change			Submit through the usual Type 1A or 1B route

UK NATIONAL NOTIFICATIONS

24	Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	(a) New solvents and reagents used in the process – Not a BROMI – submit through usual Type IB route			
<input type="checkbox"/>	(b) With no change to solvents or reagents used in the process	1, 2, 3, 4	1, 2, 3, 4	IA
Conditions				
<input type="checkbox"/>	1. Specifications are not adversely affected; no change in qualitative and quantitative impurity profile or in physico-chemical properties.			
<input type="checkbox"/>	2. The excipient is not a biological substance.			
<input type="checkbox"/>	3. There have been no changes to the reagents or solvents used in the process.			
<input type="checkbox"/>	4. The specification of the excipient is unchanged.			
Documentation				
<input type="checkbox"/>	1. Amendment to relevant sections of the dossier in CTD format.			
<input type="checkbox"/>	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.			
<input type="checkbox"/>	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.			
<input type="checkbox"/>	4. Copy of approved and new (if applicable) specifications of the excipient			

UK NATIONAL NOTIFICATIONS

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
<input type="checkbox"/> 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 (biological materials) Not a BROMI change			Submit through usual Type 1B route
2. Excipient (biological materials)- Not a BROMI change			Submit through usual Type 1B route
<input type="checkbox"/> 3. Active substance (non biological materials)	1, 2, 3	1, 2, 3, 4, 5	IA
<input type="checkbox"/> 4. Excipient (non biological materials)	1, 2, 3	1, 2, 3, 4, 5	IA
<input type="checkbox"/> b) Change to comply with an update of the relevant monograph of the European Pharmacopoeia or national pharmacopoeia of a Member State			
<input type="checkbox"/> 1. Active substance	1, 2, 3	1,2	Self Certification
<input type="checkbox"/> 2. Excipient	1, 2, 3	1,2	Self Certification
<input type="checkbox"/> c) Change to current pharmacopoeial specification reference from national (e.g. BP) to Ph Eur. For an active substance or an excipient	1, 2, 3	1,2	Self Certification
Conditions			
<input type="checkbox"/> 1. The change is made exclusively to comply with the pharmacopoeia.			
<input type="checkbox"/> 2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.			
<input type="checkbox"/> 3. The material concerned is not a biological substance.			
Documentation			
<input type="checkbox"/> 1. Amendment to the relevant section of the dossier in CTD format.			
<input type="checkbox"/> 2. Comparative table of current and proposed specifications.			
<input type="checkbox"/> 3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 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.			

UK NATIONAL NOTIFICATIONS

26 Change in the specifications of the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Tightening of specification limits	1, 2, 3	1, 2	Self Certification
Tightening of specification limits – where condition (1) is not met – Not a BROMI change – submit through usual Type IB procedure			
<input type="checkbox"/> b) Addition of a new test parameter - Not a BROMI change – submit through usual Type IB procedure			
<input type="checkbox"/> c) Addition of a new test parameter - not a consequence of previous assessments or commitments	1, 2, 4, 5	1, 2, 3, 4	IA
Conditions			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 2. The change should not be the result of unexpected events arising during manufacture.			
<input type="checkbox"/> 3. Any change should be within the range of currently approved limits.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/> 5. Any new test method has been validated in accordance with current guidance.			
Documentation			
<input type="checkbox"/> 1. Amendment to relevant section of the dossier in CTD format.			
<input type="checkbox"/> 2. Comparative table of current and proposed specifications.			
<input type="checkbox"/> 3. Details of any new analytical method and validation data.			
<input type="checkbox"/> 4. Batch analysis data on two batches for all tests in the new specification.			

UK NATIONAL NOTIFICATIONS

27 Change to a test procedure of the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Minor change to an approved test procedure	1, 2, 5	1	Self Certification
<input type="checkbox"/> b) Other changes to a test procedure, including replacement or addition of a test procedure – Not a BROMI change			Submit through Type 1B route
<input type="checkbox"/> c) Other changes to a test procedure, including replacement or addition of a test procedure – with no consequential change to the finished product specification	2, 3, 4, 5	1, 2	IA
Conditions			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines and show that the updated procedure is at least equivalent to the previous one.			
<input type="checkbox"/> 3. Results of method validation show the new test procedure to be at least equivalent to the former procedure.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way			
<input type="checkbox"/> 5. The finished product specification is unchanged.			
Documentation			
<input type="checkbox"/> 1. Amendment to relevant sections of the dossier in CTD format which includes a description of the analytical methodology and a summary of validation data.			
<input type="checkbox"/> 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)) – Metered dose inhalers are excluded.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	1	1	Self Certification
Conditions			
<input type="checkbox"/> 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			
<input type="checkbox"/> 1. Amendment to the relevant section of the dossier in CTD format.			

