Guideline on non-clinical local tolerance testing of medicinal products: regulatory perspectives

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Outline of the presentation

- Introduction
- What has changed after revision of the guideline?
- Most important elements
- Examples for local tolerance testing
- Summary – Possible testing strategy for cutaneous application
Guideline on non-clinical local tolerance testing of medicinal products


- Evaluation of local tolerance
- Particular routes of administration
- Sensitising potential
- Photosafety

- ICH S10 Photosafety evaluation
- ICH M3 (R2) Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals
Why non-clinical local tolerance testing?

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

→ distinguish between physical consequences of administration or purely physico-chemical actions from local toxicological or pharmacodynamic effects
Key changes after revision of the guideline in 2016

→ deleted points:
- testing for systemic toxicity
- in vivo repeat-dose local tolerance tests for a maximum of four weeks
- reversibility testing when relevant
- positive controls / references may be included
- testing different routes of administration in one animal is permissible

→ added points:
- transdermal systems
- local tolerance testing as part of general toxicity studies
- use whenever possible a scientifically satisfactory method or testing strategy, not entailing the use of live animals

3R / in vitro!
General considerations:

- **timing:**
  - evaluation of local tolerance before first trials in humans
  - evaluation of accidental exposure before exposure of large number of patients (e.g. Phase III)

- all available data relevant to the potential adverse effects of the substance should be evaluated before starting **in vivo** testing

- formulation used for local tolerance testing should be identical to the intended clinical formulation → otherwise justify!
**In vitro local tolerance tests**

- validated and regulatory accepted OECD methods, e.g.
  - skin irritation (OECD TG 439)
  - eye irritation (OECD TG 437, 438)
- internationally validated methods not yet included in OECD
- methods not undergone international validation

- no validated in vitro assay available
- results of in vitro testing are inconclusive

**in vivo study**
Design of „stand alone“ in vivo local tolerance studies preferably not stand alone but within general toxicity study! animal welfare!

Species: - one relevant species, single sex
Duration: - no longer than 2 weeks, frequency according to clinical use
- for accidental exposure single dose only
Reversibility: - no need to test reversibility
Preparation: - use of clinical preparation
Dose: - highest concentration of active substance in clinical formulation
Route of administration: - according to clinical route
Different routes of administration:

- oral
- parenteral (intravenous, intra-arterial, intramuscular, intrathecal, subcutaneous)
- ocular
- cutaneous
- rectal
- vaginal
- transdermal
Testing: particular routes of administration

 oral route:

• local tolerance testing **generally not required**

• excipients with irritant potential → justify!

• degradation products → characterise (literature, in silico, in vitro)!

• if study necessary: separate single dose study in single sex
Testing: particular routes of administration

cutaneous route:

- local tolerance + sensitising potential
- testing range of doses → altering amount of product applied and/or change area of administration
- include vehicle controls, use of occlusive dressings?
- (irritancy tests → guinea pig, rabbit or minipig → shaved intact/abraded (!) skin → examine skin lesions (erythema, oedema, desquamation) up to 72 hours (8 days) after administration)
  → conduct histopathological examination → if not, justify)
- perform photosafety assessment (→ ICH S10 / 5.2)
Testing: particular routes of administration

**Parenteral** (intravenous, intra-arterial, intramuscular, intrathecal, subcutaneous) **systems:**

- dose → consider maximum applicable volume in animal species
- suitable application site in animals according to clinical use
- consider histopathological examination case-by-case → justify
- local tolerance at unintended injection sites (ICH M3)
  - US: generally not recommended
  - EU/Japan: single dose paravenous application for iv, other parenteral sites case-by-case
Sensitising potential

• for substances applied to the skin (cutaneous, transdermal) or mucosae (vaginal, rectal)
• before Phase I studies
• at least in one approved in vivo test:
  - local lymph node assay
  - guinea pig assay

regulatory experience with in vitro testing on sensitisation?
• **Photosafety evaluation (ICH S10)**

  - phototoxic potential of active substance/excipients:
    - MEC values greater than 1000 Lmol\(^{-1}\) cm\(^{-1}\)
    - light absorption at wavelengths 290 – 700 nm
      (- positive photoreactivity test)

  - **timing (ICH M3):**
    - assessment of phototoxic potential before Phase I
      → if risk identified → appropriate protective measures
    - experimental evaluation of phototoxic potential before Phase III (3T3NRU test> reconstructed human skin> in vivo animal = clinical evaluation)

**photoallergy:** evaluation for cutaneous and transdermal products if phototoxic potential identified
→ clinical assessment (during Phase III)

MEC: **molar extinction coefficient**
Example: New Active Substance (known excipients)

- Check physico-chemical properties of substance in its formulation (pH, solubility, stability ionisation, solid state properties ...)
- Are literature data available?
- What about findings from structurally related substances?
- Are results from in vitro or ex vivo studies available?

Perform weight-of-evidence-analysis!

sufficient data→
no in vivo local tolerance study necessary

insufficient data→
perform in vivo local tolerance study before Phase I (preferably no „stand alone“ study!)
Example: Known Active Substance (new formulation)

- Are the excipients known, respectively are data available?
- Are the excipients used in similar concentrations in products that are already on the market?
- Are data on local tolerance available for the active substance, e.g. in a different formulation?

**Yes**
local tolerance testing might be possible within clinical trial

**No**
non-clinical local tolerance testing might be necessary
Local tolerance – Possible testing strategy for cutaneous application

for Phase I:

- physico-chem. properties
- in vitro data
- literature data
- data from related substances

- local tolerance testing within general toxicity studies, e.g.
  - 2 week study with dermal application minipig + tk
  - 2 week study sc application rat + tk
- skin sensitisation test
- photosafety assessment

for Phase III:

- stand alone 2 week local tolerance study
- general toxicity studies, e.g.
  - 2 week study with dermal application minipig + tk
  - 2 week study sc application rat + tk
- skin sensitisation test
- photosafety assessment

- experimental evaluation of phototoxicity
- clinical evaluation of photoallergy during Phase III
I presented my personal opinion and not the opinion of the institution BfArM.