

Marketing Authorisation Variations - Supplementary Guidance

The following includes specific guidance in relation to some common scenarios which are presented as variations and as appropriate these should be taken into consideration when preparing the relevant submissions.

1. Administrative Changes

1.1 Changes to company names etc.

1.1.1 Marketing Authorisation Holder (MAH)

1.1.1.1 Company name

A change to the name and/or address of the marketing authorisation holder should be submitted as a Type IA (change code A.1) notification. The change can only be accepted if there is no change to the legal entity and the application will need to be accompanied by proof of this such as, in the UK, a copy of an updated Companies House certificate. It is possible to submit a grouped variation application for several products. This should list each of the products and be supported by the following:

- formal document from a relevant official body e.g. in the UK, a copy of an updated Companies House certificate
- updated Summary of Product Characteristics (SPC) fragment for each product
- clean full-colour mock ups of the revised product literature for all licences being varied should be included in the application. **As an exception**, however, if all mock-ups are not available at the time of application, and valid justification is provided, clean full colour mock-ups for at least one product (the smallest pack size in the lead marketing authorisation of the bulk) may be provided together with a declaration that the remaining artwork for the lead licence and other products in the bulk would be updated and submitted for registration via the Patient Information Quality Unit (PIQU) label and leaflet Better Regulation of Medicines Initiative (BROMI) notification scheme.

If both national and Mutual Recognition (MR) marketing authorisations are held, separate variations should be submitted for each group of marketing authorisations. The MR variations should be handled in accordance with the relevant MR procedures and will need to take account of whether the MHRA is the Reference Member State (RMS) or a Concerned Member State (CMS) and the submission requirements for each of the Member States concerned.

1.1.1.2 Trading style

A change in trading style of the marketing authorisation holder (MAH) will also be handled under the same Type IA change code. The following requirements will apply:

- formal document from a relevant official body, such as, in the UK, a copy of an updated Companies House certificate naming the new trading style; alternatively, a letter from the company secretary or a director confirming the trading style will suffice
- updated SPC fragment for each product

- clean full colour mock-ups of the revised product literature for all licences being varied should be included in the application. **As an exception**, however, if all mock-ups are not available at the time of application, and valid justification is provided, clean full-colour mock-ups for at least one product (the smallest pack size in the lead marketing authorisation of the bulk) may be provided together with a declaration that the remaining artwork for the lead licence and other products in the bulk would be updated and submitted for registration via the label and leaflet BROMI notification scheme

In addition, it should be noted that a trading style cannot be a different legal entity, so it must not include 'Limited'. This should be supported by a letter from the company secretary or a director confirming the use of the proposed trading style/mark for the marketing authorisation holder.

In view of the significant amount of work involved in preparing a Type IA notification concerning the change code A.1 change (which potentially affects a large number of marketing authorisations) and the fact that, under the procedure, any deficient application will not be accepted, MAHs are strongly recommended to contact the MHRA at variationqueries@mhra.gsi.gov.uk for advice, prior to submitting.

1.2.1 Type IA notifications

1.2.1.1 Interpretation of implementation

For quality changes, implementation is when the company makes the change in its own Quality System.

This interpretation allows companies to manufacture conformance batches and generate any needed stability studies to support a Type IAIN variation before making an immediate notification because the change will not be made in their own Quality System until these data are available.

For changes to the pharmacovigilance system, 'implementation' is when the Company makes the change in its pharmacovigilance system (i.e. when it internally approves the summary of pharmacovigilance system incorporating the changes).

For product information, it is when the Company internally approves the revised product information. The revised product information should normally be used in the next packaging run.

Additional guidance relating to changes impacting product information

Type IA variations impacting product information, including packaging should be implemented in practice in accordance with CMD(h) guidance, i.e. normally at the next packaging run.

Any required changes should be introduced into packaged product at the earliest opportunity, especially if they concern important safety related changes. However, in instances where it is not logistically possible to implement the change at the next packaging run, then the change may be implemented at a subsequent packaging run. If

this is the case, any required changes should nevertheless be incorporated into any new packs being batch released, at the latest, within 6 months of the actual implementation date, which should be specified in any Type IA/IAIN notification form submitted to the MHRA.

In addition, the Qualified Person should not certify a medicinal product for release to the market if, at the time of certification, the relevant elements of the product information have not been updated with the new information within the required six months period following internal approval (implementation), unless a different timeframe has otherwise exceptionally been agreed with the MHRA. In the event that there is likely to be any difficulty in meeting the 6 months period, please contact variationqueries@mhra.gsi.gov.uk .

