Mr Nicolas Rossignol
European Commission
DG Enterprise and Industry
Unit F2 Pharmaceuticals
B-1049 Brussels
Belgium

4 January 2008

Dear Nicolas,

UK Response to the Commission's Public Consultation Paper:
"*Better Regulation of Pharmaceuticals: towards a simpler, clearer and more flexible framework for variations.*" (24 October 2007)

1. Thank you for the opportunity to comment on the draft proposals for a new Variations Regulation. The MHRA fully supports the "better regulation" aims of this initiative: to provide a simpler, clear and flexible regime for the handling of licence variations, but one that continues to maintain high levels of public health protection. We note the recently announced proposals for changes to the pharmacovigilance system for human medicines that will further facilitate this simplification programme.

2. Our UK veterinary colleagues have provided their comments separately on this occasion, although our responses are broadly complementary. Our comments and suggestions are described below under each of your Key Item headings, followed by our comments on some other aspects of the proposed legislation.

Key Item 1: Purely National Authorisations

3. We welcome the proposal for a single regulation to apply to the variation of any marketing authorisation, approved by any procedure. However, we remain concerned that we should not lose significant advances in 'better regulation' already made in the UK for purely national authorisations. In order to have some certainty about the overall scope and shape of the future regulatory model, we think that the timetable for finalisation of the legislative texts should allow for development of a broad consensus on the operational details (such as variations classification) through the various scientific and regulatory committees before agreeing to the harmonisation proposals and amended legal basis in respect of purely national variations.

Key Item 2: ICH

4. We fully support your proposals with regard to realising benefits from manufacturing flexibility within an established 'design space' (without the need for notifications) and for facilitating 'continuous improvement of manufacture' (by means of the new variations classification system).

Key Item 3: "Do and Tell" Procedure

5. We support the Commission's proposals for the introduction of a "do and tell" type of notification, and indeed have already implemented and audited a system of "self-certification" in the UK for certain Type IA and product information (label and patient leaflet) changes for human medicines. The Annex to this response gives further details of those Type IA changes now being handled by self certification. Those competent authorities, such as the MHRA, with experience of operating and auditing such a system will no doubt provide valuable input into discussions of detail on these issues at the scientific and regulatory committees.

6. We agree that some of the Type IA changes are of such relatively minor significance that they need only be notified annually. The classification of changes suitable for annual reporting will also need to be agreed by the various scientific and regulatory committees.

7. We consider that introducing a "do and tell" procedure should provide:
   - benefits for both MA holders and regulators;
   - an annual reporting system that is simple to use but avoids peaks in work volume (and hence burden on resources) such as might occur immediately before the end of reporting years or before new fee scales.

8. However, we consider that a single annual report from each MA holding company, covering all minor changes to all of their MAs, could present an increase in administrative work, and one which would not lend itself to an easy IT solution. We would prefer annual reports to be submitted for each (or a small group of) MAs according to their authorisation 'birth date'. MA holders will be familiar with such a routine for PSUR and renewal cycles.

9. Experience has shown that any complex system of classification, conditions and other rules, whether new or not-so-new, can lead to errors by applicants. In the case of "do and tell" applications, any errors identified in their annual lists will have to undone. As for current Type IA notifications, the new immediate or annually reported changes will require audit. We support the CMDh proposal to provide a role in the audit of "do and tell" annual reports for MRP/DCP authorised products. Audit experience can inform any future changes in the classification guideline.

Key Item 4: Worksharing

10. We agree with the Commission's assessment that the worksharing proposals as drafted may entail a significant increase in the workload of the EMEA and we are concerned that the existing expert committee structure may not be able to absorb this additional work.

11. We see no advantage to a worksharing assessment system for variations to MAs granted through centralised or decentralised (mutual recognition) procedures. This could undermine the responsibilities of the Rapporteurs and the Reference Member State authorities. However such arrangements could be usefully applied to variations for purely national MAs or possibly to a combination of those with MAs granted in MR or DC procedures.

