

# **Guidance for the Pharmaceutical Industry on the use of BRIDGING STUDIES to demonstrate compliance with article 59(3) of Council Directive 2001/83/EC [Consultation with Target Patient Groups]**

## **A PURPOSE:**

1. Guidance from the CMD(h) and the MHRA indicate that although all patient information leaflets (PILs) for medicines must reflect the results of consultation with target patient groups (user testing) not every leaflet needs be the subject of a separate test. PILs may be able to rely on testing applied to PILs for similar products. This document provides guidance on when such bridging studies will be accepted by MHRA and the type of evidence which will need to be provided in support of applications where data in line with the requirements of article 59(3) are required.

## **B SCOPE:**

2. The guidance is applicable to all applications where a user test (or other evidence of compliance with article 59(3)) is required. It will apply to applications for new marketing authorisations, significant variations to MAs, renewal applications where significant changes are proposed and for applications submitted under article 61(3) to the Patient Information Quality Unit within MHRA. The guidance is equally applicable to national and European applications. This guidance does not apply to parallel import licences.

## **C DEFINITIONS**

3. Minor changes to content or layout of a document can impact adversely on the readability. These differences can affect whether or not the resultant PIL is clear, legible and easy to use as required by law. The term **bridging** has been described to apply to leaflets which are sufficiently similar in both content and layout. In bridging, a successful user test on one PIL [the “parent” PIL] can be used as a justification for not testing other similar leaflets [“daughter” PILs]. In some circumstances it may be appropriate for some “daughter PILs to rely on the results of testing for more than one “parent” PIL.
4. Since the design and layout of the information is crucial to how the information is used and understood, “daughter” PILs should be of the same design, layout and writing style as the “parent” PIL in order for bridging to be successful. A bridging proposal is unlikely to be acceptable to the regulatory body where this concept has not been adhered to.

## **D KEY MESSAGES FOR SAFE USE**

5. A successful user test will have identified up-front the key messages for safe use with the particular medicine in question. For each medicine these messages will be different. The questionnaire will have to address these key messages and provide evidence that patients can find and understand these messages so that they can use the medicine safely. Such a user test could then be relied upon to

support a PIL drawn up in the same manner for a closely related medicine. In a bridging study the key messages for safe use for both the “parent” and “daughter” PILs need not be identical. However, high profile safety issues should be included in the key points tested for each daughter PIL.

## **E FORMAT, DESIGN AND LAYOUT OF THE PIL**

6. The design and layout of the information in the PIL is crucial to the way in which patients access the key messages for safe use. Most marketing authorisation holders have a recognisable “house style” in this regard. In order for bridging to be successful both the “parent” and “daughter” PILs should have a common design and layout. Common design and layout will include the following important aspects:
  - Font and font size
  - Headings and sub-headings including consistency of placement
  - PIL dimensions including whether the document is laid out in portrait or landscape format
  - Use of colour and choice of colour
  - Style of writing and language used
  - Layout of critical safety sections of the PIL
  - Use of pictograms

Each different leaflet design (with particular dimensions) or variations in format (such as a booklet, or peelable leaflet) will need to have been the subject of a number of successful user test exercises in order for other leaflets to claim similarity to a particular format in a bridging study. The number of tests required for a particular format will depend on the complexity of the information conveyed in each case and will be judged on a case-by-case basis.

## **F APPLYING BRIDGING IN PRACTICE**

7. Earlier guidance from MHRA and CMD(h) indicated that there may be particular circumstances where bridging could be used. Each of these is discussed in this section and acceptance criteria are explored. In all cases the target patient population will be similar.
  - (a) **Line Extensions**
8. Bridging will normally be acceptable for PILs of the same active moiety for different strengths or routes of administration. In these cases the “parent” PIL should be the one which contains the more/most complex information for the patient. For example the PIL for diazepam oral solution could be designated the “parent” PIL for diazepam tablets (“daughter” PIL). Where a medicine is presented in a formulation not normally supplied to patients for self-medication the relevant PIL could be bridged to that for the same medicine which is self-administered. For example the PIL for diazepam injection (“daughter”) could be bridged to the PIL for diazepam oral solution (“parent”).

