The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

CPMP/EWP/239/95 final

CPMP

NOTE FOR GUIDANCE ON THE CLINICAL REQUIREMENTS FOR LOCALLY APPLIED, LOCALLY ACTING PRODUCTS CONTAINING KNOWN CONSTITUENTS

DISCUSSION IN THE WORKING PARTY	SEPT. 92-OCTOBER 94
TRANSMISSION TO THE CPMP	OCTOBER 1994
TRANSMISSION TO INTERESTED PARTIES	OCTOBER 1994
DEADLINE FOR COMMENTS	15 APRIL 1994
RE-SUBMISSION TO THE WORKING PARTY	OCTOBER 1995
RE-SUBMISSION TO THE CPMP	NOVEMBER 1995
FINAL APPROVAL BY THE CPMP	NOVEMBER 1995
PROPOSED DATE FOR COMING INTO OPERATION	JUNE 1996

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CLINICAL REQUIREMENTS FOR LOCALLY APPLIED, LOCALLY ACTING PRODUCTS, CONTAINING KNOWN CONSTITUENTS

Note for Guidance
[EMEA status as of November 1995]

This guideline should be read in conjunction with Directive 65/65 /EEC as amended, the Note for Guidance on abridged application (III/3879/90), the Notice to Applicants for the new system and, where relevant, the Note for Guidance on non-clinical local tolerance testing of medicinal products.

Introduction

This Note for Guidance defines the clinical requirements (part IC3, IV of a dossier) for locally applied, locally acting products with a known active substance.

Locally acting products are products which are applied locally and are assumed to exert their effect at the site of application; systemic action, if any, would be considered as an undesired effect. Examples are dermatological products (e.g. creams, ointments), inhalatory products like powders or aerosols for inhalation. eye drops, ear drops, nasal products. but also orally, vaginally, or rectally applied products which act locally (see also: Note for Guidance CPMP list for allowed terms III/3593/91).

In these products a change in formulation or in dosage form may influence the efficacy and /or safety- of the product. This may occur for instance by changing the physicochemical properties of the product or by changing the non-active ingredients and thereby the extent of penetration of the active compound. Moreover, at least in dermatology, the vehicle itself may influence the disorder.

None of these products can be considered essentially similar. However, full toxicological and clinical data would not normally be necessary. Abridged applications for locally acting products should therefore be regarded as hybrid applications. Omission of data should be justified in the expert reports. Also in case of a type II variation, therapeutic equivalence with the original product has to be ensured. Choice of studies and omission of data have to be justified in the expert reports.

Application for a locally acting product with a known active substance, not used locally before

With regard to the clinical dossier, either a full dossier or appropriate bridging studies may be required, depending on the product.

Abridged applications

As is the case for systemically acting products, it is necessary to show for locally acting products that the product to be approved (either a generic or a reformulated product) is therapeutically equivalent to the product already approved i.e. that both products are “equivalent" with regard to efficacy and safety, so that data generated for the "innovator"

product (i.e. a product for which the marketing authorisation has been obtained on the basis of a dossier with full documentation) apply also to the other product.

In order to demonstrate therapeutic equivalence clinical trials are in principle necessary, especially for locally applied dermatological preparations but other models may be used or developed. For this purpose, depending on the situation, human pharmacodynamic studies, local availability studies or where appropriate even animal or in vitro studies can be considered, provided that all studies used are adequately validated. Moreover, safety and local tolerance have to be addressed appropriately.

EFFICACY

Clinical studies

It is important to note that criteria and norms for 'equivalence' have to be defined beforehand and that the number of patients should be determined in the protocol prior to the trial, using appropriate statistical methods. The limits between which a product is still defined as being "equivalent" depend on the compound to be studied and the parameters used, so a reference to the bio-equivalence guideline, where a variation of 20% is found acceptable in most cases, is not acceptable as such.

Also, to show therapeutic equivalence, a difference from placebo as such is not enough. Depending on the placebo response expected and the need for a 'negative' control, 3-arm studies comparing placebo, the new product and the product already approved may be necessary, though two-arm comparative studies may be sufficient (see biostatistical guideline). The choice of the study set-up has to be justified.

Other models

If instead of clinical trials another model is chosen to show therapeutic equivalence the relevance of this model must be demonstrated/justified, i.e. the model must be validated: in particular its relationship with the therapeutic situation must be demonstrated. It should be noted that at the moment very few models are available and most of them have not (yet) been validated sufficiently.

For locally applied products bio-equivalence generally is not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety.

SAFETY

Generally safety and local tolerance may be guaranteed by knowledge of the active substance and the choice of known inactive ingredients, although certain additional studies of the whole product (as a mixture of the active substance and all inactive ingredients) may be necessary in animals as well as in human subjects.

If it is expected or shown that the amount of active ingredient reaching the site of action and/or the systemic circulation is higher than for the original product appropriate toxicological data

and human safety data may be necessary. In some cases, argumentation that these data are not necessary, may be acceptable and should be justified in the expert report.

Also if inactive ingredients used for the first time in pharmaceuticals are used, appropriate toxicological, pharmacological and human safety data will be required, both to show, that the compound is indeed inactive and safe and to detect interaction with the active ingredient, if any.

All these situations have to be addressed in the expert reports and the choice of data or lack of them has to be justified.

Moreover, when assessing the risk of the new product the fact that the disorder itself may influence the absorption / penetration of the locally applied compound and therefore the need of patient safety data, has to be taken into account.

OTHER INFORMATION

If specific claims are made for a reformulated product, these have to be substantiated with relevant data.

Type II -variations

In case of a change in formulation not requiring a new (abridged) application but capable of being dealt with as a type II variation, therapeutic equivalence should be addressed including, when appropriate, local tolerance. Generally the same data will be required as are indicated above for an abridged application. In case of minor variations argument that these data are not necessary, may, be acceptable. However this should be justified in the expert reports.

SUMMARY TABLE

Requirements for the clinical dossier on locally applied/locally acting products

I	known active ingredient, not used locally before	full dossier, or appropriate bridging studies
II	abridged/hybrid application	
a.	different indication	relevant clinical studies
b.	different dosing schedule	relevant clinical studies
c.	different strength, but usual dosing schedule	if possible pharmacodynamic studies or local availability studies; possibly in vitro studies (e.g. eye drops) or argumentation in case of minor differences. Otherwise clinical studies. Any safety issue has to be addressed appropriately .
d.	different formulation (e.g. cream Æ ointment; aerosol Æ powder for inhalation)	clinical studies to demonstrate efficacy/safety and/or if possible pharmacodynamic studies; if necessary, studies of absorption, penetration and local tolerance
e.	generic products	see II c
III	type II variations	
a.	change in active ingredient(s) \with regard to specification of the physical properties	see II c
b.	change in inactive ingredient(s)	see II c
c.	change in application with regard to application device (e.g. inhalation chamber)	see II c

In categories II a, b and d partial reference to the original dossier is possible; however relevant studies must be submitted.

In categories III a-c and generics (category II e) therapeutic equivalence with the previously approved product must be demonstrated. If possible this may be achieved via validated models. In some cases, if only minor changes are proposed, which are not considered to be of significance in terms of safety/efficacy, the absence of data may be justified in the expert reports. For the time being, however, clinical studies will be required in many cases.

It should be noted there is often no clear distinction between the categories in the table. In dermatological products the addition for instance of a penetration enhancer falls under III b but makes more extensive investigations as under II d necessary.

For all categories described in the summary table expert reports should provide a critical account of the choice of studies or provide adequate justification for their absence.