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REVIEW ARTICLE

Current guidelines applicable for the approval of topically applied dermatological drugs in the EU

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ABSTRACT

Dermatologicals as well as other medicinal products are submitted to the rules governing medicinal products in the European Union (EU) (Directive 2001/83/EC). With appreciation of the EU enlargement those regulatories deserve a recent consideration with special regard to the peculiarities of external dermatological therapy, recently passed novel and future guidelines. As regards the criteria for authorization of a medicinal product it is set out in Regulation (EEC) 2309/93 Article 11(1) that a marketing authorization shall be refused if it appears that the quality, the safety or efficacy of the medicinal product have not been adequately or sufficiently demonstrated by the applicant. Article 26(1) of Council Directive 2001/83/EC is worded a little differently but the criteria are the same irrespective of the procedure for the marketing authorization. For the final evaluation of the benefit/risk profile of a topically applied dermatological medicinal product not only the active agent but the whole galenic formulation as well has to be taken into account as the extent of penetration of the active compound might be influenced by changing the non-active substances. Furthermore the vehicle itself – independent of the active agent – influence the dermatological disorder, often in dependence on the stage of the dermatopathy. With special concern to safety/tolerability the (photo)toxic and (photo)allergic potential of the dermatological drug have to be taken into consideration too. In case of total body therapy in children the differing percutaneous resorption due to another body surface/body weight relation deserves special concern. The following review gives a survey of the current most important EU-guidelines for the evaluation of the benefit/risk profile of topically applied dermatological medicinal drugs and an outlook on further developments. As systemically applied dermatological medicinal products are assessed like other systemically applied drugs they are not treated in the following contribution.

INTRODUCTION

In the European Union (EU), the requirements and standards for clinical trials using medicinal products are set out in regulations, directives and guidelines. The legislation provides for flexibility in the type and design of trials required for the demonstration of efficacy and safety. Annex I of Council Directive 2001/83/EC states that 'in general clinical trials shall be done as controlled clinical trials if possible, randomized and as appropriate vs. placebo and vs. an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control group will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo' [1,2].

Table I CPMP-guidelines for the evaluation of the benefit/risk ratio of topical drugs.

Clinical requirements for locally applied, locally acting products, containing known constituents
Fixed-combination medicinal products
Clinical investigation of medicinal products in children
Note for guidance on clinical investigation of medicinal products indicated for the treatment of psoriasis
Clinical investigation of corticosteroids intended for use on the skin
A guideline on summary of product characteristics
Excipients in the label and package leaflet of medicinal products for human use
Non-clinical local tolerance testing of medicinal products

In external dermatological therapy a change in formulation (or in dosage form) may influence the efficacy and/or safety of the product [3–5]. By changing the non-active substances the extent of penetration of the active compound may influence the disorder. The vehicle deserves special concern with particular regard to the stage of the dermatopathy. For example, if a cream vehicle will be chosen for acute forms of atopic dermatitis the question arises how long this therapy will be tolerated by patients whose stage of atopic dermatitis changes from acute to subacute or chronic, i.e. when regularly a formulation with a more grease vehicle would be preferred. Theoretically an increasing exsiccation effect – because of the inadequate vehicle with consequently less refatting character – might worsen the disease (the choice of the vehicle is dependent on the stage of the dermatitis).

In external therapy in acute resp. subacute stages the treatment is vehicle-accentuated (solutions, lotions, pastas) – in those cases an active agent is often superfluous – in more subchronic resp. chronic stages the active agent gains more importance [6].

The following guidelines should be regarded as help and not as (general) directions for the final evaluation of the benefit/risk ratio of external dermatologicals; a convincing benefit/risk profile is the prerequisite for the approval on the German resp. European market [1,2,7,8] (*Table I*).

CLINICAL REQUIREMENTS FOR LOCALLY APPLIED, LOCALLY ACTING PRODUCTS, CONTAINING KNOWN CONSTITUENTS (CPMP/EWP/239/95)

This guideline should be read in conjunction with Directive 65/65/EEC (Directive 2001/83/EC), as amended, the notice to applicants and, where relevant, the note for guidance on 'Non-clinical local tolerance testing of medicinal products'.