12. We see no advantage in applying a worksharing system for the assessment of minor (Type IB) variations because:

- The case-by-case organisation of the worksharing itself would add to the burden on applicants and the individual competent authorities, outweighing any efficiency gains in reducing numbers of individual scientific assessments;
- For Type IB variations to unharmonised national dossiers, the down-classification of such applications to Type IA status would preclude the proper examination of the applicability of a worksharing decision to an individual national MA.

13. We do not consider that it is appropriate to include extension applications within a regulation for variations because:

- Extension applications are usually intended to result in grant of a new MA, and cannot be 'down classified' as a variation to an existing MA;
- MA holders can already benefit from "worksharing" by submitting extension applications via the Decentralised Procedure, resulting in a new, harmonised MA;
- Extension applications potentially require an examination of both new and existing dossiers which, if unharmonised between the participating competent authorities, could result in an unsound or unacceptable opinion or decision.

14. Experience of the existing schemes of worksharing (master files, pharmacopoeial certification, paediatric investigation plans, etc.) leads us to believe that the following are important for success:

- Procedural timetables (for work allocation, assessment reports and contributions, and for decision-making);
- Availability of resources (including adequate remuneration for the lead contributor so that many can participate);
- High-quality 'peer-reviewed' assessments (so that opinions and recommendations are readily accepted);
- Opportunities and time for others to comment on and contribute to the final assessment.

15. In general we support the worksharing proposals made by CMD and specifically suggest that:

- Worksharing should be triggered by the simultaneous submission of Type II variation applications in two or more Member States, following the regulatory processes and best practice that apply in the MR procedure for variations;
- For variations to two or more purely national MAs, the nomination of a 'Temporary Reference Member State' should be made following a pre-submission recommendation and consultation with CMD who will ensure that a Temporary RMS and all the other MS are willing to participate in a worksharing procedure;
- For variations to three or more authorisations, at least two of which have been granted by an MR or DC procedure, the existing RMS should be chosen;
- A single procedure should be followed rather than the two stage procedure envisaged by the Commission (which we understand to be worksharing assessment followed by down-classified applications in the other MS.) All participating Member States would then have the opportunity and time to comment on the preliminary and final assessment reports;
- Validation of the application in a Member State would constitute acceptance of the worksharing principles and procedure;

- Following a validation period the usual Type II procedure timescales should apply (including extended or expedited timetables and, if necessary, a referral procedure – see below);
- A divergence of opinion between the participating Member States should be examined by CMD in a 60-day referral procedure but only in terms of any potential serious risk to public health presented by the proposed change. Agreement at CMD should enable them to issue a binding decision with regard to any MR or DC authorised products and to issue a persuasive opinion with regard to any purely national MAs (by analogy to the previous 'Multi-state procedure);
- A divergence of opinion at CMD could only be referred for CHMP opinion and Commission decision for those MAs approved in MR or DC procedures.

Key Item 5: Type IB by Default

16. We support the general principle of a default Type IB classification system and the provision that enables NCAs to upgrade the procedure to Type II should they have emerging concerns about the impact on quality, safety or efficacy. However we would welcome clarification that the assessment timescale for a Type II procedure should begin on the date that the NCA chooses to upgrade the classification from Type IB to Type II.

17. For variations the nature of which was unforeseen by the classification guideline or where there is uncertainty as to impact on product quality, safety or efficacy, we agree with the CMD that it (and its existing sub-group) should provide a scientifically-reasoned recommendation.

Comments on Other Commission Proposals

Classification of variations

18. We support the Commission's proposals for generic definitions for Type IA, Type IB and Type II variations within the text of the Regulation and for replacement of the Annex on detailed classification by a Guideline. This Guideline will need close examination by the scientific working parties so, at this stage, we make just two comments:
    - Whilst there is scope for re-examining the lack of parity between biological and chemical-based products for some changes, there are circumstances where, in the current state of knowledge, the precautionary principle is still the preferred risk-based approach and a full and detailed assessment of supporting data is appropriate. It will be important to ensure that the classification guideline clearly identifies changes to biological products that must be handled as major variations.

