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Revidierte ICH M3
Auswirkungen auf die präklinische Arzneimittelentwicklung

Pharmakologie, ADME, Missbrauchs-Potential und Kombinations-Toxizität

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Präklinik
Fachgebiet Klinische Prüfung
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M3 (R1)	M3 (R2)
2. Safety Pharmacology	2. Pharmacology Studies
3. Toxicokinetic and Pharmacokinetic Studies	3. Toxicokinetic and Pharmacokinetic Studies
	15. Nonclinical Abuse Liability
	17. Combination Drug Toxicity Testing

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- Introduction
- What has changed?
  - Pharmacology
  - ADME
  - Nonclinical Abuse Liability
  - Combination Drug Toxicity Testing
- Consequences for drug development? Examples
- Conclusion

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2. Safety Pharmacology

2. Pharmacology Studies

- ✓ ICH S7A and ICH S7B
- ✓ Safety Pharmacology
- ✓ Timing
- ✓ Primary PD studies (non-GLP)

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Pharmacology Studies

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Example:

DOP-2: novel dopamine D2 receptor-antagonist for the treatment of schizophrenia

- **core-battery of safety pharmacology (CNS, cardiovascular, respiratory) prior to FIH (first in human) → ICH S7A, S7B**
- **follow-up studies in case of concern later during clinical development**
- **primary PD-studies (in vitro-receptor binding, in vitro/in vivo functional assays) → select dose for nonclinical and clinical studies**

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Toxicokinetic and Pharmacokinetic Studies

ADME

M3 (R1):

- **general aspects concerning exposure data**
- **timing → exposure data prior to FIH, further ADME-data after completion of Phase I**

M3 (R2):

- **details of which ADME-studies are requested**
- **timing**
- **nonclinical characterization of metabolites**

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Toxicokinetic and Pharmacokinetic Studies

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- in vitro metabolic and plasma protein binding animals/ humans + systemic exposure data in species used for repeated-dose toxicity studies

prior to FIH

- further ADME-data (PK)
- in vitro drug interaction

before exposing large number of patients or long duration of trial (prior to Phase III)

- nonclinical characterization of human metabolite(s), if exposures greater than 10 % of total drug-related exposure and significantly greater levels in humans than in animals → case by case → if cause of concern (e.g. unique human metabolite)

prior to phase III

Toxicokinetic and Pharmacokinetic Studies

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nonclinical characterization of human metabolite(s)

→ which nonclinical studies are needed?

→ ICH M3 (R2): no specific studies are requested

? **Guidance for Industry, Safety Testing of Drug Metabolites, CDER, FDA, February 2008**

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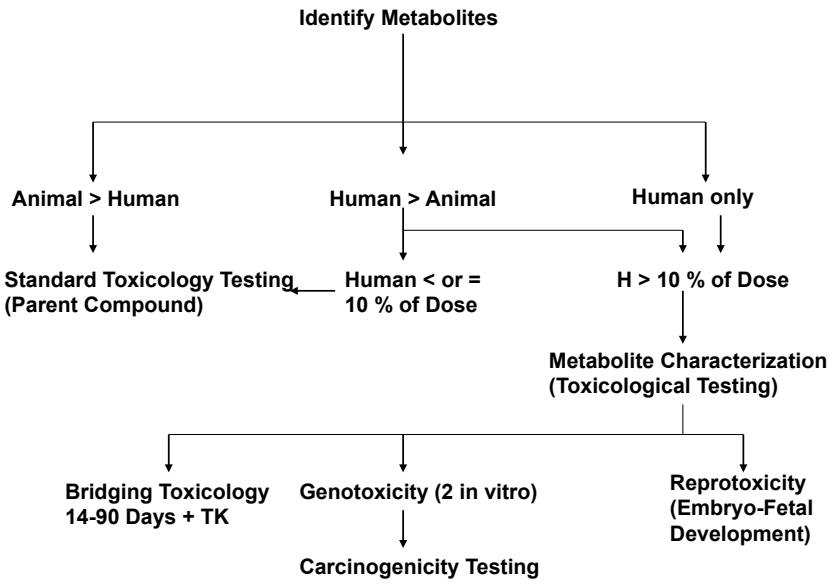
FDA decision tree for safety testing of metabolites

S.C.Gad, Preclinical Development Handbook



Toxicokinetic and Pharmacokinetic Studies

nonclinical characterization of human metabolite(s)

→ which nonclinical studies are needed?