Locally acting products 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*, inhalatory products like powders or aerosols for inhalation, eye- and ear drops, nasal products but also orally, vaginally or rectally applied products to act locally.

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 or by changing the non-active substances and thereby the extent of penetration of the active compound. Moreover, at least in dermatology, the vehicle itself may influence the (dermatological) disorder.

For locally applied products bioequivalence generally is not a suitable way to show therapeutic equivalence as plasma levels are not relevant for local efficacy, although they may play a role with regard to safety. Generally safety and local tolerance may be guaranteed by knowledge of the active substance and the choice of known inactive substances, although certain additional studies of the whole product (as a mixture of the active substance and all inactive substances) may be necessary in animals as well as in human subjects.

When assessing the risk of the 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 as well (*Table II*).

FIXED-COMBINATION MEDICINAL PRODUCTS (CPMP/EWP/240/95)

Note for guidance concerning the application of section C.6 Part 4 of the Annex to Directive 75/318/EEC (Directive 2001/83/EC), as amended, with a view to the submission of an application for a marketing authorization for a new medicinal product. This guideline should be read in conjunction with current EC guidelines (e.g. biostatistical methodology in clinical trials; dose–response information to support product authorization).

Each substance of the fixed combination must have documented contribution within the combination, that is to say the presence of each active substance should make a contribution to the claimed effect; the dosage of each substance within the fixed combination must be such as

Table II Important aspects of the guideline 'Clinical requirements for locally applied, locally acting products, containing known constituents'.

Applied for: dermatological drugs, inhalatory products, eye- and ear drops, nasal, orally, vaginally, rectally applied products to act locally
Peculiarity: extent of penetration depends on physicochemical properties; the vehicle itself may influence the (dermatological) disorder
Bioequivalence: generally not applicable to show therapeutic equivalence as plasma levels are not relevant for local efficacy (but for safety concerns)
Assessing the risk: the disorder itself may influence the absorption/penetration of the topically applied drug, consequently the need of patient safety data has to be taken into account

the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone.

Potential advantages of fixed combinations include:

1. An improvement of the benefit/risk assessment due to:
- **i.** Addition or potentiation of therapeutic activities of their substances, which results in:
  - **a.** a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile; or
  - **b.** a level of efficacy above the one achievable by a single substance with an acceptable safety profile;
- **ii.** The counteracting by one substance of an adverse reaction produced by another one.

2. A simplification of therapy which improves patient compliance. When it is the only claim, it would be restricted to particular situations (e.g. non-prescription products)

Disadvantages of fixed combinations include:

1. The fact that even a combination which meets the needs of the average patient is unlikely to be ideally adjusted for the needs of each individual patient;

2. the addition of the different adverse reactions specific to each substance.

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN CHILDREN [9]†

This note for guidance should be read in conjunction with Part 4 of Directive 75/318/EEC (Directive 2001/83/EC), as amended, which requires '…details concerning patients who may be at increased risk' and is intended to assist applicants in its application in respect to specific problems presented by medicinal product testing in children.

Medicinal product testing in children is a difficult topic. A controlled trial in children involves certain technical and ethical problems which are not of such magnitude in adults. Apart from the ethical view from a physiological and pathological standpoint, children, especially very young children, cannot be considered as small adults; reasons are:

1. *Pharmacokinetic peculiarities*: These are well known in the premature infant and in the first weeks of life (e.g. modification of penetration/absorption, limited capacity of elimination because of the immaturity of metabolic pathways and renal function, small volumes of distribution). In later infancy and early childhood, faster rates of biotransformation and relatively increased volumes of distribution may necessitate the administration of higher doses per unit of body weight or surface area than in adults in order to obtain identical plasma levels.

2. *Altered pharmacodynamic responses*: For example, immature receptor functions and effector systems.

3. *Specific age-related vulnerability*: As organ functions mature, there is a risk that medicinal products may adversely affect development (e.g. weight gain and retarded growth with corticosteroids).

4. *Specific pathology*: Children may need medicinal products for diseases which differ from adults either because of increased frequency, severity, specific pathology [e.g. often bacterial superinfection (secondary impetiginization) in (atopic) dermatitis].

