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Guideline on non-clinical local tolerance testing of medicinal products

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* References update

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Guideline on non-clinical local tolerance testing of medicinal products

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Executive summary

This document provides guidance for the development and evaluation of medicinal products that will, or have the potential to, come into contact with different sites of the human body following normal clinical use, as well as after unintentional administration.

In order to reduce the number of animals as much as possible, local tolerance testing should, whenever 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. Separate studies on excipients with prior clinical safety data are generally not required.

1. Introduction (background)

Non-clinical local tolerance testing is intended to support human exposure to a drug product (both active substance and excipients) at contact sites of the body following clinical use. Such 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 physical consequences of administration, e.g. local trauma following injection, or purely physico-chemical actions of the product from local toxicological or pharmacodynamic effects. Separate studies on excipients with prior clinical safety data are generally not required.

In accordance with Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes, a scientifically satisfactory method or testing strategy, not entailing the use of live animals should be used wherever possible. 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 that would replace, reduce and refine the use of animals. The Guideline on regulatory acceptance of 3R testing approaches should be consulted before conducting non-clinical studies.

It is recommended that if animal studies are necessary for an evaluation of local tolerance by the intended clinical route of administration, such an evaluation is included as part of the general toxicity studies whenever possible, and not as a “stand-alone” study.

2. Scope

This document provides guidance on the non-clinical local tolerance testing to support the clinical development and marketing authorisation of medicinal products for human use. 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 directly 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. However, for biotechnology-derived pharmaceuticals reference should also be made to the ICH S6(R1) guideline.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC, as amended, 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, in addition to the Council Directive on 2010/63/EU, the Council Decision on the European Convention on the protection of vertebrate animals, (1999/575/EC) should also be taken into account.

Any non-clinical studies conducted should be performed in conformity with the provisions relating to good laboratory practice (GLP) laid down by Directives 2004/9/ECand 2004/10/EC.

4. General considerations with regard to local tolerance testing

Local tolerance should be evaluated for those sites that come into immediate contact with the medicinal product as a result of the method of administration. This evaluation, which may not require *in vivo* testing, should take 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) on a case by case basis. A justification as to why *in vivo* testing is not considered to be necessary may be possible.

The site of administration can be the same organ or tissue that 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 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 can include the physico-chemical properties of the product in its intended formulation, literature data, findings from one or more structurally related substances, and results from *in vitro* or *ex vivo* studies using accepted assays (see the guideline on regulatory acceptance of 3R testing approaches).

For an *iv* microdose study that is supported by an oral toxicology package (see ICH M3(R2)), testing for local tolerance of the drug substance is generally not warranted. Similarly, for microdose studies using other routes of administration and standard vehicles, testing for local tolerance of the formulation is generally not warranted. However, if a vehicle containing novel excipients is being employed for a microdose study, then local tolerance of that vehicle should be evaluated and, if necessary, assessed in an appropriate study, preferably *in vitro*.

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 Cmax) 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. If the formulation changes during clinical development, an additional local tolerance evaluation should be considered to determine whether further testing is appropriate. Generally speaking, changes in formulation composition will not necessitate further testing unless the concentration of active substance increases beyond that previously tested or a major change of formulation has been introduced (e.g. novel excipients).

5. Points to consider on *in vitro* local tolerance tests

When using *in vitro* methods, consideration should be given to internationally validated and regulatory accepted OECD methods as well as internationally validated methods not yet included in OECD test guidelines. *In vitro* methods not having undergone international validation could be considered, if scientifically justified, on a case by case basis in a specific context of use (*e.g.* in a weight-of-evidence approach).

Current *in vitro* methods for skin (e.g. OECD TG 439, 437) and eye (e.g. OECD TG 438) irritation cannot fully replace an *in vivo* test. However, these *in vitro* methods may be used as a partial replacement within a tiered testing strategy or as a stand-alone replacement depending on the outcome of the study. As such, within the limitations and applicability, results obtained from a suitable *in vitro* method indicating irritation potential, could obviate further confirmation in a stand-alone *in vivo* local tolerance test.

6. Points to consider in the design of *in vivo* local tolerance

This section only relates to those cases where no validated *in vitro* assay is available or results from *in vitro* testing are inconclusive and local tolerance cannot be assessed as part of another toxicology study.

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, consideration should be given to investigating these in the same study.

6.1. 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, in those cases where local tolerance is being assessed in a “stand-alone” study, the application period should generally not exceed two weeks. Investigation of local tolerance to mimic “accidental administration” may be performed using single dose studies.

6.2. 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.

6.3. 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.

6.4. Choice of dose

It is not considered essential to demonstrate the maximum tolerated dose (MTD) or frank toxicity in local tolerance studies. The actual highest concentration of active substance in the clinical formulation to be used 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. The anatomy and physiology of the application site in the selected test model also have to be taken into consideration when selecting dose levels.

6.5. Animal welfare

Animal welfare should be one of the highest priorities when investigating local tolerance. In cases where unexpected local intolerance occurs, the experiment should be terminated before the point where severe adverse reactions are seen and/or the continuation of the experiment is not expected to provide results essential for risk assessment.

6.6. Route of administration

If an animal study is deemed to be necessary, the route of administration in the test model has to be selected according to the envisaged route of administration for humans. Testing different routes of administration in the same animal should be avoided if it is likely to adversely affect the welfare of an individual animal. 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.

6.7. 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.