UK NATIONAL NOTIFICATIONS

29 Change in the qualitative and/or quantitative composition of the immediate packaging material	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Semi-solid and liquid pharmaceutical forms – Not a BROMI change submit as Type IB through usual route			
<input type="checkbox"/> b) All other pharmaceutical forms – Not a BROMI change submit through usual Type IA route			
<input type="checkbox"/> c) All other pharmaceutical forms – change concerns more resistant packaging and stability data are not yet available	1, 2, 3, 4	1, 2, 3, 4 5, 6	IB
Conditions			
<input type="checkbox"/> 1. The product concerned is not a biological or sterile product.			
<input type="checkbox"/> 2. The change only concerns the same packaging type and material (e.g. blister to blister).			
<input type="checkbox"/> 3. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
<input type="checkbox"/> 4. The proposed packaging is more resistant than the existing packaging e.g. thicker blister packaging and three months' stability data are not yet at the disposal of the applicant. Assurance is given that these studies will be initiated and 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			
<input type="checkbox"/> 1. Amendment to the relevant sections of the dossier in CTD format.			
<input type="checkbox"/> 2. Appropriate data on the new packaging (comparative data on permeability e.g. for O ₂ , CO ₂ moisture), if available.			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 4. The batch numbers of batches used in the stability studies should be indicated, if applicable.			
<input type="checkbox"/> 5. Comparative table of the current and proposed specifications, if applicable.			
<input type="checkbox"/> 6. Justification for omission of stability data			

UK NATIONAL NOTIFICATIONS

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
<input type="checkbox"/>	a) Deletion of a supplier	1	1	Self Certification
<input type="checkbox"/>	b) Replacement or addition of a supplier	1, 2, 3, 4	1, 2, 3	IA
Conditions				
<input type="checkbox"/>	1. No deletion of packaging component or device.			
<input type="checkbox"/>	2. The qualitative and quantitative composition of the packaging components/device remains the same.			
<input type="checkbox"/>	3. The specifications and quality control method are at least equivalent.			
<input type="checkbox"/>	4. The sterilisation method and conditions remain the same, if applicable.			
Documentation				
<input type="checkbox"/>	1. Amended section of the dossier in CTD format.			
<input type="checkbox"/>	2. For devices for medicinal products for human use, proof of CE marking.			
<input type="checkbox"/>	3. Comparative table of current and proposed specifications, if applicable.			

UK NATIONAL NOTIFICATIONS

31 Change to in-process tests or limits applied during the manufacture of the product	Conditions to be fulfilled	Documents to be supplied	Procedure type
<input type="checkbox"/> a) Tightening of in-process limits	1, 2, 3, 7	1, 2	Self Certification
<input type="checkbox"/> b) Addition of new tests and limits (non- biological products)	1, 2, 4, 5, 6, 7	1, 2, 3, 4	IA
Addition of new in process tests and limits – biological products – Not a BROMI change			Submit through usual Type 1B procedure
Conditions			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
<input type="checkbox"/> 3. Any change should be within the range of the currently approved limits.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/> 5. The product is a non-biological product			
<input type="checkbox"/> 6. The new test method has been validated in accordance with the appropriate guideline			
<input type="checkbox"/> 7. The finished product specifications are unchanged.			
Documentation			
<input type="checkbox"/> 1. Amended section of the dossier in CTD format, where relevant.			
<input type="checkbox"/> 2. Comparative table of current and proposed specifications.			
<input type="checkbox"/> 3. Details of any new analytical method and validation data.			
<input type="checkbox"/> 4. Batch analysis data on two production batches of the finished product for all tests in the new specification.			

