

**CONSULTATION WITH TARGET PATIENT GROUPS -
MEETING THE REQUIREMENTS OF ARTICLE 59(3) WITHOUT
THE NEED FOR A FULL TEST -
RECOMMENDATIONS FOR BRIDGING**

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1. INTRODUCTION

Guidance has already been issued from the CMD(h) which indicates that although all package leaflets (PLs) for medicines must reflect the results of consultation with target patient groups (user testing) and include within the marketing authorisation, data in module m-1-3-4- of the eCTD, not every leaflet needs be the subject of a separate test. PLs may be able to rely on testing applied to PLs for similar products.

The guidance is available from:

http://www.hma.eu/116.html#irfaq_31_14bfd

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/user_consultation_200605.pdf

Additional guidance is available from the European Commission in the guideline on the readability of the labelling and on the package leaflet. A link to the draft guidance is attached: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/09_2006/readability_consultation_2006_09_25.pdf

This document provides guidance on when bridging will be accepted by competent authorities 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) of Council Directive 2001/83/EC are required. Even though some examples are provided within this document this is not exhaustive and each case will be judged on its merits.

2. SCOPE

The guidance is applicable to all applications for marketing authorisations held by one company 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 and applications where harmonisation of the PL is undertaken and which must be accompanied by data demonstrating compliance with article 59(3).

3. DEFINITIONS

Minor changes to content or layout of a document can impact adversely on the readability. These differences can affect whether or not the resultant PL 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 PL [the “parent” PL] can be used to support a justification for not testing other similar leaflets [“daughter” PLs]. In some circumstances it may be appropriate for some “daughter” PLs to rely on the results of testing for more than one “parent” PL.

Since the design and layout of the information is crucial to how the information is used and understood, “daughter” PLs should be of the same design, layout and writing style as the “parent” PL in order for bridging to be successful. A bridging proposal is unlikely to be acceptable to the competent authority where this concept has not been adhered to.

4. KEY MESSAGES FOR SAFE USE

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 although the leaflet will cover the same sort of information in the same manner. The questionnaire within the protocol will have to address these key messages and provide evidence that these messages can be found and understood so that the medicine can be used safely. Such a user test could then be relied upon to support a PL 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” PLs need not be identical. However, high profile safety issues should be included in the key points tested for each daughter PL.

5. FORMAT, DESIGN AND LAYOUT AND WORDING OF THE PL

The design and layout of the information in the PL 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” PLs should have a common design, layout and style of writing. The following important aspects should be considered:

- Font and font size
- Headings and sub-headings including consistency of placement
- PL 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 PL
- Use of pictograms
- Paper weight

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 tests 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.

6. APPLYING BRIDGING IN PRACTICE

Earlier guidance from CMD(h) (see above) 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 for the particular medicines will be similar. However, the PLs of some medicines may need to be the subject of a specific user test particularly where there is evidence of risk.

(a) Line Extensions

Bridging will normally be acceptable for PLs of the same active moiety for different strengths or routes of administration. In these cases the “parent” PL should be the one which contains the more/most complex information concerning safe and effective use. For example the PL for diazepam oral solution could be designated the “parent” PL for diazepam tablets (“daughter” PL). Where a medicine is presented in a formulation not normally supplied to patients for self-medication the relevant PL could be bridged to that for the same medicine which is self-administered. For example the PL for diazepam injection (“daughter”) could be bridged to the PL for diazepam oral solution (“parent”).

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, an auto-injection pen 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” PL could rely on user tests carried out on the PLs associated with more than one product. For example a “double bridge” could be applied to the PL for a salbutamol inhaler (“daughter”) which could be bridged to a successful user test for a PL for an oral salbutamol preparation (covers information relating to the active moiety) and to the PL for a beclometasone product with an identical inhaler device (covers information relating to delivery).

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 PLs must be of the same design, layout and writing style.

(b) Medicines in the same “drug class”

Bridging will normally be acceptable for PLs for medicines in the same therapeutic class where the key safety information set out in the summary of product characteristics (and therefore the information in the PL) is similar. It would be expected that such products would be authorised for similar indications. Importantly the key messages for safe use with the related medicines should be similar. However, the format and layout of the PLs to be bridged should also be identical for the reasons set out above. This means that the “daughter” PL should be revised and drawn up in a design, layout and linguistic style which conform to the “parent” PL which will already have been the subject of a successful user test.

