DECISION

No. 22/07.11.2008

on approval of the Guideline on consultations with target patient groups - meeting the requirements of Article 59(3) of Directive 2001/83/EC without the need for a full test - recommendations for bridging

The Scientific Council of the National Medicines Agency,
set up based on Order of the Minister of Health No. 1027/22.05.2008, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 07.11.2008 in accordance with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as amended, agrees on the following

DECISION

Single Article – The Guideline on consultations with target patient groups - meeting the requirements of Article 59(3) of Directive 2001/83/EC without the need for a full test - recommendations for bridging is approved, in accordance with the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
Consultation with target patient groups - meeting the requirements of Article 59(3) of Directive 2001/83/EC without the need for a full test - recommendations for bridging

CHAPTER I
Introduction and legal basis

Art. 1. - This Guideline is a translation into Romanian and an adaptation of the Guideline issued by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) Consultation with target patient groups - meeting the requirements of Article 59(3) of Directive 2001/83/EC without the need for a full test.

Art. 2. – (1) This Guideline provides recommendations for the situations in which, in order to meet the requirements of Art. 59(3) of Directive 2001/83/EC transposed through Art. 769(3) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, the competent authorities may accept reporting to previous testing done with the users' help; moreover, recommendations concerning he type of proofs required in order to be a part of the documentation accompanying the application for marketing authorisation in this case shall be provided.

(2) Although this Guideline contains several examples, it is not exhaustive and each case is should be considered individually.

CHAPTER II
Scope

Art. 3. – (1) The recommendations of this Guideline apply to all applications for authorisation owned by a company which requires the consultation of the client's opinion (or other compliance proofs to provisions of Art. 769 (3) of Law No. 95/2006, Title XVII – The medicinal product).

(2) The content of this Guideline applies to the new application for marketing authorisations, major application for variations of marketing authorisations (MA), applications for renewal of the marketing authorisation and applications involving the harmonisation of the package leaflet and should be accompanied by data assessing compliance with Art. 769 (3) of the Law.

CHAPTER III
Definitions

Art. 4. – (1) Minor changes to content or layout of a document can impact adversely on the readability; these differences may also affect whether or not the resultant PL is clear, legible and easy to use as required by law.

(2) The term **bridging** has been described to apply to leaflets which are sufficiently similar in both content and layout.

Art. 5. – (1) 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].

(2) In some circumstances, it may be appropriate for some "daughter" PLs to rely on the results of testing for more than one "parent" PL.

Art. 6. – (1) 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.

(2) A bridging proposal is unlikely to be acceptable to the competent authority where this concept has not been adhered to.

CHAPTER IV
Key messages for safe use of the medicinal product

Art. 7. – (1) A successful user test will have identified up-front the key messages for safe use with the particular medicinal product in question; for each medicinal product these messages will be different although the leaflet will cover the same sort of information in the same manner.

(2) The questionnaire within the protocol will have to address these key messages and provide evidence that these messages can be found and understood, ensuring the medicinal product's safe use.

(3) Such a user test could then be relied upon to support a PL drawn up in the same manner for a closely related medicinal product.

(4) 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.

CHAPTER V
The Package Leaflet (PL) - design, layout, organisation and utterance

Art. 8. – (1) 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.

(2) Most marketing authorisation holders have a recognisable "house style" in this regard.

(3) In order for bridging to be successful both the "parent" and "daughter" PLs should have a common design, layout and style of writing.

(4) The following important aspects should be considered:

- Font and font size ;
- Headings and sub-headings including consistency of placement;
- PL dimensions including paging styles;
- Including whether the document is laid out in portrait or landscape format
- Use and choice of colours;
- Style of writing and language used ;
- Layout of critical safety sections of the PL
- Use of pictograms;
- Paper weight.

Art. 9. - (1) 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.

(2) 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.

CHAPTER VI
Enforcement of the reporting to previous tests

Art. 10. – (1) Earlier guidance from CMD(h) indicated that there may be particular circumstances where bridging could be used.

(2) Each of these is individually discussed in this section and acceptance criteria are explored.

(3) In all cases the target patient population for the particular medicinal products will be similar.

(4) However, the PLs of some medicinal products may need to be the subject of a specific user test particularly where there is evidence of risk.

VI. 1. Line Extensions

Art. 11. – (1) Bridging will normally be acceptable for PLs of the same active moiety for different strengths or routes of administration.

(2) In these cases the "parent" PL should be the one containing the more/most complex information concerning safe and effective use; for example the PL for diazepam oral solution for injection could be designated the "parent" PL for diazepam tablets ("daughter" PL).

