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Consultation with target patient groups -meeting the requirements of Article 59(3) without the need for a full test -recommendations for bridging

1. Introduction

Guidance has already been issued from the CMDh which indicates that although all package leaflets (PLs) for medicines must reflect the results of consultation with target patient groups (user consultation) and include within the marketing authorisation (MA), data in module 1 (section 1.3.4) of the application, not every leaflet needs to be subject to a full test. Applicants and marketing authorisation holders (MAH) may be able to rely on testing applied to PLs for similar products. The guidance is available from: <http://www.hma.eu/218.html>

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 guidance is attached.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf

This document provides guidance on when, in general, competent authorities will consider that because they are sufficiently similar in both content and layout, an applicant/MAH, may rely on the user consultation already carried out for one leaflet to demonstrate that another leaflet meets the requirements of article 59(3) of Council Directive 2001/83/EC. It also provides guidance on 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 will apply to, but are not restricted to, applications for new MAs, significant variations to MAs 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. In this guidance the term **bridging** is used to describe the situation where, because the leaflets are sufficiently similar in both content and layout, a successful user consultation on one leaflet can be used to demonstrate that another leaflet meets the requirements of article 59(3) of Council Directive 2001/83/EC.

In bridging, a successful user test on one PL [the “parent” PL] can be used to support a justification for not performing a full test of 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. For example it would be possible to refer to the design and layout of one leaflet and to the content of the leaflet for another product.

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 consultation 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 which has been submitted with the application for the “parent” PL will have to address these key messages and provide evidence that people who are likely to rely on the PL can find and understand these messages and act appropriately so that the medicine can be used safely. Such a user consultation could then be relied upon to support a PL drawn up in the same manner for a closely related medicine. In a bridging report submitted for the “daughter” PL the key messages for safe use for both the “parent” and “daughter” PLs need not be identical.

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 text 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 sizes) or variations in format (such as a booklet, or peelable leaflet) will need to have been the subject of a number of successful user consultations in order for other leaflets to claim similarity to a particular format in a bridging study. The number of consultations 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 CMDh (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 consultation particularly where there is evidence of risk.

(a) Line Extensions

Bridging will normally be acceptable for PLs for medicines 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 (as in the case of the diazepam example above) 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. In such cases, it will be important to ensure that the information in relation to the posology has been the subject of a successful user consultation. However, a “daughter” PL could rely on user tests carried out on the PLs associated with more than one product. For example a “double bridging” 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 product includes a new method or route of administration but is otherwise identical to an existing presentation, the leaflet could be supported by reference to the data for the existing product accompanied by a focus test concentrating on the new method or route of administration.

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 consultation.

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 Q5 of CMDh Q&As on Product Information / Information on medicinal products. 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	15 mg
C10AA02	Lovastatin	30 mg
C10AA03	Pravastatin	20 mg
C10AA04	Fluvastatin	40 mg
C10AA05	Atorvastatin	10 mg
C10AA06	Cerivastatin	0.2 mg
C10AA07	Rosuvastatin	10 mg
C10AA08	Pitavastatin	2 mg

Another example would be the diuretic bendroflumethiazide:

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

C03AB07	Cyclopenthiiazide and potassium	0.5 mg
C03AB08	Methyclothiazide and potassium	5 mg
C03AB09	Cycllothiazide and potassium	5 mg

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

As stated in the introduction, each case will be judged on its merits. Particular consideration will be given to medicines which are considered to be a “group” in terms of the therapeutic area they cover but which actually contain many different medicines with differing modes of action and key messages for safe use.

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 therapeutic areas where many different medicinal products are authorised 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 indicated and 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. Applicants/MAHs will need to make sure that

any key messages for safe use relating to the individual components have been addressed in the questionnaire submitted in the protocol 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 that any differences in layout and length of the combination PL have been the subject of a successful user consultation 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 consultation. It will be sufficient to rely on the successful consultations carried out for other products within the portfolio even though these products may not belong to 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 consultation. 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.

When submitting a bridging report, the “QRD Form for submission and assessment of user testing bridging proposals” available from: <http://www.hma.eu/218.html> should be used. This form has been developed to provide guidance and facilitate the submission of user testing bridging proposals by applicants as well as to facilitate the assessment by the RMS. When applying for bridging, all sections of this form should be completed by applicants and submitted for assessment in Module 1.3.4 as well as in word-format in the working-documents folder.

A bridging report will not include the original data submitted in respect of the “parent” PL. The user consultation 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 also be submitted in order 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 5 mg tablet is relying on the user consultation information submitted for the 10 mg 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 which belongs to 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. 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 understood or misunderstood.