

**Symposium**  
***Anforderungen an neue Rezepturbestandteile***  
***für Dermatika und Kosmetika***  
***21. Oktober 2008***

**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.  
EMA/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*

**EMA/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)]

# ***Toxicological assessment of excipients in MP***

## **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

# *Toxicological assessment of excipients in MP*

## **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 ( $\leq 14$ d)**

***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 nutritional or health status)

<b>Nature of test</b>	<b>Species</b>	<b>MFD</b>
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***

<b>TOX study</b>	<b>Cage-side observ.</b>	<b>Food/water intake</b>	<b>bw / gain</b>	<b>Gross pathol.</b>	<b>Organ wght/ratio</b>	<b>Histo-pathol.</b>	<b>CC/urinalysis/haematol.</b>
[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 <sup>a</sup>	N	N

<sup>a</sup>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)**

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

<sup>a</sup>: include toxicokinetic study in RD study; <sup>b</sup>: HET-CAM test; <sup>c</sup>: Lymph node assay

# ***Toxicological assessment of excipients***

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

# ***Toxicological assessment of excipients in MP***

## ***Reproduction TOX (ICH GfI 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.

# ***Toxicological assessment of excipients in MP***

**Intermediate clinical use ( $\geq 14d$  -  $\leq 3m$ )**

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

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

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

# ***Toxicological assessment of excipients in MP***

## **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 Gfl S2B)

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

**2-y carcinogenicity study** (see ICH Gfl 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*

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

<sup>a</sup>Sex organ weight ratios

## ***Toxicological assessment of excipients in MP***

**Add studies upon topical, injectable or pulmonary MP application**

***Topical use (dermal, intranasal, ophthalmic, 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

# ***Toxicological assessment of excipients in MP***

## **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***