    - Our Annex to this response provides examples of where we have successfully 'down-classified' certain changes as part of our national 'better regulation' initiative. This provides for a self certification procedure for some type 1A notifications, a scientific validation procedure for some type 1B changes and a 30 day assessment procedure for some type II variations.

Grouping variations

19. In the UK we have for many years accepted what we call 'bulk' variation applications i.e. one change to many MAs. These are accepted for national authorisations and in our MR variation procedures. The Variation Application form

is easily adapted to accept multiple MA numbers and – as long as there is an acceptance by all MS of a single application form - information management systems can process such collections of applications efficiently. Our fee systems reflect the administrative efficiencies made. We therefore support the Commission's 'horizontal' grouping proposals (Figure 5 in your Public Consultation Paper).

20. Your Annex II to the draft Regulation specifies the 'vertical' groupings permitted, whether consequential or non-consequential. Again we can support most of your proposals, as they might apply to a single MA, because they could achieve some significant processing economies. We would however point out (as have others) that these introduce some elements of risk and complexity, for example:
    - Group type 1 we think would be unworkable for the reasons discussed above under 'Worksharing'.
    - Group types 4, 11 and 12 may have such a wide scope that they require allocation to more than one assessor.

21. Where we have most difficulty with your grouping proposals is the permitted combination of the 'horizontal' (many MAs) and the 'vertical' (many changes) groupings into a single large submission group. We think that in practice this may be unworkable because:
    - Such complexity will inevitably lead to submission errors, very protracted 'validation' discussions and submission withdrawals;
    - If one of the changes to one of the MAs is un-approvable (and an 'all-or-nothing' decision is required) then none of the changes to any of the MAs could be approved. This would appear to require re-submission of the approvable variations in a new procedure and hence 'better regulation' efficiencies would be lost. It will be important to learn from the EMEA experience in permitting partial group approvals and whether these apply to 'horizontal' or 'vertical' groups or a combination of both;
    - This complexity is further compounded if applied in full to worksharing arrangements involving MAs authorised in different procedure types.

Clarification of deadlines

22. These are important and useful additional measures that enhance the flexibility of the regime.

Comments on other aspects of the proposals

Safety Variations

23. We are pleased that provisions around urgent safety restrictions remain within the regulations: they are a very important tool for serious and urgent safety changes. We strongly support an expedited process for making urgent safety variations, and believe that the current provisions, which are working well, should be replicated in the new legislation.

Referral and arbitration procedures

24. We support the proposals made by CMD for a 60-day referral stage within any mutual recognition variation procedure where there is disagreement with the opinion or draft decision of the RMS. A consistent definition of 'potential serious risk to public health' should be applied as the basis of the referral. That definition should be consistent with the terms in which the evaluation of risk:benefit balance is described in Article 1(28a) of Directive 2001/83 EC.

Legislative timetable

25. To ensure the successful introduction of the revised regime throughout the EU it will be important to allow sufficient time (2 years) after finalisation of the texts for all the competent authorities to put in place their new processes and IT system changes.

26. We are of course pleased to discuss any of these comments with you in more detail or to provide further written explanations.

Yours sincerely and with kind regards,

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UK 'BROMI'
(Better Regulation of Medicines Initiative)
– Dossier Requirements for Type IA and Type IB UK National Notifications and Variations (human pharmaceuticals)

- Simplified processing for certain categories of notifications
- Additional information for simplified procedures for UK Nationally authorised human medicinal products
- Changes introduced include (note colour coding in table):

	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	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			
□	1. The marketing authorisation holder shall remain the same legal entity.			
	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			
□	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.			
□	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			
□	1. The active substance shall remain the same.			
□	2. The change in active name is the only change made to the SPC, label and PIL.			
	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			
□	1. Revised SPC, label and leaflet artwork			

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			
□	1. The manufacturing site remains the same.			
	Documentation			
□	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.			
□	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			
□	1. The manufacturing site shall remain the same i.e. the same location.			
□	2. If changes to the label and or leaflet are necessary, the only changes made are the name and address of the manufacturer			
	Documentation			
□	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.			
□	2. Replacement page(s) of the dossier in the CTD format.			
□	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			
□	1. Change following granting of or amendment to ATC Code by WHO.			
	Documentation			
□	1. Revised SPC (if applicable).			