7. Testing procedures for particular routes of administration

This section only relates to those cases where no validated in vitro assay is available or the results from in vitro testing are inconclusive, and local tolerance cannot be assessed as part of another toxicology study.

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. For medicinal products administered by the oral route of administration, whether coated or uncoated tablets or oral solutions, local tolerance investigations are considered to be unnecessary unless excipients are used that are likely to have an irritant potential. In such cases, a justification for the use of such excipients would generally be sufficient. In rare cases, a separate single dose study in a single sex may need to be conducted.

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.

7.1. Ocular tolerance testing

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 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, and a “stand-alone” study in a species that might be considered more appropriate to evaluate human risk will not be required.

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, when an in vitro assay is inconclusive

or cannot be used (e.g. out of applicability domain), an ocular tolerance test using a single administration should be performed. In addition, in these cases, a screening approach should be used where the product is applied to a single animal first and an evaluation made before considering whether additional animal testing is necessary.

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 considered.

Histopathological examination should be considered. A justification can be made why this need not be undertaken on a case-by-case basis.

An evaluation of potential photosafety should be undertaken (see Section 8), in order to determine the need for specific testing in this respect.

7.2. Cutaneous tolerance testing

The complete evaluation of cutaneous tolerance for products intended for administration to the skin requires a repeated dose cutaneous tolerance test, and evaluation of sensitising potential. Medicinal products applied to the skin in order to obtain systemic effects, as well as novel vehicles, should also be evaluated.

A photosafety assessment should be undertaken (see Section 8).

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 (see Section 4 for considerations relating to formulation changes during clinical development). If a range of doses is to be tested (e.g. determination of systemic toxicity by cutaneous 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 mainly depends on the intended clinical use of the product, but also on practical considerations, e.g. to avoid ingestion by animals during grooming. Vehicle controls should generally be included.

Irritancy tests are generally performed in the guinea pig, rabbit or minipig (their skin is considered to be anatomically more similar to humans), 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.

The skin should be examined to evaluate the degree of erythema, oedema, desquamation, scab formation and any other lesions. The duration of the observation period will depend on the changes observed for up to 72 hours after administration. If changes persist, observation should continue on a daily basis and may require amendment to the original protocol. Observation periods for up to 8 days after administration should generally be sufficient to allow a full assessment of local tolerability

Histopathological examination should be conducted. A justification can be made why this need not be undertaken on a case-by-case basis.

7.3. 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. As for other types of products, if the composition of the transdermal system changes during clinical development, an additional local tolerance evaluation should be conducted to determine whether further testing is appropriate. Generally speaking, changes in composition will not necessitate further testing unless the concentration of active substance increases beyond that previously tested or novel excipients are introduced.

Ideally, the systems should be tested in a similar manner to clinical use, i.e. not under additional occlusion. The duration of the animal study will depend on the intended clinical use duration.

Histopathological examination should be considered on a case-by-case basis. A justification can be made why this need not be undertaken.

7.4. Parenteral tolerance testing

Parenteral tolerance testing includes iv, intra-arterial (ia), intramuscular (im), intrathecal, and subcutaneous (sc) routes. The dose to be administered should take into consideration the maximum applicable volume for the animal species used.

According to the intended clinical route, suitable veins of the ear, the tail or the front or 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.

Histopathological examination should be considered on a case-by-case basis. A justification can be made why this need not be undertaken.

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) as stated in ICH M3(R2).

7.5. Sensitising potential

For materials applied to skin or mucosae (cutaneous, transdermal, rectal or vaginal) the sensitising potential of the material should be evaluated. In the absence of a accepted in vitro integrated testing strategy, evaluation of sensitising potential should be conducted in at least one approved in vivo 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 cutaneous and transdermal products (see Section 8).

8. Photosafety evaluation of pharmaceuticals

The ICH M3(R2) Guideline provides certain information regarding timing of the photosafety assessment relative to clinical development. It recommends that an initial assessment of phototoxicity potential be conducted, and if appropriate, an experimental evaluation be undertaken before exposure of large numbers of subjects (Phase III). Similarly, the ICH S9 Guideline describes the timing of photosafety testing for oncology products. However, neither ICH M3(R2) nor ICH S9 provides specific information regarding testing strategies. The ICH S10 guideline outlines further details on when photosafety testing is warranted, and on possible assessment strategies and should, therefore, be consulted.

References

Directive 2001/83/EC, on the Community code relating to medicinal products for human use.

Directive 2010/63/EU on the protection of animals used for scientific purposes.

Council Decision on the European Convention on the protection of vertebrate animals, (1999/575/EC).

Directive 2004/9/EC of the European Parliament and of the Council on the inspection and verification of good laboratory practice (GLP).

Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.

ICH Guideline M3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals.

ICH Guideline S6 (R1) – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceutical ICH Guideline S9 Nonclinical Evaluation for Anticancer Pharmaceuticals.

ICH Guideline S10 Photosafety Evaluation of Pharmaceuticals.

ICH Guidelines Q3 A-Impurities In New Drug Substances.

ICH Guidelines Q3 B-Impurities In New Drug Products.

ICH Guidelines Q3 C (R5)-Impurities: Guidelines on Residual Solvents.

ICH Guidelines Q3 D-Elemental Impurities.

Guideline on Regulatory Acceptance of 3R (Replacement, Reduction, Refinement) Testing Approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012) DRAFT.