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Guideline on non-clinical local tolerance testing of medicinal products

Draft

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The proposed guideline will replace the 'Note for Guidance on non-clinical local tolerance testing of medicinal products' (CPMP/SWP/2145/00).

Comments should be provided using this template. The completed comments form should be sent to SWP-H@ema.europa.eu

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1. Introduction

Local tolerance testing is intended to support human exposure to a medicinal product (both active substance and excipient) at contact sites of the body following clinical use. Although the final formulation may not be confirmed until late in clinical development, local tolerance testing should aim to support initial testing in clinical trials, as well as intending to support the final product. The non-clinical study design should aim to distinguish between any mechanical consequences of administration, or purely physico-chemical actions of the product, from toxicological or pharmacodynamic effects.

It is recommended that evaluation of local tolerance by the intended clinical route of administration is included as part of the general toxicity studies.

Wherever possible, studies on animals should be substituted by validated *in vitro* tests in accordance with Directive 2010/63 on the Protection of Animals Used for Scientific Purposes. Where no alternative method is recognised by the legislation of the Union, the numbers of animals used may be reduced by resorting to other methods and by implementing testing strategies, such as the use of *in vitro* and other methods that would reduce and refine the use of animals.

2. Scope

This document provides guidance on the non-clinical strategies to be considered when developing a drug product (both active substance and excipients) that will, or potentially could, come into contact with different sites of the body following normal clinical use, as well as after unintentional administration.

Studies on impurities arising from the active substances or excipients present in the drug product or extracted or leached from a container closure system are not covered by this guideline.

The principles outlined in this guidance should be applicable to all types of drug products, including biotechnology-derived pharmaceuticals and herbal products.

3. Legal Basis

This guideline should be read in conjunction with Directive 2001/83 as amended, Directive 2010/63 and all relevant ICH and CHMP guidelines. The guideline is also applicable for Clinical Trial Applications in line with EU Regulations.
With respect to animal husbandry, the Council Directive on 2010/63 and Council Decision on the European Convention on the protection of vertebrate animals, (1999/575/EC) should also be taken into account.

Studies should be carried out in conformity with the provisions relating to good laboratory practice (GLP) laid down by Council Directives 87/18/EEC and 88/320/EEC.

4. General Considerations with Regard to Local Tolerance Testing

Tolerance should be determined at those sites that come into immediate contact with the medicinal product as a result of the method of administration. This should be taken place before the first trials in humans with any formulation.

In addition, for those sites that might come into contact through accidental or unavoidable exposure to the product, an evaluation for local tolerance should be conducted before exposure of large numbers of patients (*e.g.*, Phase III clinical trials).

The site of administration can be the same organ or tissue which is intended to be the therapeutic target (*e.g*. the skin for externally administered dermatological products, the eye for ophthalmic medicinal products), or the site of administration can be remote from the intended therapeutic target (*e.g*. transdermal patches, intravenous (*iv*) administered medicinal products).

In order to reduce the number of animals as much as possible, local tolerance testing should if possible be part of other toxicity studies, and efforts should be made to include appropriate endpoints. "Stand alone" studies on local tolerance are generally not recommended.

In vivo testing should not be undertaken until all available data relevant to the potential adverse effects of the substance have been evaluated in a weight-of-the-evidence analysis. Such data will include the physico-chemical properties of the product in its intended formulation, findings from one or more structurally related substances, and results from *in vitro* or *ex vivo* studies using validated assays.

For an *iv* microdose study that is supported by an oral toxicology package (see ICH M3R2 - CPMP/ICH/286/95), evaluation of local tolerance of the drug substance is not warranted. However, if a novel vehicle is being employed for such a study, then local tolerance of that vehicle should be assessed.

To support limited human administration by non-therapeutic routes (*e.g*., a single *iv* dose to assist in the determination of absolute bioavailability of an oral drug), a single dose local tolerance study in a single appropriate species can be considered appropriate. In cases where the anticipated systemic exposure (AUC and C_{max}) from the non-therapeutic administration is covered by the existing toxicology package, the endpoints in the local tolerance study can be confined to clinical signs and macroscopic and microscopic examination of the application site.

A justification is needed if the formulation used for local tolerance testing is not identical to the intended clinical formulation.