Medicinal products should not normally be tested in children until complete animal studies (including pharmacology, pharmacokinetics, acute and chronic toxicitiy, carcinogenicity, mutagenicity, and reproduction studies) have been performed. Data should be generated before marketing authorization not only when a medicinal product to be used wholly or mainly in children but also for reasons of public health when a new medicinal product is likely to be used in children because of its uniqueness (a novel therapeutic effect which is particularly applicable to a pediatric disease or a convenient dosage form) *and* a medicinal product represents a major therapeutic advance and is likely to be used in children. An undergone post-marketing surveillance is very important in order to detect adverse effects and information on efficacy; this will enable the dosage schedule and data sheets to be updated early in the lifetime of the approved medicinal products.

†Based on this guideline the International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use (ICH) passed a further corresponding guideline, CPMP/ICH/2711/99, ICH 11.

NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PSORIASIS (CPMP/EWP/245402)

This 'brand-new' guideline draft was recently finished and circulated in pharmaceutic industry. These notes are intended to give guidance to applicants in planning the overall clinical development studies of new compounds to demonstrate clinical efficacy and safety. They are for guidance only. This note should be read in conjunction with Directive 75/318 (Directive 2001/83/EC), as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations (e.g. dose–response information to support drug registration/ICH E4, clinical investigation of medicinal products in children, see above/ICH topic E11 [10] – The International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use [ICH] is a unique project that brings together the regulatory authorities of Europe, Japan and the US and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration).

This guidance focuses mainly on development of topical and systemic treatments of 'chronic plaque psoriasis'. Although general principles of this guidance can be extrapolated to the evaluation of drugs indicated for severe forms of psoriasis with systemic impairment (such as psoriatic erythroderma, generalized pustular psoriasis, psoriatic arthritis), these forms are not within the scope of this guideline (*Table III*).

Characteristics of chronic stable plaque psoriasis

Chronic stable plaque psoriasis is the commonest form of the disease (psoriasis vulgaris), accounting for 85–90% of cases. The circumscribed infiltrated skin lesions are silvery-white scaly and erythematous and often symmetrically distributed over the body. Topical agents are expected to be evaluated in patients with mild and moderate psoriasis. If justified, topical agents might also be evaluated in patients with more severe forms. In certain circumstances a beneficial safety profile of a systemically administered product could justify systemic treatment also in more moderate disease. Patients with flexural, scalp, nail, palmar and plantar lesions are important to study in clinical trials. As these areas may react differently, i.e. may respond more quickly or slowly to treatment than lesions of disseminated chronic plaque psoriasis elsewhere, they should be evaluated in separate trials. In addition, the efficacy evaluation of these forms of psoriasis may differ from that recommended for disseminated chronic plaque psoriasis.

Psoriasis in children and pregnancy

Psoriasis in children is quite common (it begins in childhood in 3% of patients), especially guttate psoriasis and classical plaque psoriasis. Pregnancy has no effect on chronic plaque psoriasis in about half of patients, but improvement is more common than the worsening. Both in children and during pregnancy, even in cases with severe forms of chronic plaque psoriasis, topical treatments are preferred to systemic ones due to toxicity.

However, due to a possible systemic passage of topically applied agents, therapeutic trials are not performed in pregnant women. If there are no particular safety concerns, specific studies in children with plaque psoriasis are not warranted.

Efficacy studies may be necessary when specific locations (e.g. face) or forms of psoriasis (guttate psoriasis) are aimed to be studied. In case of safety concerns, pediatric studies should specifically focus on long-term potential systemic effects, especially in very young children.

In elderly, psoriasis characteristics are similar to those in general adult population and specific trials are generally not necessary.

Table III Most important aspects of 'Note for guidance on clinical investigation of medicinal products indicated for the treatment of psoriasis'; it should especially be read with the included guidelines and regulations.