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, 8**	**1, 2, 5, 10**	**Self Certification**
□	**b)**	**Primary packaging site**			
□		**1. Solid pharmaceutical forms, e.g. tablets and capsules**	**Not a BROMI change. Submit by usual route**		
□		**2. Semi-solid or liquid pharmaceutical forms**	**"**		
□		**3. Liquid pharmaceutical forms (suspensions, emulsions)**	**"**		
□	**c)**	**All other manufacturing operations except batch release**	**"**		
□	**d)**	**Additional Distributor or Own Label Supplier**	**1, 5, 6, 7**	**1, 2, 10**	**IA**
□	**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

□	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.	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.
□	4.	Product concerned is not a biological medicinal product.
□	5.	The addition of the new distributor or own label supplier is not associated with a change of the product name.
□ □	6.	The only changes made to the label and leaflet concern the company logo and name and address of the distributor/ supplier Or: 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.
□ □	7.	The distributor has been appropriately authorised for wholesale dealing, where relevant Or The proposed distributor is a retail outlet and the product concerned has GSL status.
□	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

□	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 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.
□	10.	Copy of revised label and PIL artwork (if applicable).

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
□	**a) Replacement or addition of a site where batch control/testing takes place**			
□	**b) Replacement or addition of a manufacturer responsible for batch release**			
□	**1. Not including batch control/testing**			
□	**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
□	**a)**	**1**	**1**	**Self Certification**
□	**b) Deletion of a UK distributor**	**None**	**1**	**Self Certification**
	Conditions			
□	1. An appropriately authorised site remains registered on the authorisation to undertake the manufacturing operation concerned.			
	Documentation			
□	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
□	**(b)**	**1, 2, 3, 4, 5**	**1, 2, 3**	**IA**
	Conditions			
□	1. No change in qualitative and quantitative impurity profile or in physico-chemical properties, including residual solvent levels.			
□	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.			
□	4. There are no changes to the reagents or solvents used in the process			
□	5. The specifications of the active substance are unchanged			
	Documentation			
□	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.			
□	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. 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			

11	Change in batch size of active substance or intermediate	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**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	
□	1.	Any changes to the manufacturing methods are only those necessitated by the change in scale, e.g. use of different-sized equipment.
□	2.	Test results of at least two batches according to the specifications are 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.
	6.	The specifications of the active substance (and/or intermediate if applicable) are unchanged.
	Documentation	
□	1.	Amended section of the dossier in the CTD format.
□	2.	The batch numbers of the tested batches having the proposed batch size.
	3.	Copies of the specifications of the active substance and/or intermediate as 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	Documentation to be supplied	Procedure type
□	**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**
□	**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

□	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.	The change is 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.
□	6.	The change does not concern a new unqualified impurity.
□	7.	The new method has been adequately validated in line with current guidance.
□	8.	There have been no changes to the total impurity limits
□	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

□	1.	Amendment to relevant section of the dossier 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.

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**
☐	**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			
☐	1. Appropriate validation studies have been performed in accordance with relevant guidelines.			
☐	2. Results of method validation show the new test procedure to be at least equivalent to the former procedure.			
☐	3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
☐	4. The active substance, starting material, intermediate or reagent is not a biological substance.			
☐	5. The change does not concern a new unqualified impurity.			
☐	6. There have been no changes to the total impurity limits			
☐	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			
☐	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.			
☐	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
☐	**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
☐	**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			
☐	1. The finished product release and end of shelf life specifications remain the same.			
☐	2. Supplementary tests and limits listed on the CEP are unchanged – including residual solvents, particle size profile and polymorphic form			
☐	3. This notification concerns an update to only one certificate of suitability			
☐	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. A copy of the current (updated) CEP			
☐	2. Amended page(s) of the dossier in CTD format.			
☐	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.			