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.

Bridging across ATC codes is permitted as indicated by Q17 FAQ for MRP and DCP applications. For example, results from consultation with target patient groups for a simvastatin-containing medicine could apply to all products in the C10AA group.

C10AA01	Simvastatin	15mg
C10AA02	Lovastatin	30 mg
C10AA03	Pravastatin	20mg
C10AA04	Fluvastatin	40mg
C10AA05	Atorvastatin	10mg
C10AA06	Cerivastatin	0.2mg
C10AA07	Rosuvastatin	10mg
C10AA08	Pitavastatin	2mg

Another example would be the diuretic bendroflumethiazide:

C03AA01	Bendroflumethiazide	2.5mg
C03AA02	Hydroflumethiazide	25mg
C03AA03	Hydrochlorothiazide	25mg
C03AA04	Chlorothiazide	0.5g
C03AA05	Polythiazide	1mg
C03AA06	Trichlormethiazide	4mg
C03AA07	Cyclopenthiiazide	0.5mg
C03AA08	Methyclothiazide	5mg
C03AA09	Cyclothiazide	5mg
C03AB01	Bendroflumethazide and potassium	2.5mg
C03AB02	Hydroflumethazide and potassium	25mg
C03AB03	Hydrochlorothiazide and potassium	25mg
C03AB04	Chlorothiazide and potassium	0.5g
C03AB05	Polythiazide and potassium	1mg
C03AB06	Trichlormethiazide and potassium	4mg
C03AB07	Cyclopenthiiazide and potassium	0.5mg
C03AB08	Methyclothiazide and potassium	5mg
C03AB09	Cyclothiazide and potassium	5mg

In these cases, the chosen “parent” PL will be that containing the widest range of information.

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.

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

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
- mucolytic preparations
- vitamins
- mouthwashes
- emollients and skin cleansers.

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

(c) Same Key Messages for Safe Use

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

(d) Same Patient Population

Medicines within the same therapeutic class are normally used within the same patient population. However, some 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” PLs to which the “daughter” PLs are bridged covers all key messages for safe use.

(e) Combination medicines

Generally, the PL for the combination medicine should be considered as the “parent” PL for the purpose of bridging to the individual component “daughter” PLs. 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 PL. Exceptionally, it may be possible to use the individual component PLs as the “parent” PLs and bridge to the combination PL as the “daughter” provided any differences in layout and length of the combination PL have been the subject of successful user testing within the company portfolio.

(f) Short PLs for medicines with minor therapeutic actions and very low risk profile.

Short PLs 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) Pictograms

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” PLs should have the same design, dimensions and colours as those in the “parent” PL.

NOTE: In general, pictograms if used should be the subject of a common understanding across all member states.

7. DRAFTING AND SUBMITTING A SUCCESSFUL BRIDGING REPORT

Each marketing authorisation will have to address the requirements of Article 59(3) and include information which demonstrates that patients can find and understand the information which is necessary for safe and effective use. A bridging report will not include the original data submitted in respect of the “parent” PL. The user test for the “parent” PL should have been submitted in another application and the leaflet approved prior to the approval of the “daughter” PL(s). Simultaneously to the bridging report, a focused test may be submitted in addition to address 1 or 2 points differing from the parent PL.

How much information is required will depend on the relationship between “parent” and “daughter” PLs and there will be a spectrum of complexity of information required. For example, where the leaflet for a 5mg tablet is relying on the user consultation information submitted for the 10mg strength of the same product, the bridging report will by necessity be brief. However, where the leaflet for a medicine is relying on the user test submitted in support of a leaflet for a medicine in a different therapeutic class, a more fulsome report will be required. The issues which will need to be addressed in bridging report are set out below.

(a) Identifying the Key Messages for Safe Use

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

(b) Design and Layout Issues

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

(c) Complexity of Message and Language Used

A critical discussion of the complexity of the messages contained within the “parent” and “daughter” PLs should be presented. The language used in both PLs should be discussed and compared. Again similarities and synergies should be discussed.

All reports should address any general issues raised by participants in the user test concerning aspects of the PL which they liked or disliked.