Applied for: topical and/or systemic therapy of chronic plaque psoriasis

Excluded: severe forms of psoriasis such as psoriatic erythroderma, generalized pustular psoriasis, psoriatic arthritis

To be read with: Directive 75/318 (Directive 2001/83/EC), dose-response information to support drug registration (ICH E4, CPMP/ICH/378/95), statistical principles for clinical trials (ICH topic E9, CPMP/ICH/363/96), choice of control group in clinical trials (ICH E10, CPMP/ICH/364/96), the extent of population exposure to assess clinical safety (ICH E1A, CPMP/ICH/375/95), fixed-combination medicinal products (EU), pharmacokinetic studies in Man, note for guidance on the investigation of drug interactions (CPMP/EWP/560/95), clinical investigation of medicinal products in the pediatric population (ICH topic E11, CPMP/ICH/2711/99)

Safety

Topical treatment usually allows a reduction in systemic exposure and hence an increase in the margin of safety. However, specific data concerns may arise from the topical administration and for these agents local adverse effects including skin atrophy should be assessed as well as the extent of systemic absorption and the potential systemic effects [11]. Long-term safety is of primary importance in psoriasis as this is a chronic condition and safety data beyond 1 year may be requested, especially for new systemic agents, based on new pharmacological mechanisms. These agents may be subjected to post-approval long-term surveillance studies. Depending on the product these may focus on events related to carcinogenic effects such as skin and lymphoproliferative malignancies as well as other immunosuppressive effects such as potential for infections, suppression of humoral and cell immune response and possible potential for induction of auto-immunity. Cohort studies, case–control and/or registry studies are very valuable and should be started as soon as possible after marketing authorization with a duration of at least 5 years to evaluate the effects of systemic treatment.

Efficacy

Among the different measures [e.g. visual assessment of index lesions, physician's global assessment of improvement, psoriasis area and severity index score (PASI)], visual assessment of index lesions is the endpoint particularly adapted to proof-of-concept and early therapeutic exploratory trials with topical agents, because it acceptably reflects a global response of psoriatic lesions. Among skin signs, induration is considered the most critical, scaling the least. Due to moderate incidence of pruritus, this symptom is not considered pivotal in psoriasis. PASI score has been the most frequently used primary endpoint in therapeutic confirmatory trials. However, clinical significance of observed changes is not always well understood; furthermore PASI combines the evaluation of plaque changes (erythema, squames, induration) and of plaque surface, the evaluation of which is always subjective. This is further complicated my multiplying the obtained result by the constant weighed value assigned to each body part; furthermore PASI score is not adapted for palmo-plantar, flexural, scalp and nail locations of psoriasis. For all these forms, there are no validated tools to assess efficacy; local skin signs and physician's global assessment can only be used. For nail psoriasis, the number of healthy nails after treatment can also be assessed.

Up to now, there is no accepted definition of what constitutes meaningful clinical improvement in psoriasis. In a majority of clinical trials using PASI, both >50% and >75% improvements compared with baseline have been considered as clinically meaningful. However, except for patients 'cleared or almost cleared' on a global scale (correspond to PASI >90% improvement), the clinical relevance of less important PASI is always subject for discussion.

CLINICAL INVESTIGATION OF CORTICOSTEROIDS INTENDED FOR USE ON THE SKIN (EUDRALEX VOL. 3C)

This note for guidance should be read in the light of the Annex to Directive 75/318/EEC (Directive 2001/83/EC), as amended, and is intended solely to assist applicants in the interpretation of the latter with respect to specific problems presented by topical forms of corticosteroids. To be locally effective, corticosteroids must penetrate the skin [12]. The extent of absorption and therefore the clinical activity, as well as most of the adverse reactions, have been demonstrated to depend, both on the substance itself and, for a given corticosteroid, on several factors (*Table IV*).

The influence of these different factors should be taken into consideration during clinical trials. With the majority of corticosteroids, under normal conditions of use, it is not the possible systemic adverse effects due to percutaneous resorption which are the first concern, but the often irreversible local adverse effects on the skin, such as the following.

