Skin sensitisation testing of human medicinal products

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Skin Sensitisation

Toxicological endpoint associated with topically applied pharmaceuticals as part of non-clinical local tolerance testing
Regulatory framework – EU EMA

Draft Revised Guideline on non-clinical local tolerance testing of medicinal products (EMA/CHMP/2145/2000 Rev. 1)

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.

Regulatory framework – US FDA


... the most common methods for evaluating the dermal sensitizing potential of drugs have been the Buehler assay (BA) and the guinea pig maximization test (GPMT)

... These methods, along with the split adjuvant technique and the Draize test, are currently accepted by CDER for determining the sensitizing potential of drugs intended for topical use. Other methods (such as the optimization assay) have also been used for the nonclinical evaluation of topical drugs and have been accepted by CDER.

... Techniques using mice, rather than guinea pigs, have also been developed. The mouse ear-swelling test (Gad et al., 1986, 1987) uses an induction and challenge pattern similar to the traditional guinea pig tests. This method has not been extensively used in drug safety evaluation.
Results obtained with the murine LLNA can be used to support the safety of proposed clinical trials with topical drug products. When a murine LLNA is conducted to support the safety of clinical trials, the sensitizing potential of the drug substance, clinical excipient, and clinical formulation should be evaluated. In addition, a concurrent positive control should be used, and individual animal data should be provided.

Other determinations could be valuable in assessing the sensitizing potential of experimental drugs. Although covalent binding to proteins should not be considered a predictor of allergenic potential, in certain situations it could be useful to determine if a drug has this potential (Park and Kitteringham, 1990). For example, if an investigational drug belongs to a class known to produce hypersensitivity reactions through covalent binding (e.g., b-lactams, sulfonamides), demonstration of in vitro and/or in vivo covalent binding to proteins could be taken as a biomarker of sensitization potential (Dewdney and Edwards, 1992; Sarlo and Clark, 1992).

Skin sensitisation tests may be classified systematically into two types, one involving the concomitant use of Freund’s complete adjuvant (FCA), and the other not involving the use of adjuvant.

Usually, those test methods not incorporating the use of an adjuvant are employed for further evaluation of the intensity of positive responses that have been noted in a test with the concomitant use of an adjuvant. These cited in the present Guideline include 1) the Draize test, 2) the Buehler test and 3° the open epicutaneous test.

Testing procedure need not be limited to those cited herein, and in cases where any other test method is employed, justification of its application should be stated along with citation of the appropriate literature.

Test methods cited: adjuvant and patch test, Buehler test, Praise test, Freund’s complete adjuvant test, Maximization test, open epicutaneous test, optimisation test, split adjuvant test.
Development of an integrated testing strategy (ITS)

- based on combination of *in silico*, *in chemico* and *in vitro* methods
- Discussion for the implementation of future ITS in the EU chemicals legislation and at OECD level (Test Guidelines and ITS Guidance)
- What about pharmaceuticals?

The global regulatory context ....

EU: EMA (European Medicines Agency; www.ema.europa.eu)

ICH: International Conference on Harmonisation (www.ich.org)

WHO: World Health Organisation (www.who.int)

EU: EDQM (European Directorate for the Quality of Medicines and Healthcare; www.edqm.eu)
In June 2013 the Steering Committee had agreed that all ICH regions and observers will submit topics to be considered for new ICH guidelines, revision of guidelines, Q&A documents.

Proposal to ICH

ICH Guidance for a mechanistically-based integrated testing strategy for skin sensitisation testing of topically applied pharmaceuticals

Note:
EU legislation on the protection of animals used for scientific purposes (2010/63/EU) drives the choice of methods to be used and will drive the regulatory acceptance at EU level of a future animal-free integrated testing strategy. This situation is prone to international disharmonisation.
What is needed to achieve this?

An evaluation of the applicability of the existing validation data for the ITS for skin sensitisation and individual in silico, in chemico, and in vitro models for topically applied pharmaceuticals

A safe harbour approach may be relevant to gather real-life datasets from pharmaceutical companies.

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Proposals on non-clinical topics were submitted, discussed and prioritised in the November 2013 ICH Meeting (Osaka, Japan) during a Safety Brainstorming Meeting

At the same meeting the ICH SC has further prioritized and selected an number of topics for preparation of Concept Papers by January 2014

Skin sensitisation was not selected as a priority topic
What can be done at EU level?

Qualification of the ITS for use with topically applied pharmaceuticals – data review needed

Submission of data to the regulatory authorities is encouraged:
- either on a **product basis** - data generated in parallel to the conventional animal model
- either via the **EMA procedure for qualification of novel methodologies in drug development**

EMA Draft Guideline on regulatory acceptance of 3R (Replacement, Reduction, Refinement) testing approaches – JEG 3Rs

- Guideline describes
  - regulatory acceptance
  - a new procedure for submission and evaluation of a proposal for regulatory acceptance of 3R testing approaches for use in the development and quality control during production of human and veterinary medicinal products.
  - scientific and technical criteria for regulatory acceptance of 3R testing approaches (incl. Safe Harbour)
  - pathways for regulatory acceptance of 3R testing approaches
- Link with **Guideline on Qualification of Novel methodologies for Drug Development (EMEA/CHMP/SAWP/72894/2008_Corr1)**
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