UK NATIONAL NOTIFICATIONS

32 Change in the batch size of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation	1, 2, 3, 4, 5	1, 4	Self Certification
<input type="checkbox"/> b) Downscaling down to 10-fold	1, 2, 3, 4, 5, 6,	1, 4	Self Certification
<input type="checkbox"/> c) Other situations – Not a BROMI change – submit through usual Type IB route			
<input type="checkbox"/> d) Other situations for formulations other than immediate release oral and non-sterile liquids.	1, 3, 4, 5, 6, 7, 8	1, 2, 3, 4, 5	IB
Conditions			
<input type="checkbox"/> 1. The change does not affect reproducibility and/or consistency of the product.			
<input type="checkbox"/> 2. The change relates only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms.			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 5. It does not concern a medicinal product containing a biological active substance.			
<input type="checkbox"/> 6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 8. The product concerned is not a controlled or modified release formulation.			
Documentation			
<input type="checkbox"/> 1. Amended of the dossier in CTD format.			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 3. Copy of approved release and end-of-shelf life specifications.			
<input type="checkbox"/> 4. The batch numbers (≥ 3) used in the validation study should be indicated or validation protocol (scheme) be submitted.			
<input type="checkbox"/> 5. The batch numbers of batches used in the stability studies should be indicated.			

UK NATIONAL NOTIFICATIONS

33 Minor change in the manufacture of the finished product (non-sterile product)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> (b)	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6	IA
Conditions			
<input type="checkbox"/> 1.	The overall manufacturing principle remains the same.		
<input type="checkbox"/> 2.	The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.		
<input type="checkbox"/> 3.	The medicinal product does not contain a biological active substance.		
<input type="checkbox"/> 4.	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).		
<input type="checkbox"/> 5.	The finished product specifications are unchanged		
<input type="checkbox"/> 6.	The change does not require the submission of a new bioequivalence study according to the <i>Note for Guidance on The Investigation of Bioavailability and Bioequivalence</i> .		
Documentation			
<input type="checkbox"/> 1.	Amended section of the dossier in CTD format.		
<input type="checkbox"/> 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.		
<input type="checkbox"/> 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.		
<input type="checkbox"/> 4.	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).		
<input type="checkbox"/> 5.	Copy of the approved release and end of shelf life specifications		
<input type="checkbox"/> 6.	Please provide batch numbers of the batches used in the stability studies.		
Other changes to manufacture of the finished product and changes to manufacture of sterile products – Not BROMI submit as Type IB 33(a)			

UK NATIONAL NOTIFICATIONS

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
<input type="checkbox"/> a) Reduction or deletion of one or more components of the			
<input type="checkbox"/> 1. Colouring system	1, 2, 3, 4, 5, 6	1, 2, 3	Self Certification
<input type="checkbox"/> 2. Flavouring system	1, 2, 3, 4, 6	1, 2, 3	Self Certification
<input type="checkbox"/> b) Increase, addition or replacement of one or more components of a colouring or flavouring system – Not a BROMI change			Submit through usual Type 1B route
Conditions			
<input type="checkbox"/> 1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 5. If the product colour has been deleted or changed the product can still be readily identified and in the case of colour coded products (e.g. warfarin tablets) can still be recognised.			
<input type="checkbox"/> 6. The only changes to the SPC, label and PIL concern the deletion of the colour or flavour (if applicable)			
Documentation			
<input type="checkbox"/> 1. Amended pages of the relevant sections of the dossier in CTD format (including identification method for any new colorant, where relevant).			
<input type="checkbox"/> 2. The batch numbers of the batches used in the stability studies should be indicated.			
<input type="checkbox"/> 3. Revised SPC, label and PIL (if applicable)			

UK NATIONAL NOTIFICATIONS

35 Change in coating weight of tablets or change in weight of capsule shells	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Immediate release oral pharmaceutical forms	1, 2, 3, 4, 5	1, 2	Self Certification
<input type="checkbox"/> b) Gastro-resistant, modified or prolonged release pharmaceutical forms – Not a BROMI change			Submit changes through usual Type 1B route
Conditions			
<input type="checkbox"/> 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.			
<input type="checkbox"/> 2. The coating is not a critical factor for the release mechanism.			
<input type="checkbox"/> 3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 5. The formulation of the coating is unchanged			
Documentation			
<input type="checkbox"/> 1. Amended pages of the relevant sections of the dossier in CTD format.			
<input type="checkbox"/> 2. The batch numbers of the batches used in the stability studies should be provided. (1) (2)			

UK NATIONAL NOTIFICATIONS

36 Change in shape or dimensions of the container or closure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Sterile pharmaceutical forms and biological medicinal products	1, 2, 3	1, 2	IA
<input type="checkbox"/> b) Other pharmaceutical forms (excluding metered dose inhalers)	1, 2, 3	1, 2	Self Certification
Conditions			
<input type="checkbox"/> 1. No change in the qualitative or quantitative composition of the container.			
<input type="checkbox"/> 2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
<input type="checkbox"/> 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			
<input type="checkbox"/> 1. Amended section of the dossier in CTD format (including description, detailed drawing and composition of the container or closure material).			
<input type="checkbox"/> 2. The batch numbers of the batches used in the stability studies should be indicated, where applicable.			