9. Where potentially similar products require the patient to understand significantly different methods of administration different criteria will apply. Examples include but are not restricted to an inhalation device and a patch. Here it will be important to ensure that the information in relation to the posology has been the subject of a successful user test. However, a “daughter” PIL could rely on user tests carried out on the PILs associated with more than one product. For example a “double” bridge could be applied to the PIL for a salbutamol inhaler (“daughter”) which could be bridged to a successful user test for a PIL for an oral salbutamol preparation (covers information relating to the active moiety) and to the PIL for a beclometasone product with an identical inhaler device (covers information relating to delivery).
10. Where a company portfolio includes a range of conventional topical dosage forms (ointments; creams; eye, ear or nose drops or ointments/creams; scalp applications; lotions), individual tests of the administration instructions will not normally be required unless these contain untested pictograms (see below). However, the requirement remains that the daughter PILs must be of the same design, layout and writing style.

**(b) Medicines in the same “drug class”**

11. Bridging will normally be acceptable for PILs for medicines in the same therapeutic class where the clinical information set out in the summary of product characteristics (and therefore the information in the PIL) is similar. Importantly the key messages for safe use with the related medicines should be similar. However, the format and layout of the PILs to be bridged should be identical. This means that the “daughter” PIL should be revised and drawn up in a design, layout and linguistic style which conforms with the “parent” PIL which will have been the subject of a successful user test.
12. A therapeutically similar product is defined as a group of medicines which have similar modes of action. The following examples are included but this list is not exhaustive and inclusion of these therapeutically similar examples within particular classes does not necessarily mean that bridging will automatically be accepted by the MHRA for PILs in these categories:

<b>Cardio-vascular:</b>	<ul style="list-style-type: none"> <li>• thiazide and related diuretics,</li> <li>• beta-blockers,</li> <li>• ace-inhibitors</li> </ul>
<b>CNS:</b>	<ul style="list-style-type: none"> <li>• SSRIs</li> <li>• tricyclic and similar anti-depressants</li> <li>• anti-histamines</li> <li>• benzodiazepines</li> <li>• opioid analgesics</li> </ul>
<b>Anti-infectives:</b>	<ul style="list-style-type: none"> <li>• penicillins, cephalosporins &amp; macrolides</li> <li>• antifungals</li> </ul>
<b>Musculo-skeletal:</b>	<ul style="list-style-type: none"> <li>• NSAIDs</li> </ul>
<b>Endocrine:</b>	<ul style="list-style-type: none"> <li>• Glucocorticoids</li> </ul>
<b>Malignant Disease:</b>	<ul style="list-style-type: none"> <li>• alkylating cytotoxics</li> </ul>
<b>Nutrition:</b>	<ul style="list-style-type: none"> <li>• intravenous nutrition</li> </ul>
<b>Obstetrics/Gynaenaecology:</b>	<ul style="list-style-type: none"> <li>• oral contraceptives</li> </ul>

13. Medicines which are considered to be a “group” simply in terms of the therapy area they cover but which actually contain many different medicines with differing modes of action and key messages for safe use will be considered on a case by case basis.
14. For example the following medicines will not normally be considered appropriate for successful bridging due to the differing clinical considerations:
- Anti-arrythmics such as amiodarone and disopyramide
  - Anti-epileptics such as valproate, lamotrigine and phenytoin
  - Disease modifying anti-rheumatics such as gold and penicillamine
15. In therapy areas where there are many different medicines with differing modes of action but the key issues around safe use are much less critical, bridging may be acceptable. The following are given as examples
- Antacids and anti-spasmodics
  - cough preparations
  - vitamins
  - mouthwashes
  - emollients and skin cleansers.

In most cases, the chosen parent PIL will be that containing the widest range of information.

**(c) Same Key Messages for Safe Use**

16. Where the key messages for safe use which have been identified for a range of medicines are similar and the PILs are designed, laid out and written in an identical manner bridging here will be easiest to justify.