5. Points to consider in the design of local tolerance tests

5.1. Choice of Species

The choice of species should be chosen in relation to the intended route of administration of the product and on the endpoints to be investigated. Usually, an evaluation in one species and in a single sex should be sufficient. If two or more different endpoints need to be investigated in the same study, a species appropriate to the test will need to be used.

5.2. Frequency and Duration of Administration

The frequency and duration of administration to animals should be determined by the proposed conditions of administration in clinical use. However, if local tolerance is being assessed in a "stand alone" study, the application period should generally not exceed four weeks. Investigation of local tolerance to mimic "accidental administration" may be performed using single dose studies.

5.3. Reversibility

Additional groups of animals to assess reversibility are usually not needed and should only be considered when it is anticipated that there will be findings that merit particular investigation.

5.4. Preparation to be Tested

Local tolerance testing should be conducted with the intended final product in man, using the vehicle and/or excipients in treating the control group(s). A justification will have to be made when the clinical preparation is not used. Positive controls/reference substances are not considered to be necessary.

5.5. Choice of Dose

It is not considered essential to demonstrate the maximum tolerated dose (MTD) in local tolerance studies. The actual concentration of active substances to be used in humans should be tested. The dose may then be adjusted by varying the frequency of administration. Other regimens are discussed in the sections pertaining to the individual routes of administration.

5.6. Animal Welfare

Animal welfare should be a high priority when investigating local tolerance. Care should be taken to minimise exposure of animals to irritants by terminating the experiments before the point where severe adverse reactions are seen and the continuation is not expected to provide results essential for risk assessment.

5.7. Route of Administration

The route of administration in the test model has to be selected according to the envisaged route od administration for humans. The anatomy and physiology of the application site in the selected test model have to be taken into consideration when selecting dose levels and frequency of administration. Testing different routes of administration in the same animal should be avoided. Contra-lateral administration of the control preparation is acceptable if it does not compromise the scientific integrity of the study, and the welfare of the animal.

5.8. Evaluation of Results

The overall evaluation of results should include a discussion on the adequacy of the design of the local tolerance test and on the significance of the findings for the clinical use of the product.

6. Testing procedures for particular routes of administration

Guidance on testing procedures by common routes of administration is given below. For routes not mentioned, the General Consideration and the Points to Consider (sections 4 and 5) should be adequately applied.

6.1. Ocular Tolerance Testing

The type and extent of ocular tolerance testing will be determined by the context in which the eyes are exposed to the product. The evaluation of ocular tolerance is also necessary for products which are not intended to be administered to the eye, but which might reasonably be expected to result in exposure during the course of their normal clinical use (*e.g.* lotions or gels used for the treatment of the skin of the face, medicinal shampoos, *etc*.). In these cases an ocular tolerance test using a single administration should be performed.

Consideration should be given to the inclusion of validated *in vitro* tests. However, it should be appreciated that such tests are generally used, under certain circumstances and with specific limitations, to classify substances as "ocular corrosives and severe irritants". A product being

developed for ocular use or one that might reasonably be expected to result in exposure during the course of their normal clinical use, is unlikely to be a severe irritant Products that are intended to be repeatedly administered to the eye, therefore, will require more extensive testing than those for which accidental exposure may occur and *in vivo* studies may be required. However, for ocular products, the local tolerance testing should be part of the general toxicity studies as stated in Sections 1 and 4.

Investigations on the different tissues in contact with the product as well as of the lens, the vitreous body and the ocular fundus should be included. The areas surrounding the eyes, including the lids, conjunctiva, nictitating membrane, cornea and iris, should also be examined during the test. Investigations on the anaesthetising properties of the administration compound should also be included.

Histopathological examination should be considered on a case-by-case basis.

An evaluation of potential photosafety should be undertaken (see ICH S10), in order to determine the need for specific testing in this respect.

6.2. Dermal Tolerance Testing

The complete evaluation of dermal tolerance for products intended for administration to the skin requires a repeated dose dermal tolerance test, and evaluation of sensitising potential. A photosafety evaluation should be undertaken (see ICH M3 R(2) and ICH S10). Medicinal products applied to the skin in order to obtain systemic effects as well as new vehicles should be tested in a similar manner to the above.

