SUBMITTING CHANGES TO LABELLING AND PATIENT INFORMATION LEAFLETS

1. Background

Council Directive 2001/83/EC as amended, requires that marketing authorisation holders (MAH) inform the competent authority of all changes to the labelling and patient information leaflets which are not connected with changes to the Summary of Product Characteristics (SPC) [Article 61(3)]. Notwithstanding the need for the applicant to notify the competent authority of the amendment, responsibility for the information presented on the packaging and in the patient information leaflet rests solely with the MAH.

In line with the principles of Better Regulation the MHRA is expanding the notification scheme for changes to labelling and patient information leaflets. This notification procedure provides for a rapid and efficient processing of changes submitted to the competent authority under article 61(3) of Council Directive 2001/83/EC. The notification scheme will be the default position from July 2012. Only those changes defined in section 3 (below) will be eligible for full assessment by the Patient Information Quality Unit. This guidance document applies to changes in relation to the packaging components for all medicines with the exception of parallel imported products, Traditional Herbal Registrations and homoeopathic medicines.

2. General Guidance

Most changes to labelling and/or patient information leaflets which are not connected with changes to the summary of product characteristics are subject to self-certification by the marketing authorisation holder and subsequent notification to the MHRA (but see section 3 below for details of exceptions). These changes cannot be submitted for formal assessment and will not be accepted as full applications by the Information Processing Unit.

Notifications made under article 61(3) will not be subject to formal assessment and approval by MHRA but will be self-certified by the applicant. As foreseen by the Directive, the national competent authority is required to have a record of the packaging components. Notifications made to the MHRA under these provisions are deemed “tell and do” and will be accepted within 14 days of receipt. Changes notified in this manner can be introduced once the acceptance letter has been received from the MHRA. Any fee which may apply to such notifications is defined within the relevant statutory instrument.

Full colour mock-ups¹ of the proposed final version of the packaging components must accompany the notification. This should be in the form of a consolidated artwork file including the changed labelling elements and those elements not affected by the change.

Acceptance of these notifications is based on declarations by the MAH that the necessary supporting documentation has been submitted. MHRA will undertake an audit based on both random and targeted sampling of
notifications to monitor the validity and quality of the submissions. Outcome reports from these audits will be published on our website.

Changes which require a full PIQU application or variation application as described in section 3 (below) cannot be made by means of a notification and must be the subject of a full application to PIQU or a variation application. Should the audit process identify any notifications including changes which should have been the subject of a full application these notifications are liable to be rescinded and a further application will be required. This may also necessitate the removal of stock from the market place where a risk to public health is identified.

3. Applications for full assessment by the MHRA

First approval of full colour mock-ups for labelling and PILs will usually be undertaken at grant of the marketing authorisation (but see below). Similarly the assessment of new artwork associated with changes to the SPC will be carried out at the time of the assessment of the variation application.

Subsequent changes to product information which require a submission for full assessment and approval by the Patient Information Quality Unit are detailed below, together with the change codes which should be used on the application form:

P1 First approval of mock-ups following grant of a marketing authorisation where only text versions were submitted and approved as part of the MAA.

P2 Changes to patient information leaflets which include significant changes to content and/or design and layout and must therefore be supported by additional data demonstrating continued compliance with article 59(3) of Council Directive 2001/83/EC [user testing or bridging data] or data in connection with article 62 of the directive. Full details on when a new user test or bridging report are needed are included in the Best Practice Guidance on Leaflets April 2012.

P3 Changes to pack design and layout will always be the subject of an application. This will encompass changes to any or all of layout of the information, changes to the content of the information and changes to graphics on the pack.

Where such changes have been subject to pre-approval by third party these applications will be eligible for expedited review. Applications in this category will be assessed within 30 days of the application being considered valid by the MHRA.

P4 Changes which are notified to the MAH by the MHRA and for which a full application is solicited. Where such changes are made by means of a variation application the artwork will be considered as part of the variation assessment provided only changes consequential to the
variation are introduced. In some cases the variation applications will be handled within PIQU. These may include but are not restricted to:

- Approval of artwork for a new own-label supplier
- Approval of artwork following a product name change
- Introduction of significant new safety information following consideration by an expert advisory committee
- Amendment of artwork following a complaint in relation to patient safety

4. How to submit

Details on how to submit notifications and applications are set out on the MHRA website. A flow chart is also available which describes the decisions to be made in determining the correct route for changes to packaging and patient information to be registered with the MHRA.

**SUBMISSIONS FOR FORMAL ASSESSMENT (APPLICATION)**

Marketing authorisation holders submitting applications for assessment should indicate clearly on the application form in word [Application for changes to labels and patient information leaflets] /or portal form in Adobe PDF format [Changes to the Marketing Authorisation]:

“This application is submitted under article 61(3) of Council Directive 2001/83/EC. The changes applied for fall into the following category (ies) [insert the change code P1, P2, P3 and/or P4 as appropriate]”. Applicants should also describe these in the covering letter and include details of any supporting data being included with the submission. Changes not encompassed by codes P1 – P4 must be the subject of a notification and will not be accepted for full assessment by PIQU or variation application.

- Make sure that you reference the details of what is being changed on the respective packaging components.
- More than one change may be applied for at any one time but you must ensure that all changes are referenced correctly on the notification form appropriately.
- Where change codes P1 – P4 apply, you may include other changes which would normally be subject to self-certification in the submission.
- Any applications submitted which do not encompass changes in P1 – P4 will be rejected and will need to be resubmitted as notifications.
- Full colour mock-ups of the proposed final version of the packaging components must accompany the application as described above.

**SUBMISSIONS FOR SELF-CERTIFICATION (NOTIFICATION)**

Marketing authorisation holders submitting changes under the notification process must state clearly on the notification form in word format [Notification of changes to labels and patient information leaflets for self-certification] or the portal form in Adobe PDF format (i.e. as an Information Update using the General Product Licence submission form):
“This notification is submitted under article 61(3) of Council Directive 2001/83/EC. Changes notified are as follows: [insert the precise nature of the changes being notified]. I confirm that no other changes have been introduced.”

- Make sure that you reference the details of what is being changed on the respective packaging components.
- More than one change may be notified at any one time but you must ensure that all changes notified are referenced correctly on the notification form appropriately. NOTE: there will no longer be change codes associated with this procedure.
- Any changes introduced to the packaging components but not formally notified, or changes which should be the subject of a formal application to PIQU or variation application as set out in 3 above, may render the notification invalid.
- Full colour mock-ups\(^1\) of the proposed final version of the packaging components affected by the change must accompany the notification as described above.

Please send electronic notifications for the attention of Area 9, as set out in Special Mail 5.

5. Effective date:

This process becomes effective from 1 July 2012. All changes to labelling and PILs from this date will fall to be considered under this process.

VRMM
JULY 2012

\(^1\) A mock-up is a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the labelling text is clear. This mock-up is generally referred to as a paper copy and not necessarily in the material of the sales presentation.