→ case by case decision

→ of importance are pharmacologically / toxicologically active metabolites

Example:

- **pharmacologically active metabolite:** desloratadine a metabolite of loratadine with a 10-fold increase in its potency, longer half-life, and greater exposure
- **toxicologically active metabolite:** cyclophosphamide is not directly cytotoxic, several toxic metabolites → 4-hydroxycyclophosphamide with 8 % of total plasma exposure

Example: DOP-2

- in vitro plasma protein binding studies for animals used for repeat-dose testing (rat, dog) and humans → prior to FIH
- in vitro metabolic studies (hepatocytes, microsomes) in rat, dog and human preparations → prior to FIH
- A (animal iv, po PK); D (distribution study rat); M (in vivo metabolism rat, dog); E (elimination feces, urine, (bile) rat, dog, humans), in vitro drug interaction → prior to Phase III
- no specific human metabolite identified with 10 % of total drug-related exposure → no nonclinical characterization necessary

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Nonclinical Abuse Liability

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Nonclinical Abuse Liability

- requested for drugs producing central nervous system activity regardless of indication

- specific study designs ⇒ regional guidance documents:

Guideline on the non-clinical investigation of the dependence potential of medicinal products EMEA/CHMP/SWP/94227/2004

DRAFT Guidance for Industry: Assessment of Abuse Potential of Drugs – FDA – CEDER

- early indicators of abuse potential available prior to FIH:
  - ✓ PK/PD profile
  - ✓ similarity of chemical structure to drugs with known abuse potential
  - ✓ receptor binding profile / functional assays
  - ✓ behavioural/clinical signs from in vivo studies

if negative ⇒ no further studies

if positive or novel mechanism of action on CNS

⇒ further nonclinical studies to support large clinical trials (Phase III)

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- **for further nonclinical studies on abuse liability:**
  - ✓ **use proper animal species**

    (general rodents, primates only under exceptions)
  - ✓ **abuse liability studies:**

    drug discrimination

    self-administration

    assessment of withdrawal

  - ✓ **dosing: maximum dose should produce plasma-concentrations several fold higher than therapeutic plasma levels**

Nonclinical Abuse Liability

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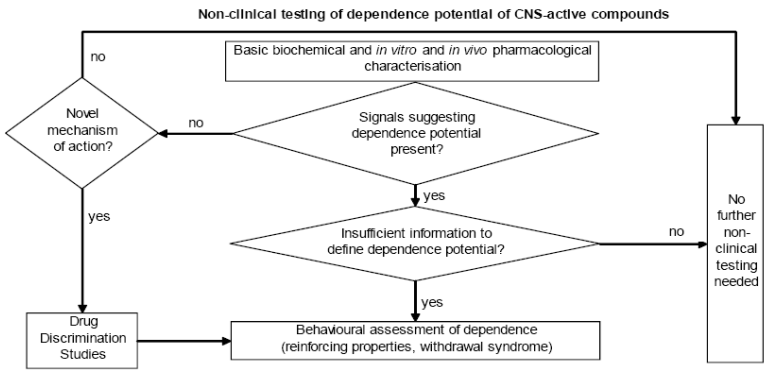
Guideline on the non-clinical investigation of the dependence potential of medicinal products EMEA/CHMP/SWP/94227/2004



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Example: DOP-2

- DOP-2 may produce CNS activity
- DOP-2 penetrates into brain
- further receptor binding studies: dopamine-, norepinephrine-, serotonin-, GABA-, acetylcholine-, opiod-, NMDA-receptor → receptor binding profile shows broad safety margins except for dopamine receptor
- further in vitro functional assays at dopamine receptor (primary PD) → no agonistic, only antagonistic activity
- safety pharmacology study and repeat-dose studies → behavioural/ clinical signs → exaggerated pharmacologic effects?
- perform further abuse liability studies

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COMBINATION DRUG TOXICITY TESTING

- What are combination drugs?
- Which kind of combinations are possible?
- For which drug combinations when to perform drug combination toxicity testing?
- What kind of combination toxicity testing?