2. General Advice

2.1 Variations fees – complex fees

The legal basis for charging fees is described in [The Medicines \(Products for Human Use Fees\) Regulations \[SI 1995/116\]](#) as subsequently amended. Variations accompanied by extensive and complex data are charged a higher fee to take account of the additional work involved in the assessment.

The following quality changes will attract a complex fee:

Quality changes

- reformulation of the product introducing a novel excipient that has previously not been included in a medicinal product
- a new route of synthesis that has not previously been assessed and a Ph. Eur. Certificate of Suitability is not available*
- new method of sterilisation of the product*
- new container materials for a sterile product*
- new active ingredient manufacturer not previously approved to manufacture the active ingredient concerned and who does not hold a Ph. Eur. Certificate of Suitability for the substance concerned*.
- flu Vaccine – new manufacturer or process
- reformulation of the product that is supported by bioavailability studies
- change in the product's preservative system
- change in excipients which significantly affects the pharmaceutical or therapeutic properties.

* specific to the active ingredient.

Clinical changes

- variation applications supported by the results of clinical trials or other data (including pharmacological and toxicological tests as well as extensive evidence from post marketing experience or publications) that need to be newly assessed are classed as Type II Complex variations and will attract a

complex fee. SPC changes for established generic products would attract a standard fee provided it is not necessary for the proposed amendments to be supported by clinical data and they are solely for the purpose of updating the generic licence to the level of the brand leader

- if you are submitting separate related variations and only one is supported by clinical data, that variation will attract a complex fee and the others will attract a standard fee
- if two or more concurrent applications are supported by substantial amounts of data each, that have not previously been assessed, they will each attract a complex fee
- it should be noted that the application would fall into the Extended Type II Complex Variation Application fee category if the changes in indications for use are:

(a) in a therapeutic area for which the product was not previously indicated for use; or

(b) in respect of an organ, or any other part of the human body for which the product was not previously indicated for use, if the application is supported by data which comprises or includes the results of clinical trials or physico-chemical, microbiological or pharmacological and toxicological tests.

2.2 Own label supplier/distributor

An own label supplier relates to situations where a medicinal product is marketed in the livery of a company which is different to that of the MAH and possibly under a different product name. In these situations, in addition to the details of the MAH, the product information will also include details of the own label supplier/distributor. This guidance is specific to the UK and is consequently not relevant for other Member States.

Own label distribution can apply to any UK Marketing Authorisation. However, the possible inclusion of a separate product name is restricted to purely UK Marketing Authorisations only and as a consequence it is important to note that additional product names will not be permitted to any Marketing Authorisation which has been authorised under the mutual recognition or decentralised procedures.

The following changes concerning own label suppliers/distributors will be handled under Type IB change code B.II.b.1.z:

- The addition of an own label supplier/distributor, including a possible new product name
- A change to the trading style of an own label supplier.

The following changes concerning own label suppliers/distributors will be handled under Type 1A change code A5:

- A change to the name and/or address of an own label supplier that is not linked to the product name. (If appropriate, an updated wholesale dealer's licence should be provided.)

These changes will need to be accompanied by the following:

- A copy of a wholesale dealer's licence, where relevant
- Colour mock-ups with all changes clearly highlighted.

The following changes concerning own label suppliers/distributors will be handled under Type IA change code A7:

- Deletion of own label supplier/distributor, including the deletion of any associated product name.

2.3 Variations to Marketing Authorisations where UK is CMS

For Type IA and Type IB applications in the Mutual Recognition (MR) procedure the Reference Member State (RMS) has the responsibility of acknowledging or assessing the variations on behalf of the involved CMSs.

The CMS is not normally involved in the assessment of Type IB applications, with the exception of changes to product names (change code A2), pack sizes (change code B.II.e.5), and all variations under the C.I.1- C.I.3 and C.I.6.b – C.I.7 codes as well as C.I.z. In these cases, as appropriate the CMS will send comments to the RMS. The RMS will inform the MAH of the acceptability of the application and therefore acknowledgement and approval letters will not be issued by the MHRA where the UK is CMS.

Please note that where the patient information leaflet (PIL) and Summary of Product Characteristics (SPC) have been amended as a result of the variation, the English language versions will need to have been received and agreed where appropriate with the assessor.