UK NATIONAL NOTIFICATIONS

37 Change in the specification of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) Tightening of specification limits	1, 2, 3	1, 2	Self Certification
Tightening of specification limits where condition (1) not met – Not a BROMI change			Submit through usual Type IB procedure
<input type="checkbox"/> b) Addition of a new test parameter - Not a BROMI change			Submit through usual Type IB procedure
<input type="checkbox"/> c) Addition of a new test parameter and/or limit	1, 2, 4, 5, 6, 7, 8	1, 2, 3, 4	IA
<input type="checkbox"/> d) Deletion of organoleptic tests	1, 2	1, 2	IB
Conditions			
<input type="checkbox"/> 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).			
<input type="checkbox"/> 2. The change should not be the result of unexpected events arising during manufacture.			
<input type="checkbox"/> 3. Any change should be within the range of currently approved limits.			
<input type="checkbox"/> 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
<input type="checkbox"/> 5. The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.			
<input type="checkbox"/> 6. The change does not concern a new unqualified impurity.			
<input type="checkbox"/> 7. The new method has been satisfactorily validated in line with current guidance			
<input type="checkbox"/> 8. The limit for total impurities are unchanged			
Documentation			
<input type="checkbox"/> 1. Amendment to relevant section of the dossier in CTD format.			
<input type="checkbox"/> 2. Comparative table of current and proposed specifications.			
<input type="checkbox"/> 3. Details of any new analytical method and validation data.			
<input type="checkbox"/> 4. Batch analysis data on two production batches of the finished product for all tests in the new specification.			

UK NATIONAL NOTIFICATIONS

38	Change in test procedure of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	a) Minor change to an approved test procedure	1, 2, 3, 4	1	Self Certification
<input type="checkbox"/>	b) Minor change to an approved test procedure for a biological active substance or biological excipient – Not a BROMI change			Submit through usual Type 1B route
<input type="checkbox"/>	c) Other changes to a test procedure, including replacement or addition of a test procedure – Not a BROMI change			Submit through usual Type 1B route
Conditions				
<input type="checkbox"/>	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).			
<input type="checkbox"/>	2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.			
<input type="checkbox"/>	3. Results of method validation show new test procedure to be at least equivalent to the former procedure.			
<input type="checkbox"/>	4. The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.			
Documentation				
<input type="checkbox"/>	1. Amended relevant sections of the dossier in CTD format, which includes a description of the analytical methodology, a summary of validation data.			
<input type="checkbox"/>	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 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
<input type="checkbox"/>	a) No changes to scoring/break lines	1, 2, 3, 4	1, 3	Self Certification
<input type="checkbox"/>	b) Deletion of a tablet score line	1, 2, 5	1, 3	IB
<input type="checkbox"/>	c) Removal of tablet markings	1, 2, 3	1, 2, 3	IB
<input type="checkbox"/>	d) Addition of alternative tablet markings – if required for alternative distributors or product names registered on the licence	1, 2, 3, 4	1, 3	IB
Conditions				
<input type="checkbox"/>	1. Finished product release and end of shelf life specifications have not been changed (except for appearance).			
<input type="checkbox"/>	2. Any ink must comply with the relevant pharmaceutical legislation.			
<input type="checkbox"/>	3. There are no changes to tablet score/break lines			
<input type="checkbox"/>	4. In the case of alternative inks– the inks used have the same qualitative composition.			
<input type="checkbox"/>	5. The deletion of the score/break lines has no effect on the posology.			
Documentation				
<input type="checkbox"/>	1. Amendment to the relevant sections of the dossier in CTD format (including a detailed drawing or written description of the current and new appearance).			
<input type="checkbox"/>	2. Justification for removal of tablet markings and information on how the product can be distinguished from other tablets/capsules.			
<input type="checkbox"/>	3. Revised SPC and leaflet (if applicable)			

UK NATIONAL NOTIFICATIONS

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 – Not a BROMI Change			Submit through usual Type 1B route
<input type="checkbox"/>	b) All other tablets, capsules, suppositories and pessaries	1, 2	1	Self Certification
Conditions				
<input type="checkbox"/>	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.			
<input type="checkbox"/>	2. Release and end of shelf-life specifications of the product have not been changed (except for dimensions).			
Documentation				
<input type="checkbox"/>	1. Amendments to the relevant sections of the dossier in CTD format (including a detailed drawing of the current and proposed situation).			