Unintentional application to other sites of the body when the product is used clinically (*e.g.* the eyes) should also be considered. As a general rule, the formulation that is intended to be used clinically should be used in all tests. If a range of doses is to be tested (*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, since modifications of the concentration of the formulation or of the vehicle may lead to non-proportional changes in absorption and/or local tolerance. Whether or not occlusive dressings are employed depends on the intended clinical use of the product.

Irritancy tests are generally performed in the rabbit or minipig, often on shaved intact skin and on an equivalent area of shaved and abraded skin. It should, however, be noted that abrasion can lead to an oversensitive model, and that the need to use it should be evaluated on a case-by-case basis. Alternatively, minipigs may be another species of choice, as their skin is anatomically more similar to humans. Vehicle controls should be included. The skin should be examined to evaluate the degree of erythema, oedema, desquamation, scab formation and any other lesions. The duration of the study will depend on the changes observed at 24, 48 and 72 hours after administration. If the changes persist, observation may in some cases be necessary for up to 8 days after administration and may require amendment to the original protocol.

Histopathological examination should be conducted unless a justification can be made why this need not be undertaken.

Consideration should also be given to the type and amount of any degradation products produced. Where appropriate these products should be characterised and evaluated separately, using literature data, *in silico* methods and or *in vitro* studies. Stand-alone studies in animals are generally not expected to characterise degradation products.

6.3. Transdermal Systems

Transdermal systems can be either immediate or delayed/prolonged release. The systems frequently include permeation enhancers and pressure sensitive adhesives, materials that help in maintaining an intimate contact between the transdermal system and the skin surface.

The complete transdermal system should be tested for local tolerance, rather than separate tests on the individual components and the test material, even if the components have been tested previously. Ideally, the systems should be tested in a similar manner to clinical use, *i.e.* not under occlusion. The duration of the animal study will depend on the intended clinical use duration.

Histopathological examination should be conducted, unless a justification can be made why this need not be undertaken.

Consideration should be given to the type and amount of any degradation products produced. Where appropriate these products should be characterised and evaluated separately as discussed above.

6.4. Parenteral Tolerance Testing

Parenteral tolerance testing includes *iv*, intra-arterial (*ia*), intramuscular (*im*), intrathecal, and subcutaneous (*sc*) routes.

According to the intended clinical route, suitable veins of the ear, the tail or the front of hind limbs; central artery of the ear in rabbits, femoral arteries or other suitable arteries in other species; dorsal or femoral muscles; subcutaneous tissue of the lateral chest wall or other suitable application sites can be used.

Evaluation for local tolerance at unintended injection sites need only be conducted if considered appropriate (see section 4 "General Considerations with Regard to Local Tolerance Testing" for information of timings).

6.5. Rectal Tolerance Testing

The envisaged human therapeutic dose volume of the formulation or the maximum applicable volume for the animal species should be used.

Observation of the anal region and anal sphincter, clinical signs and faeces (*e.g*. blood, mucus) should be conducted. Macroscopic and microscopic examination of the rectum should be conducted, unless a justification can be made why this should not be undertaken.

6.6. Vaginal Tolerance Testing

The envisaged therapeutic dose volume of the formulation or the maximum applicable volume for the animal species should be used.

Observation of the vaginal region, clinical signs and vaginal secretion (*e.g*. blood, mucus). Macroscopic and microscopic examination of the vaginal tract and associated reproductive organs should be conducted unless a justification can be made why this should not be undertaken. Additional investigations (*e.g*. effect on cervical mucus, spermicidal action) should be considered case by case.

7. Sensitising potential

For materials applied to skin (dermal, transdermal, rectal or vaginal) the sensitising potential of the material should be evaluated. Evaluation of sensitising potential should be conducted in at least one

approved test system, with the physical chemical properties of a compound being the main rationale for the choice of the assay, *e.g.,* hydrophilic compounds, metal salts and metals should preferably be tested in a guinea pig assay.

The maximum concentration tested should be the highest achievable level avoiding overt systemic toxicity and excessive local irritation. Positive and negative controls need not be included in each test if the testing facility has adequate experience in conducting the assay.

An evaluation of the photosensitisation potential should be conducted for dermal and transdermal products (see relevant ICH Guidance documents).

References

Note for Guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00).

ICH Guideline Photosafety Evaluation of Pharmaceuticals S10 (ICH S10).

ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95).