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
□	**b) Human Medicinal Products**	**None**	**1, 2, 3**	**Self Certification**
	Conditions: None			
	Documentation			
□	1. Copy of the current (or updated) European Pharmacopoeia TSE certificate of suitability.			
□	2. Amended page(s) of the dossier in CTD format.			
	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
□	**a) the re-test period of the active substance**	**1, 2, 3**	**1, 2**	**IA**
□	**b) the storage conditions for the active substance – Not a BROMI change – Submit through usual Type IB route**			
□	**c) the reduction in the re-test period of the active substance**	**1, 3, 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 active substance is not a biological substance.			
□	4. The change should not be the result of unexpected events arising during manufacture.			
	Documentation			
□	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.			
□	2. Copy of approved specifications of the active substance.			

18	Replacement of an excipient with a comparable excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) The replacement leads to a change in the summary of product characteristics – Not a BROMI change submit by usual Type IB route**			
□	**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	
□	1.	Same functional characteristics of the excipient.
□	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. *Note for Guidance on Bioavailability and Bioequivalence*, 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.
□	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.
□	4.	The product is not a biological medicinal product.
□	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).
□	6.	The only quantitative changes to the excipients are minor adjustments to accommodate the new excipient.
	Documentation	
□	1.	Amended pages of the relevant sections of the dossier in 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.
□	6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test method (if appropriate).
□	7.	The batch numbers of the batches used in the stability studies should be given.

19	Change in specification of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
☐	**a) Tightening of specification limits**	**1, 2, 3**	**1, 2**	**Self certification**
☐	**b) Addition of new test parameter to the specification- Not a BROMI change – submit by usual Type IB route**			
☐	**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

☐	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.
☐	6.	The change does not concern a new unqualified impurity.
☐	7.	The new method has been adequately validated in line with current guidance.
☐	8.	There have been no changes to the limit for total impurities in the specification.
	9.	The change does not require a new bioequivalence study to be conducted (according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence).*

Documentation

☐	1.	Amendment of the relevant section of the dossier in CTD format.
☐	2.	Comparative table of current and proposed specifications for the excipient affected by this specific change.
☐	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.

20	Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Minor changes to an approved test procedure**	**1, 2, 3, 5**	**1**	**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**
□	**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

□	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.
□	6.	There are no changes to limits for total impurities.

Documentation

□	1.	Amendment to relevant sections of the dossier in CTD format including a description of the analytical methodology, a summary of validation data.
□	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 (CEP) for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	(a) & (b) Changes to European Pharmacopeia 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**
□	**(c) An updated CEP from a manufacturer currently approved**	**1, 2, 3**	**1, 2**	**Self Certification**
	Conditions			
□	1. The finished product release and end of shelf life specifications remain the same.			
□	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).			
□	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 updated CEP (i.e. current version)			
□	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
□	**a) From a manufacturer currently approved or a new manufacturer (replacement or addition)**	**None**	**1, 2**	**Self Certification**
	Conditions: None			
	Documentation			
□	1. Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.			
□	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
□	**Not a BROMI change**			**Submit through the usual Type 1A or 1B route**

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			
□	**(b) With no change to solvents or reagents used in the process**	**1, 2, 3, 4**	**1, 2, 3, 4**	**IA**
	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.			
□	3. There have been no changes to the reagents or solvents used in the process.			
□	4. The specification of the excipient is unchanged.			
	Documentation			
□	1. Amendment to relevant sections of the dossier in CTD format.			
□	2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.			
□	3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.			
□	4. Copy of approved and new (if applicable) specifications of the excipient			

25	Change to comply with European Pharmacopoeia or with the national pharmacopoeia of a Member State	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Change of specification(s) of a former non-European pharmacopoeial substance to comply with European Pharmacopoeia or with the national pharmacopoeia of a Member State**			
	1. Active substance (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**
□	**3. Active substance (non biological materials)**	**1, 2, 3**	**1, 2, 3, 4, 5**	**IA**
□	**4. Excipient (non biological materials)**	**1, 2, 3**	**1, 2, 3, 4, 5**	**IA**
□	**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, 3**	**1,2**	**Self Certification**
□	**2. Excipient**	**1, 2, 3**	**1,2**	**Self Certification**
□	**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

□	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.
□	3.	The material concerned is not a biological substance.

