Bundesinstitut
für Arzneimittel
und Medizinprodukte

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

EMA/CHMP/SWP/2145/2000 Rev. – 1.May 2016

- **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

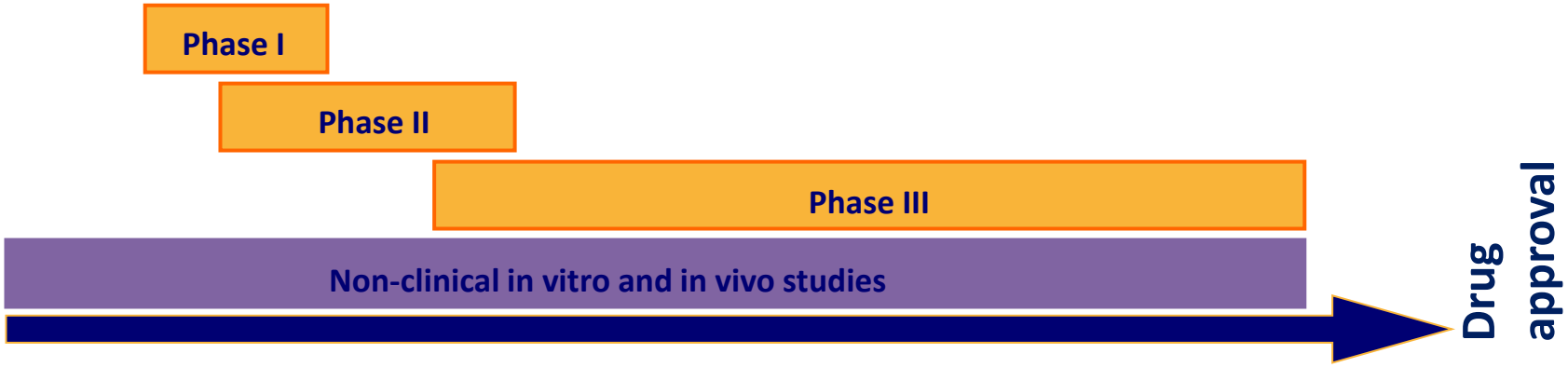
3R / in vitro!

❖ 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

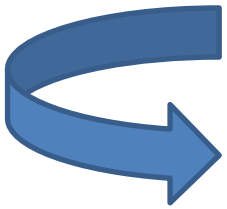
  EU/Japan: single dose paravenous application for iv, other parenteral sites case-by-case

❖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: **m**olar **e**xtinction **c**oefficient

❖ 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

→

~~- 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~~

for Phase III :

- experimental evaluation of phototoxicity
- clinical evaluation of photoallergy during Phase III

I presented my personal opinion and not the opinion of the institution BfArM