Symposium
Anforderungen an neue Rezepturbestandteile für Dermatika und Kosmetika
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Bewertung topischer Hilfsstoffe aus toxikologischer Sicht

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Toxicological assessment of excipients in MP

GUIDELINE ON EXCIPIENTS IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

London, 19 June 2007 Doc. Ref. EMEA/CHMP/QWP/396951/2006

Excipients (XP): constituents of a pharmaceutical form apart from the active substance
(no process or product-related impurities or extraneous contaminants)

***Novel* excipient (NXP):**
is an XP which is being used for the first time in a drug product, or by a new route of administration.
It may be a *new* chemical entity or a *well established one* which has not yet been used for human administration and /or for a particular human administration pathway ….

Toxicological assessment of excipients in MP

EMEA/CHMP/QWP/396951/2006:

Examples for XP:

fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring, aromatic substances;

constituents of the outer covering of the medicinal products, e.g. gelatine capsules

Toxicological assessment of excipients in MP

Different types of XP (Annex 1 of GL QWP/396951/2006)

Single chemical entities: organic / inorganic acids and their salts, sugars and alcohols

Chemically transformed XP: e.g. modified starch

Mixtures of chemically related components: e.g. polyol esters (mixture of mono, di and tri esters), hydrogenated glucose syrup (maltitol, sorbitol)

XP of natural origin („natural' XP)

Flavouring agents [flavours and aromatic substances (sucrose)]

Adjuvants [enhance the pharmacological effect of a drug (caffeine) or increase the ability of an antigen to stimulate the immune system (aluminium salts)]

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XP of special interest/for special populations
(inclusion needs special justification)

Antioxidants
improve stability of MP by delaying the oxidation of API and other XP

Antimicrobial preservatives
prevent or inhibit the growth of micro-organisms which could present a risk of infection to or degradation of the MP.
(*No* alternative to GMP)

Permeation enhancers/solubilisers
enhance the transdermal delivery of an API into the systemic circulation

Paediatric population
selection with special care (e.g. colouring agents)

Toxicological assessment of excipients in MP

Toxicological risk of XP
not all excipients are inert substances; potential toxicants

Sulfanilamide elixir (1937)
DEG (72%) as solubiliser → kidney failure (>100 children died)
→ Fed. Food, Drug and Cosmetic Act (1938):
safety testing pt marketing

Hypersensitivity reactions
e.g. by gum acacia, parabens, lanolin (wool fat)

Cardiotoxic effects, thrombophlebitis
propylen glycol (i.v.)

CNS effects: ethanol
Diarrhoea: sucrose, mannitol, sorbitol

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NXP

Are not fully qualified by existing safety data
wrto level / duration of exposure or route of administration

Evaluation of a safety database is required that admit a risk-benefit assessment / generation of permissible and safe limits of a NXP

Existing human data can substitute for certain NC safety data, e.g. previous use in approved products / GRAS status (food additive) → full battery of TOX studies is not required

However, even in case of prior use upgrading to current standards may be necessary

Toxicological assessment of excipients

(N)XP toxicological program (GLP)

- **Safety data available**
- **Route of administration**
- **Duration of use**
- **Indication**
- **Patient population** (use in pediatrics)
- **Chemical class (polymers)**

- **PK profile for (N)XP**
  when extensively absorbed or biotransformed

- **Knowlegde on potential pharmacological properties (see ICH guidance S7A)**

Toxicological assessment of excipients in MP

Directive 2001/83/EC, Annex 1

„The toxicology and pharmacokinetics of an XP used for the first time in the pharmaceutical field shall be investigated“

Guidance for Industry
Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2005

Cave: FDA guidance, not obligatory for EU authorities

Toxicological assessment of excipients in MP

Short-term clinical use (≤14d)

28-d RD-TOX (rodent /mammalian nonrodent)
clinically relevant route of administration (RoA)
including toxicokinetics *(ADME)*
(No acute TOX)

Genotoxicity: standard battery testing (ICH GfI *S2B*)

Reproductive TOX (ICH GfI *S5A*, *S5B*)

Toxicological assessment of excipients in MP

Dose selection

XP biologically nonreactive → no DR relation
→ maximum feasible dose (MFD)
(highest dose not compromising the nutrinitional or health status)

Nature of test	Species	MFD
28-d p.o. RD	Rodent/nonrodent	1 g/kg bw/day
Repro TOX	Rat	1 g/kg bw/day
Dermal irritation	Rabbit	0.5 mL liquid/0.5 g solid
[Acute p.o./dermal	Rodent/rabbit	2 g/kg bw]