41	Change in pack size of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
<input type="checkbox"/>	1. Change within the range of the currently approved pack sizes	1, 2, 3, 4	1, 2, 3	Self Certification
<input type="checkbox"/>	2. Other pack size changes – outside the current approved range and changes to fill weight/volume of non-parenteral multi dose products – Not a BROMI Change			Submit through usual Type 1B route
Conditions				
<input type="checkbox"/>	1. New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics.			
<input type="checkbox"/>	2. The primary packaging material remains the same.			
<input type="checkbox"/>	3. The current smallest or largest pack size has not been deleted i.e. pack size range remains the same			
<input type="checkbox"/>	4. The only changes to the SPC, label and leaflet concern the change in pack size			
Documentation				
<input type="checkbox"/>	1. Amendments to the relevant sections of the dossier in CTD format.			
<input type="checkbox"/>	2. If the stability parameters could be affected – a declaration that stability studies will be conducted in accordance with the relevant guidelines. Data to be reported only if outside specifications (with proposed action).			
<input type="checkbox"/>	3. Revised SPC Section 6.5 and labelling and leaflet artwork.			

UK NATIONAL NOTIFICATIONS

42 Change in:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/> a) the shelf life of the finished product			
<input type="checkbox"/> 1. As packaged for sale	1, 2, 3	1, 2	IA
<input type="checkbox"/> 2. After first opening	1, 2	1, 2	IA
<input type="checkbox"/> 3. After dilution or reconstitution	1, 2	1, 2	IA
<input type="checkbox"/> b) the storage conditions of the finished product or the diluted/reconstituted product	1, 2, 4	1, 2	IA
Conditions			
<input type="checkbox"/> 1.	Stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.		
<input type="checkbox"/> 2.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.		
<input type="checkbox"/> 3.	The shelf life does not exceed five years.		
<input type="checkbox"/> 4.	The product is not a biological medicinal product.		
Documentation			
<input type="checkbox"/> 1.	Amendment to the relevant sections of the dossier in CTD format including results of appropriate real time stability studies conducted in accordance with the relevant stability guidelines on at least two production scale batches 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. NB: If data are only available on pilot batches a normal Type IB variation should be submitted.		
<input type="checkbox"/> 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	Documentation to be supplied	Procedure type
a) Medicinal products for human use			
<input type="checkbox"/> 1. Addition or replacement	1, 2, 4	1, 2	Self Certification
<input type="checkbox"/> 2. Deletion	3		IA
Conditions			
<input type="checkbox"/> 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.		
<input type="checkbox"/> 2.	The new device is compatible with the medicinal product.		
<input type="checkbox"/> 3.	The medicinal product can still be accurately delivered.		
<input type="checkbox"/> 4.	The device meets the requirements for CE marking		
Documentation			
<input type="checkbox"/> 1.	Amended sections of the dossier in CTD format.		
<input type="checkbox"/> 2.	Proof of CE marking.		

Note: Change codes #44 and #45 in the 'Guideline on Dossier Requirements for Type IA and IB Notifications' refer to Veterinary medicinal products

UK NATIONAL NOTIFICATIONS

46		Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>	a) 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	1, 2	1, 2	IA
<input type="checkbox"/>	b) Change in the summary of product characteristics to implement a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC	1, 3	1, 2	IA
Conditions				
<input type="checkbox"/>	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.			
<input type="checkbox"/>	2. The application is submitted within 90 days after the publication of the Commission Decision.			
<input type="checkbox"/>	3. The application is submitted within 30 days after the publication of the Commission Decision.			
Documentation				
<input type="checkbox"/>	1. A copy of the summary of product characteristics attached to the Commission Decision on the relevant referral procedure.			
<input type="checkbox"/>	2. Revised SPC, label and leaflet.			

46	c) 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	Conditions to be fulfilled	Documentation to be supplied	Procedure type
<input type="checkbox"/>		1, 2	1, 2, 3	IA
Conditions				
<input type="checkbox"/>	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.			
<input type="checkbox"/>	2. No additional statements or amendments have been introduced into the SPC, labelling and leaflet			
Documentation				
<input type="checkbox"/>	1. Copy of the letter from EMEA/CHMP informing the marketing authorisation holder about the scientific opinion of CHMP and requesting specific changes to the summary of product characteristics, labelling and package leaflet/insert resulting from the opinion.			
<input type="checkbox"/>	2. Letter of undertaking, if requested by EMEA/CHMP.			
<input type="checkbox"/>	3. Revised SPC, label and leaflet			