Documentation

□	1.	Amendment to the relevant section of the dossier in 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.

26	Change in the specifications of the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**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			
	b) Addition of a new test parameter - Not a BROMI change – submit through usual Type IB procedure			
□	**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

□	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.
□	5.	Any new test method has been validated in accordance with current guidance.

Documentation

□	1.	Amendment to relevant section of the dossier in 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, 5**	**1**	**Self Certification**
□	**b) Other changes to a test procedure, including replacement or addition of a test procedure – Not a BROMI change**			**Submit through Type 1B route**
□	**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

□	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 and show that the updated procedure is at least equivalent to the previous one.
□	3.	Results of method validation show the 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 finished product specification is unchanged.

Documentation

□	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.
□	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
□		**1**	**1**	**Self Certification**

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 the dossier in CTD format.

29	Change in the qualitative and/or quantitative composition of the immediate packaging material	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Semi-solid and liquid pharmaceutical forms – Not a BROMI change submit as Type IB through usual route**			
□	**b) All other pharmaceutical forms – Not a BROMI change submit through usual Type IA route**			
□	**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

□	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.	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

□	1.	Amendment to the relevant sections of the dossier in CTD format.
□	2.	Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture), if available.
□	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, if applicable.
□	5.	Comparative table of the current and proposed specifications, if applicable.
□	6.	Justification for omission of stability data

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

Conditions

□	1.	No deletion of packaging component or device.
□	2.	The qualitative and quantitative composition of the packaging components/device remains 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 of the dossier in 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	Documents to be supplied	Procedure type
☐	**a) Tightening of in-process limits**	**1, 2, 3, 7**	**1, 2**	**Self Certification**
☐	**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

☐	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.
☐	5.	The product is a non-biological product
☐	6.	The new test method has been validated in accordance with the appropriate guideline
☐	7.	The finished product specifications are unchanged.

Documentation

☐	1.	Amended section of the dossier in 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 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	Documentation 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**	**Self Certification**
□	**b) Downscaling down to 10-fold**	**1, 2, 3, 4, 5, 6,**	**1, 4**	**Self Certification**
□	**c) Other situations – Not a BROMI change – submit through usual Type IB route**			
□	**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

□	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).
□	8.	The product concerned is not a controlled or modified release formulation.

Documentation

□	1.	Amended of the dossier in 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 (non-sterile product)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**(b)**	**1, 2, 3, 4, 5, 6**	**1, 2, 3, 4, 5, 6**	**IA**
	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. 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).			
□	5. The finished product specifications are unchanged			
	6. The change does not require the submission of a new bioequivalence study according to the *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*.			
	Documentation			
□	1. Amended section of the dossier in 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. 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).			
□	5. Copy of the approved release and end of shelf life specifications			
□	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)			

34	Change in the colouring system or the flavouring system currently used in the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Reduction or deletion of one or more components of the**			
□	**1. Colouring system**	**1, 2, 3, 4, 5, 6**	**1, 2, 3**	**Self Certification**
□	**2. Flavouring system**	**1, 2, 3, 4, 6**	**1, 2, 3**	**Self Certification**
□	**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	
□	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	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.
□	6.	The only changes to the SPC, label and PIL concern the deletion of the colour or flavour (if applicable)
	Documentation	
□	1.	Amended pages of the relevant sections of the dossier in CTD format (including identification method for any new colorant, where relevant).
□	2.	The batch numbers of the batches used in the stability studies should be indicated.
□	3.	Revised SPC, label and PIL (if applicable)

35	Change in coating weight of tablets or change in weight of capsule shells	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Immediate release oral pharmaceutical forms**	**1, 2, 3, 4, 5**	**1, 2**	**Self Certification**
	b) Gastro-resistant, modified or prolonged release pharmaceutical forms – Not a BROMI change			**Submit changes through usual Type 1B route**

	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).
□	5.	The formulation of the coating is unchanged
	Documentation	
□	1.	Amended pages of the relevant sections of the dossier in CTD format.
□	2.	The batch numbers of the batches used in the stability studies should be provided. (1) (2)

36	Change in shape or dimensions of the container or closure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Sterile pharmaceutical forms and biological medicinal products**	**1, 2, 3**	**1, 2**	**IA**
□	**b) Other pharmaceutical forms (excluding metered dose inhalers)**	**1, 2, 3**	**1, 2**	**Self Certification**

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 affects 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 the dossier in 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.