(3) Where a medicinal product is presented in a formulation not normally supplied to patients for self-medication the relevant PL could be bridged to that for the same medicinal product which is self-administered. For example the PL for diazepam solution for injection ("daughter") could be bridged to the PL for diazepam oral solution ("parent").

Art. 12. – (1) 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 patches.

(2) Here it will be important to ensure that the information in relation to the posology has been the subject of a successful user test.

(3) However, a "daughter" PL could rely on user tests carried out on the PLs associated with more than one product i.e. 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).

Art. 13. – (1) 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).

(2) However, the requirement remains that the daughter PLs must be of the same design, layout and writing style.

VI. 2. Medicinal products in the same "drug class"

Art. 14. – (1) Bridging will normally be acceptable for PLs for medicinal products 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.

(2) Importantly the key messages for safe use with the related medicinal products should be similar.

(3) However, the format and layout of the PLs to be bridged should also be identical for the reasons set out above.

(4) 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.

Art. 15. – (1) A therapeutically similar medicinal product is defined as a group of medicinal products which have similar modes of action.

(2) The following examples are mentioned but this list is not exhaustive: bridging is allowed across ATC codes; for example:

a) For example, results from consultation with target patient groups for a simvastatin-containing medicinal product 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

b) results from consultation with target patient groups for a diuretic bendroflumethiazide-containing medicinal product could apply to all products in the C03AA and C03AB groups:

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	Cyclopenthiazide	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	Cyclopenthiazide and potassium	0.5mg
C03AB08	Methyclothiazide and potassium	5mg
C03AB09	Cyclothiazide and potassium	5mg

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

Art. 17. – (1) Medicinal products which are considered to be a “group” simply in terms of the therapy area they cover but which actually contain many different medicinal products with differing modes of action and key messages for safe use will be considered on a case by case basis.

(2) For example, the following medicinal product will not normally be considered appropriate for successful bridging due to the differing clinical considerations:

a) Anti-arrythymics such as amiodarone and disopyramide;

b) Anti-epileptics such as valproate, lamotrigine and phenytoin;

c) Disease modifying anti-rheumatics such as gold and penicillamine;

Art. 18. – (1) 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; for example:

a) antacids and anti-spasmodics;

b) mucolytic preparations;

c) vitamins;

d) mouthwashes;

e) emollients and skin cleansers.

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

VI. 3. Same key messages for safe use

Art. 19. - 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.

VI. 4. Same patient population

Art. 20. – (1) Medicinal products within the same therapeutic class are normally used within the same patient population.

(2) However, some medicinal products are used in more than one therapeutic area, such as 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.

VI. 5. Combinations

Art. 21. – (1) 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.

(2) 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.

(3) 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.

VI. 6. Short PLs for medicines with minor therapeutic actions and very low risk profile.

Art. 22. – (1) Short PLs for such products are unlikely to need to be the subject of a specific user test.

(2) It will be sufficient to rely on the successful tests carried out for other medicinal products within the portfolio even though these may not be in the same therapeutic class; examples of such medicinal products are water for injection, aqueous cream, hypromellose eye drops.

VI. 7. Pictograms

Art. 23. – (1) Pictograms used within a company house style will need to be tested as part of a user test.

(2) 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.

(3) In general, pictograms if used should be the subject of a common understanding across all member states.

CHAPTER VII
Drafting and submitting a successful bridging report

Art. 24. – (1) Each marketing authorisation will have to address the requirements of Article 769 (3) and include information which demonstrates that patients can find and understand the information which is necessary for safe and effective use.

(2) A bridging report will not include the original data submitted in respect of the "parent" PL.

(3) 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).

(4) Simultaneously to the bridging report, a focused test may be submitted in addition to address 1 or 2 points differing from the parent PL.

Art. 25. – (1) How much information is required will depend on the relationship between "parent" and "daughter" PLs.

(2) For example, where the leaflet for a 5 mg tablet is relying on the user consultation information submitted for the10mg strength of the same product, the bridging report will by necessity be brief.

(3) However, where the leaflet for a medicinal product is relying on the user test submitted in support of a leaflet for a medicinal product in a different therapeutic class, a more fulsome report will be required.

VII. 1. Identifying the Key Messages for Safe Use

Art. 26. – (1) 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.

(2) 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.

(3) Synergies and similarities in the key messages should be discussed.

VII. 2. Design and Layout Issues

Art. 27. - 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.

VII. 3. Complexity of Message and Language Used

Art. 28. – (1) A critical discussion of the complexity of the messages contained within the "parent" and "daughter" PLs should be presented.

(2) The language used in both PLs should be discussed and compared.

(3) Again similarities and synergies should be discussed.

Art. 29. - All reports should address any general issues raised by participants in the user test concerning aspects of the PL which they liked or disliked.