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Guideline on the non-clinical development of fixed combinations of medicinal products EMEA/CHMP/SWP/258498/2005

Combination Drug Toxicity Testing

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What are combination drugs?

- co-packaged drugs

- drugs in single dosage form („fixed formulation“)

- drugs with product information recommendations for co-use with minimal clinical information regarding the combination

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Which kind of combinations are possible?

- late stage entities (Phase III / post-marketing)

- late stage entit(ies) + early stage entit(ies) (Phase II or less)

- more than one early stage entity

late stage entity: significant clinical experience

early stage entity: limited clinical experience

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For which drug combinations when to perform drug combination toxicity testing?

no need for combination toxicity testing:

combination of late stage entities with adequate clinical experience with co-administration

(– unless significant toxicological concern)

Example: marketed glucocorticoid + marketed β-mimetikum → indication asthma

! Cause of concern: similar organ toxicity → nonclinical evaluation prior to clinical study with combination

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For which drug combinations when to perform drug combination toxicity testing?

combination of two late stage products with no adequate experience in co-administration:

if no causes for significant toxicological concern

- **for small scale, short duration clinical studies (Phase II, up to 3 months duration) no combination toxicity testing**
- **nonclincal combination toxicity testing for large scale or long-term combination trials or marketing**

Example: Phase III renin inhibitor + marketed diuretic

! Cause of concern → nonclinical evaluation prior to clinical study with combination

Combination Drug Toxicity Testing

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For which drug combinations when to perform drug combination toxicity testing?

combination of early stage entit(ies) with clinical experience + late stage entit(ies):

no causes for significant toxicological concern

- **for proof-of-concept studies up to one month duration no combination toxicity testing (clinical study of combination no longer than clinical experience with single entities)**
- **nonclincal combination toxicity testing for later stage or longer-term combination trials**

Example: renin inhibitor (Phase II study of 1 month duration completed) + marketed diuretic → phase II study of 1 month ok without nonclinical combination testing

! Cause of concern → nonclinical evaluation prior to clinical study with combination

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For which drug combinations when to perform drug combination toxicity testing?

combination of two early stage entit(ies)

Combination toxicity studies are recommended to support clinical trials

Example: novel glucocorticoid (phase I completed) + novel β-mimetikum (phase I completed) → indication asthma

Combination Drug Toxicity Testing

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What kind of combination toxicity testing?

complete nonclinical development program conducted for single entities and combination toxicity study is warranted:

- ✓ combination study equivalent to duration of clinical trial + TK
- ✓ maximum duration of 3 month
- ✓ a single relevant species

complete nonclinical development program not conducted for single entities:

- ✓ complete nonclinical toxicology program for combination

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What kind of combination toxicity testing?

Combination genotoxicity, safety pharmacology or carcinogenicity?

↳ **not recommended if single entities have been tested**

Combination studies on embryo-fetal development?

- **if embryo-fetal risk already identified in studies with single entities → no combination embryotoxicity studies**
- **if no embryo-fetal risk was shown in studies with single entities → no combination embryotoxicity studies -! unless concerns → combination embryotoxicity studies for marketing application**

Combination Drug Toxicity Testing

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Advice!

Always provide a detailed discussion on the basis of ICH M3 (R2) and EMEA „Guidance on Fixed Combinations“ if combination toxicity testing is not performed

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Conclusions

revised M3 → more detailed guidance concerning:

- **timing of nonclinical testing**
- **which ADME studies are requested**
- **when characterization of human metabolites is recommended**
- **when nonclinical abuse liability studies are recommended**
- **when combination drug toxicity testing should be performed**

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Thank you for your attention!

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