Possible side effects

Skin atrophy, tele-angiectasia, purpura, striae, rosacea-like and perioral dermatitis, rebound which may lead to steroid 'dependence', impairment of healing, effects on the eye, increased risk of glaucoma, cataract, exacerbation of mycosis and of herpes simplex, miscellaneous: depigmentation, hypertrichosis, contact allergy (caused by the active agent and/or the excipients of the product), etc. The risk of systemic effects increases with applications over large areas, use of large amounts of material and prolonged administration. Corticosteroid-induced vasoconstriction in man provide a preliminary rough but useful guide to topical anti-inflammatory activity [13,14]. Other methods can also be used or are currently under development. It is not considered desirable to specify particular methods of investigation as obligatory.

In the case of products for which the manufacturer wishes to claim the treatment of chronic conditions in an

Table IV The extent of absorption and consequently clinical activity and side effects are dependent on several, above-mentioned factors.

Concentration of the substance: however, above a certain concentration in a given vehicle, a further increase in concentration does not result in a proportionately greater effect but does increase the occurrence of adverse reactions.
Pharmaceutical formulation: the penetration of the active substance depends on the phyico-chemical properties of the vehicle. The presence of other active substances, components or excipients can modify the penetration through the stratum corneum and/or the effect (e.g. salicylic acid, urea, propylene glycol, antibiotics and antiseptics, tar)
Site of application: a thick stratum corneum is responsible for the weak penetration in areas such as soles and palms. Because of opposite conditions, a higher absorption may occur, for example, through mucosa, the scrotal skin, eyelids, and to a somewhat lesser extent, the skin of the forehead and the hair zone of the head.
Skin condition: penetration is increased in damaged skin (e.g. abrasion or pathological situations like parakeratosis). Damaged stratum corneum, however, often recovers within a few days of treatment.
Conditions of application: occlusion promotes the penetration, it may be unintentionally produced by napkins in babies or may result from application in intertriginious areas resp. flexures

area of high absorption, an investigation of absorption will have to be performed after application to this area. If the product is to be recommended for use in young children, systemic effects should also be recorded in this age group, but particular attention should be given to the ethical aspects of such an investigation. Examples for levels of activity of known corticosteroids are: very strong, clobetasol propionate 0.05%; strong, betamethasone valerate 0.1%; hydrocortisone butyrate 0.1%; mild, hydrocortisone 1% [14].

Examples for indications in relationship to their level of activity

Very strong activity: localized and resistant plaques of psoriasis, lichenification, discoid lupus erythematosus; strong activity: psoriasis, lichen planus, lichen sclerosus and atrophicus, granuloma anulare, mycosis fungoides; moderately strong activity: atopic dermatitis, nummular/irritant/allergic contact dermatitis; mild activity: seborrhoeic dermatitis, stasis dermatitis, ano-genital pruritus.

A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Article 4a of Directive 65/65/EEC (Directive 2001/83/EC), as amended, a proposal for a summary of product characteristics (SPC) must be included in the application. Part 1 B consists of the proposal for the SPC. Further, Article 4b of Directive 65/65/EEC requires that the content must be approved by the competent authority. Thus the SPC forms an intrinsic and integral part of the marketing authorization. The SPC is the basis of information for health professionals on how to use medicinal product safely and effectively. The content of the package leaflet must be consistent with the SPC but in a wording that can be easily understood by non-professionals. The following aspects should be taken into account and implemented (*Table V*).

Table V Points to be considered for the summary of product characteristics (SPC).

Name of the medicinal product
Qualitative and quantitative composition
Pharmaceutical form
Clinical particulars
Therapeutic indication
Posology and method of administration
Contraindications
Special warning and precautions for use
Interaction with other medicinal products and other forms of interaction
Pregnancy and lactation
Effects on ability to drive and use machines
Undesirable effects
Overdose
Pharmacological properties
Pharmaceutical particulars
Marketing authorization holder
Marketing authorization number(s)
Date of first authorization/renewal of the authorization
Date of revision of the text

EXCIPIENTS IN THE LABEL AND PACKAGE LEAFLET OF MEDICINAL PRODUCTS FOR HUMAN USE (CPMP/463/00)

This is a Commission guideline pursuant to Article 65 of Directive 2001/83/EC. It contains warning statements relating to the presence of certain excipients in medicinal products (e.g. propylene glycol and esters, stearyl alcohol). Homeopathic medicinal products authorized through a special simplified registration procedure are

not addressed in this guideline. Article 54(c) requires that all excipients need to be declared on the labeling if the medicinal product is an injectable or a topical, or an eye preparation. In general, excipients may be defined as the constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.