Toxicological assessment of excipients in MP

TOX study	Cage-side observ.	Food/water intake	bw / gain	Gross pathol.	Organ wght/ratio	Histo-pathol.	CC/ urinalysis/ haematol.
[Acute	Y	Y	Y	Y	N	N	N]
28-d RD	Y TD	Y OW	Y B/OW/D	Y	Y	N	N
Repro	Y	Y	Y	Y	N[a]	N	N

[a]Sex organ weight ratios; TD: twice daily; OW: once weekly; B: before study initiation; D:death

Toxicological assessment of excipients

Summary of recommended studies (R) for NXP based on RoA (short-term clinical use)

Tests	p.o.	dermal
28-d RD	R (rat)	R (minipig)
ADME-intended route[a]	R	R
Skin irritation	--	R
Application site eval.	--	R
Eye irritation[b]	--	(R)
GenoTOX std battery	R	R
Repro TOX	R	R
Skin sensitization[c]	--	R
PhotoTOX/photoallergy	--	R

[a]: include toxicokinetic study in RD study; [b]: HET-CAM test; [c]: Lymph node assay

Toxicological assessment of excipients

Genotoxicity: standard battery testing (ICH GfI *S2B*)

i) A test for gene mutation in bacteria.

ii) An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay.

iii) An *in vivo* test for chromosomal damage using rodent hematopoietic cells.

ad i) Bacterial reverse mutation test: Ames test in *S. typhimurium*
ad ii) Clastogenic activity: mikronucleus test in human lymphocytes
ad iii) Clastogenic activity: mammalian erythrocyte mikronucleus test (included in *RD study*)

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Reproduction TOX (ICH Gfl *S5A*, *S5B*)

1.2….. The combination of studies selected should allow exposure of mature adults and all stages of development from conception to sexual maturity. …

→ *single-study rodent assay* plus teratology study in a nonrodent species.

All other pharmacological and toxicological data available *should be considered* to determine whether potential reproductive risks to humans are greater, lesser or equal to those posed by other toxicological manifestations.
…
RD toxicity studies can provide important information regarding potential effects on reproduction, particularly male fertility. To extrapolate the results to humans data on likely human exposures, comparative kinetics, and mechanisms of reproductive toxicity may be helpful.

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Intermediate clinical use (≥14d - ≤3m)

3-m RD-TOX (rodent /mammalian nonrodent)
clinically relevant route of administration (RoA)
including toxicokinetics *(ADME)*
(No acute TOX)

Genotoxicity: standard battery testing (ICH Gfl *S2B*)

Reproductive TOX (ICH Gfl *S5A*, *S5B*)

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Long-term clinical use (<3m)

6-m RD-TOX (rodent /mammalian nonrodent)
clinically relevant RoA including toxicokinetics
for nontoxic / pharmacologically inactive XP

For toxic XP:
9-12 m-RD-TOX in a nonrodent species

Genotoxicity: standard battery testing (ICH GfI *S2B*)

Reproductive TOX (ICH GfI *S5A*, *S5B*)

***2-y* carcinogenicity study** (see ICH GfI *S1A*, *S2B*)
(case-to-case decision: negative genotoxic data, no or limited systemic exposure, negative histopathology from chronic TOX studies at MFD)

Toxicological assessment of excipients

TOX study	Cage-side observ.	Food/water intake	bw / gain	Gross pathol.	Organ wght/ratio	Histo-pathol.	CC/ haematol.
RD	Y	Y	Y	Y	Y	N	N
Repro	Y	Y	Y	Y	N[a]	N	N
Chronic	Y	Y	Y	Y	Y	Y	Y
Carcinog.	Y	Y	Y	Y	Y	Y	Y

[a]Sex organ weight ratios

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Add studies upon topical, injectable or pulmonary MP application

Topical use (dermal, intransasl, opthalmic, rectal, etc.):

- sensitization study
- TOX studies for both the intended clinical route *and* the oral / parenteral route, if PK studies show systemic exposure to the XP or its metabolite

Topical dermal and ophthalmic use:

- ocular irritation study

Injectables:

- in vitro haemolysis study
- creatinine kinase levels
- evaluation of protein binding

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Conclusions

(N)XP TOX database required is similar to that of API

(N)XP TOX studies should be included in API TOX studies

Case-to-case decision: Scientific Advice is recommended