37	Change in the specification of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Tightening of specification limits**	**1, 2, 3**	**1, 2**	**Self Certification**
	Tightening of specification limits where condition (1) not met – Not a BROMI change			**Submit through usual Type IB procedure**
	b) Addition of a new test parameter - Not a BROMI change			**Submit through usual Type IB procedure**
□	**c) Addition of a new test parameter and/or limit**	**1, 2, 4, 5, 6, 7, 8**	**1, 2, 3, 4**	**IA**
□	**d) Deletion of organoleptic tests**	**1, 2**	**1, 2**	**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.
□	6.	The change does not concern a new unqualified impurity.
□	7.	The new method has been satisfactorily validated in line with current guidance
□	8.	The limit for total impurities are unchanged

Documentation

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

38	Change in test procedure of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**a) Minor change to an approved test procedure**	**1, 2, 3, 4**	**1**	**Self Certification**
□	**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**
□	**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	
□	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.	The test procedure does not apply to a biological active substance or biological excipient in the medicinal product.
	Documentation	
□	1.	Amended relevant sections of the dossier in CTD format, which includes a description of the analytical methodology, a summary of validation data.
□	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
□	**a) No changes to scoring/break lines**	**1, 2, 3, 4**	**1, 3**	**Self Certification**
□	**b) Deletion of a tablet score line**	**1, 2, 5**	**1, 3**	**IB**
□	**c) Removal of tablet markings**	**1, 2, 3**	**1, 2, 3**	**IB**
□	**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	
□	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.
□	3.	There are no changes to tablet score/break lines
□	4.	In the case of alternative inks– the inks used have the same qualitative composition.
□	5.	The deletion of the score/break lines has no effect on the posology.
	Documentation	
□	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).
□	2.	Justification for removal of tablet markings and information on how the product can be distinguished from other tablets/capsules.
□	3.	Revised SPC and leaflet (if applicable)

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**
□	**b) All other tablets, capsules, suppositories and pessaries**	**1, 2**	**1**	**Self Certification**
	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 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**
□	**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, 3, 4**	**1, 2, 3**	**Self Certification**
□	**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			
□	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.			
□	3. The current smallest or largest pack size has not been deleted i.e. pack size range remains the same			
□	4. The only changes to the SPC, label and leaflet concern the change in pack size			
	Documentation			
□	1. Amendments to the relevant sections of the dossier in CTD format.			
□	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).			
□	3. Revised SPC Section 6.5 and labelling and leaflet artwork.			

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**	**IA**
□	**2. After first opening**	**1, 2**	**1, 2**	**IA**
□	**3. After dilution or reconstitution**	**1, 2**	**1, 2**	**IA**
□	**b) the storage conditions of the finished product or the diluted/reconstituted product**	**1, 2, 4**	**1, 2**	**IA**

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 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.
□	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			
□	**1. Addition or replacement**	**1, 2, 4**	**1, 2**	**Self Certification**
□	**2. Deletion**	**3**		**IA**

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.
	4.	The device meets the requirements for CE marking

Documentation

□	1.	Amended sections of the dossier in CTD format.
□	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

46		Conditions to be fulfilled	Documentation to be supplied	Procedure type
□	**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**
□	**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
□	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.
□	3. The application is submitted within 30 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.
□	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
□		**1, 2**	**1, 2, 3**	**IA**

	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.
□	2. No additional statements or amendments have been introduced into the SPC, labelling and leaflet

	Documentation
□	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.
□	2. Letter of undertaking, if requested by EMEA/CHMP.
□	3. Revised SPC, label and leaflet