Excipients in the labeling

According to Directive 2001/83/EC, all excipients in parenteral, ophthalmic and topical medicinal products must appear on the labeling. Topical medicinal products can be taken to include those medicinal products applied externally to the skin, respiratory products delivered to the lung by inhalation and any medicinal product delivered to the oral, nasal, rectal or vaginal mucosae, i.e. where the delivery may be local or transdermal.

Excipients in the package-leaflet

According to Article 59(1)(a) of Directive 2001/83/EC, all of the excipients must be stated on the package leaflet by name. Thus, all excipients, as indicated in the section on definitions and examples above, should be declared according to the nomenclature defined in this guideline.

NON-CLINICAL LOCAL TOLERANCE TESTING OF MEDICINAL PRODUCTS

The evaluation of local tolerance should be performed in laboratory experiments prior to human exposure to the product. The purpose of these studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body which may come into contact with the product as a result of its administration in clinical use. The testing strategy should be such that any mechanical effects of administration, or purely physico-chemical actions of the product can be distinguished from toxicological or pharmacodynamic ones. Studies on animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation. Consideration should be given to developments in alternative testing methods.

Dermal tolerance testing

The evaluation of dermal tolerance for products intended for administration to the skin requires a dermal tolerance test by a single administration, a repeated dose dermal tolerance test, an evaluation of sensitizing potential and, in some cases, an evaluation of the phototoxicity and photosensitization potential. Unintentional application of the product to other sites of the body in clinical use (e.g. eyes) should be considered.

As a general rule, the formulation to be used clinically should be used in all tests. If the dose is to be varied (e.g. determination of systemic toxicity by dermal administration), this should be achieved by altering the amount of the product applied and/or by changing the area of administration, as modifications in the concentration or vehicle may lead to non-proportional changes in absorption and local tolerance. Whether or not occlusive dressings are employed depends on the intended clinical use of the product.

Outlook

In order to support resp. improve evaluation of potential side effects of local corticosteroids the therapeutic index (TIX) has been developed. This index expresses the ratio between desired effects and (undesired) side effects: the better the efficacy of a topical corticosteroid, the less its side effects, the higher its TIX. The index has been developed for the (in Germany) mainly used local corticosteroids. Its evaluation is based on the following citeria: according to desired effects – vasoconstriction, efficacy in atopic dermatitis in comparison with several corticosteroids; according to undesired effects – skin atrophy, suppression of the hypophysis-suprarenal gland-axis, allergic potential.

Referring to this evaluation the German Dermatological Society certified mometasone furoate – because of its good antiphlogistic potential and its low risk of induction skin atrophy – the highest TIX in the treatment of atopic dermatitis [15–22].

A comparable evaluation in other dermatoses, such as psoriasis, another very common disease, has not been performed; consequently the TIX may – up to now – only be applied in atopic dermatitis.

Referring to those findings resp. novel considerations the latter mentioned guideline should be revised. At present there exists no guidance for the clinical evaluation of local tolerance of topical dermatological medicinal products. For the assessment of the galenic features of a topically applied dermatological drug resp. of its (photo)toxic and/or (photo)allergic potential a range of different investigation models, varying from chamber-scarification, fast (modified) alkali-resistance-test, repeated open application test, (photo)patchtesting – according to International Contact Dermatitis Research Guidelines resp. German Contact Dermatitis Research Group guidelines, are used [8,18,21,23–28]. At present there is no

standardized procedure to evaluate irritant potential of external dermatological drugs in humans resp. patients. Consequently a future guideline that helps the pharmaceutic industry to conduct standardized reproducible test methods in order to evaluate the local tolerance of dermatologicals would be of good service.

For the assessment of topically applied dermatological drugs further recommendations of dermatological expert societies – apart from the above-mentioned official resp. administrative guidelines – are of high scientific interest.

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