**(d) Same Patient Population**

17. Medicines within the same therapeutic class are normally used within the same patient population. However, a small number of medicines are used in more than one therapeutic area. An example of this would be glucocorticoids. In such examples “double” bridging can be applied making sure that the “parent” PILs to which the “daughter” PILs are bridged covers all key messages for safe use arising from the contraindications, warnings precautions and side effects and also addresses issues relating to indications and posology.

**(e) Combination medicines**

18. Generally, the PIL for the combination medicine should be considered as the “parent” PIL for the purpose of bridging to the individual component “daughter” PILs. You will need to make sure that any key messages for safe use relating to the individual components have been addressed in the questionnaire for the combination PIL. It may be possible to use the individual component PILs as the “parent” PILs and bridge to the combination PIL as the “daughter” provided any differences in layout and length of the combination PIL have been the subject of successful user testing within the company portfolio.

**(f) Short PILs for medicines with minor therapeutic actions**

19. Short PILs for such products are unlikely to need to be the subject of a specific user test. It will be sufficient to rely on the successful tests carried out for other products within the portfolio even though these may not be in the same therapeutic class. Examples of such medicines are water for injection, aqueous cream, hypromellose eye drops.

**(g) OTC medicines with a variety of minor components**

20. Remedies and OTC products with multiple ingredients can be bridged with PILS which have been successfully tested for the main active ingredient(s) e.g. compound analgesics based on paracetamol. The requirements for the PIL format to be the same still apply.

**(h) Pictograms**

21. Pictograms used within a company house style will need to be tested as part of a user test. For bridging to encompass pictograms successfully the pictograms in “daughter” PILs should have the same design, dimensions and colours as those in the “parent” PIL.

**(h) Bridging between companies**

22. Each company is expected to rely on his own data. However, if a letter of access is provided, a second company may apply to use the same PIL as another marketing authorisation holder provided the content of the PIL (with the exception of specific company information) is identical. In both cases the design and layout for the PILs concerned should be identical in all aspects as discussed above. The use of different company logos will be acceptable provided these are placed consistently in the two PILs and take up a similar amount of space. A statement should also be made that the applicant has seen the originator's data and confirm that the user test was acceptable.

**G DRAFTING AND SUBMITTING A SUCCESSFUL BRIDGING REPORT**

23. Each marketing authorisation will have to include data which demonstrates that patients can find and understand the information which is necessary for safe and effective use. A bridging report is a full report – but will not include the original data submitted in respect of the “parent” PIL. The user test for the “parent” PIL should have been submitted and approved prior to the approval of the “daughter” PIL(s). That does not prevent a series of PILs being submitted concurrently for assessment thereby enabling you to take advantage of the bulk fee arrangements.

**(a) Identifying the Key Messages for Safe Use**

24. The bridging report will need to discuss first of all the key messages for safe use within the “daughter” PIL and justify how these are covered within the test carried out on the “parent” PIL. Where the key messages are not identical (and this will apply to many bridged PILs) the bridging report will need to critically appraise these differences and address the relevance of the questionnaire to the “daughter” PIL. Synergies and similarities in the key messages should be discussed.

**(b) Design and Layout Issues**

25. There will need to be a critical comparison of the design and layout of both “daughter” and “parent” PILs and synergies and similarities drawn out in support of the bridging exercise.

**(c) Complexity of Message and Language Used**

26. A critical discussion of the complexity of the messages contained within the “parent” and “daughter” PILs should be presented. The language used in both PILs should be discussed and compared. Again similarities and synergies should be discussed.
27. All reports should address any general issues raised by participants in the user test concerning aspects of the PIL which they liked or disliked.

## **H SUBMISSIONS**

29. All medicines on the UK market must have leaflets which comply with the requirements of articles 59(1) [new order of information] and 59(3) [consultation with target patient groups] by 1 July 2008. In order to allow sufficient time for assessment you should endeavour to submit all your applications by December 2007. Further information is available from [patient.information@mhra.gsi.gov.uk](mailto:patient.information@mhra.gsi.gov.uk)

**Information for Public Health  
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