3. Quality Changes

3.1 Active ingredient

3.1.1 Change to the European Pharmacopoeia monograph of an active ingredient

In the event that the monograph for a specific active substance is updated, a Type IA (change code B.III.2.b) variation should normally be submitted. However, there is no need to notify the competent authorities if all the following apply:

- There is an updated monograph of the European Pharmacopoeia or a national pharmacopoeia of a Member State
- the dossier of an authorised medicinal product already refers to the 'current edition' of the specific monograph

3.1.2 Changes to Active Substance Master Files (ASMFs)

ASMF holders are responsible for notifying Marketing Authorisation Holders (MAH) of any changes to the content of any ASMF and a commitment to this effect is provided as part of the procedure. See relevant EMA guidance

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000354.jsp&mid=WC0b01ac0580028bfd

Changes to the applicant's part will be immediately transparent and this information can be used to classify how the changes should be presented. However, as far as the restricted part of the ASMF is concerned this information is confidential and as a consequence the MAH does not know what has change and cannot therefore provide the required declarations. Some minor changes to the restricted part of the ASMF can be notified as a Type IB (change code B.I.a.2.e), but will need to be supported by a suitable declaration from the ASMF holder.

In addition, changes to the batch size can be notified as a Type IA, for example category B.I.a.3.a, where a declaration from the ASMF holder will also need to be provided.

3.2 Finished Product

3.2.1 Contents of Qualified Person Declaration

MAHs are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP. Depending on the number of active substances and the arrangements in place between any relevant manufacturing authorisation holders one or more declarations should be provided in support of certain changes e.g. change to the finished product manufacturing site. The situations where a declaration is required are detailed in the classification guideline.

Further guidance and a recommended template that should be used can be found on the EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000354.jsp&mid=WC0b01ac0580028bfd

3.2.2 Batch Specific Variations

All products released to the market must comply with the relevant marketing authorisation. A batch-specific variation is a variation application to request agreement for a single or small number of batches of product to be released outside of the usual conditions of the marketing authorisation. The procedure is intended to be used rarely where an unexpected or unavoidable situation has arisen (for example a production problem) and approval is needed to maintain stock on the market, consequently such variations should only be submitted in exceptional circumstances.

In each case, the applicant should provide evidence that the quality, safety and efficacy of the product are unaffected by the deviation in the batch concerned.

The most near-matched change code should be selected from the application form but all batch specific variations follow normal Type II timelines and fees.

Where it is in the interest of public health it is possible to expedite the assessment to help maintain supply levels of the product (for example where there are no alternative suppliers). The intention is to avoid an adverse impact on public health which would otherwise arise from interruption to supply if the normal assessment timeframe was applied. In these cases justification is needed as to why the variation application is considered urgent and requires expedited assessment.

In the request we would expect information to be provided on:

- The nature of the non-compliance
- An explanation of the public health impact if there was an interruption to supply
- Information about the supply and demand situation including prescription volumes or sales demand, current stock levels, information on market share and availability of alternative products.

In the case of a potential interruption to supply Marketing Authorization holders are also obliged to contact DH to advise of that risk.

To help us handle requests for expedited assessment:

- Submit requests for expedited assessment to the RIS mailbox, variationqueries@mhra.gsi.gov.uk or alternatively, contact the RIS on 020 3080 7400. If the request is agreed you will be advised of the name of the relevant assessment team manager.
- If submitting the variation via the MHRA Portal or CESP, please give us the reference number and the date of submission as soon as this information is known as this helps us to locate the submission.
- If you have not already submitted the batch specific variation, please append a copy of the agreement to expedite it to the cover letter of your submission.

4. Safety, Efficacy, Pharmacovigilance Changes

4.1 Change or addition of therapeutic indications

Depending upon the background to the change and as a consequence the level of supporting information, changes to indications can possibly be submitted under any category of variation and will therefore be processed to the associated timetable. The “C” section of the classification guideline details the various possibilities.

In the UK a Type II application will attract an extended Type II complex fee when it is a variation to a marketing authorisation (not being a parallel import licence) so that the medicinal product is indicated for use:

- (a) in a therapeutic area for which the product was not previously indicated for use
- (b) in respect of an organ, or any other part, of the human body for which the product was not previously indicated for use, if the application is supported by data which comprises or includes the results of clinical trials or physico-chemical, microbiological or pharmacological and toxicological tests.

Applications relating to changes to clinical indications that do not fall into the above definition may also be assessed on a 120-day timetable if there is a large amount of supporting data. This will be on the agreement of the marketing authorisation holder (MAH) and the Competent Authority (Reference Member State [RMS] for Mutual Recognition procedures and MHRA for UK national licences). These applications may not necessarily attract an extended Type II complex fee.