3rd EMEA Workshop
for Micro, Small and Medium-Sized Enterprises (SMEs)
„Focus on Non-clinical Aspects“
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Meeting Requirements for EU Marketing Authorization: Genotoxicity and Carcinogenicity

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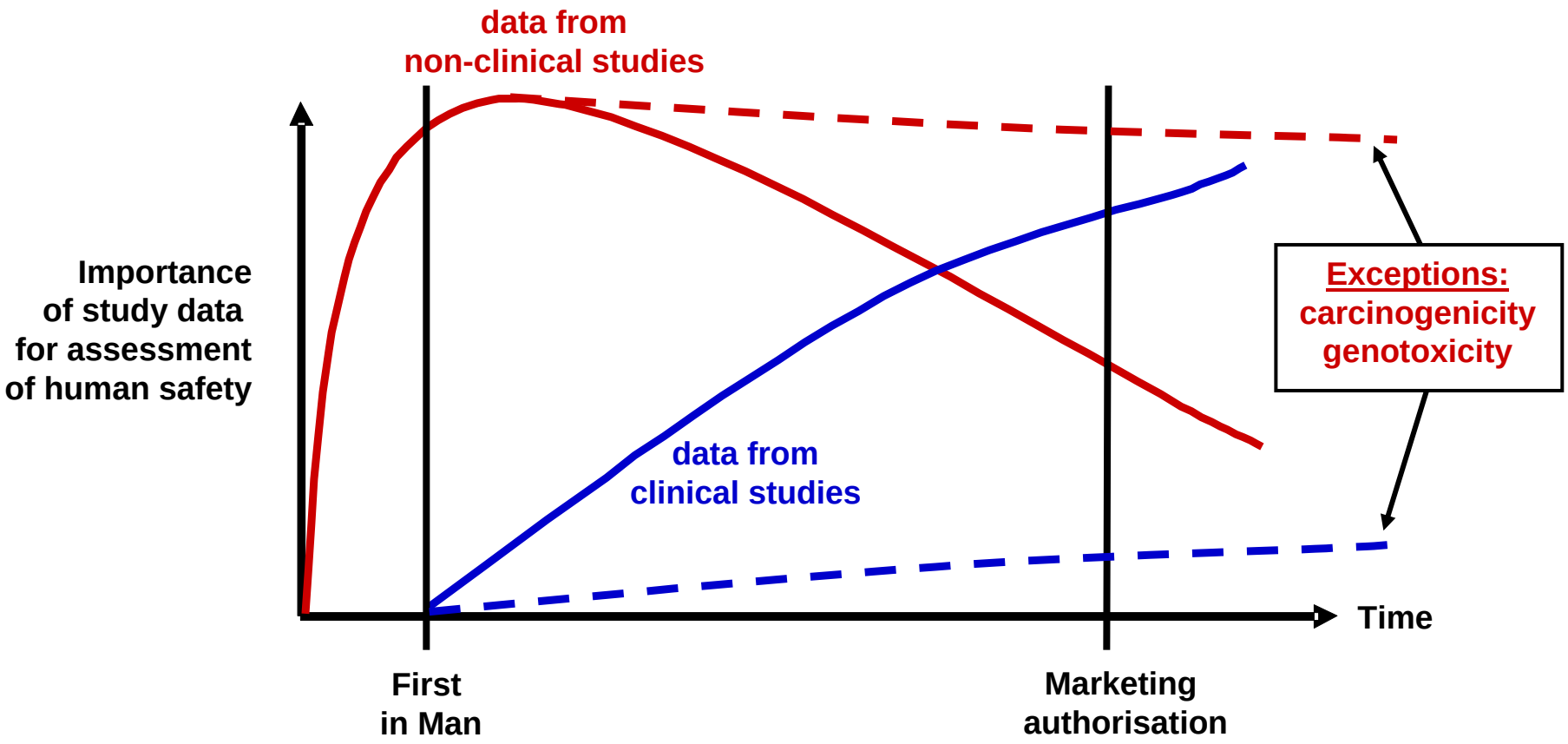
The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

Role of non-clinical data through the drug development process:
Genotoxicity / carcinogenicity data are special!



Basic testing requirements

Genotoxicity Testing

- small molecules
  - ICH S2B (under revision)
  - “standard battery“
- biopharmaceuticals
  - ICH S6 (under revision)
  - (standard) testing generally not needed
  - “cause for concern“

Carcinogenicity Testing

- small molecules
  - ICH S1A/B/C
  - rodent cancer bioassay in 2 species
- biopharmaceuticals
  - ICH S6 (under revision)
  - standard rodent bioassay not useful
  - “alternative approaches“

Genotoxicity / Carcinogenicity Testing:
The standard approaches for “small molecules“

- Genetic Toxicology (ICH S2B, under revision)
  - gene mutation in bacteria (Ames test)
  - in vitro chromosome aberration or mouse lymphoma *tk* assay
  - in vivo test for chromosomal damage in rodent hematopoietic cells (rodent bone marrow micronucleus)

- Carcinogenicity (ICH S1B)
  - 2 year rat bioassay
  - 2 year mouse bioassay or medium-term transgenic mouse model

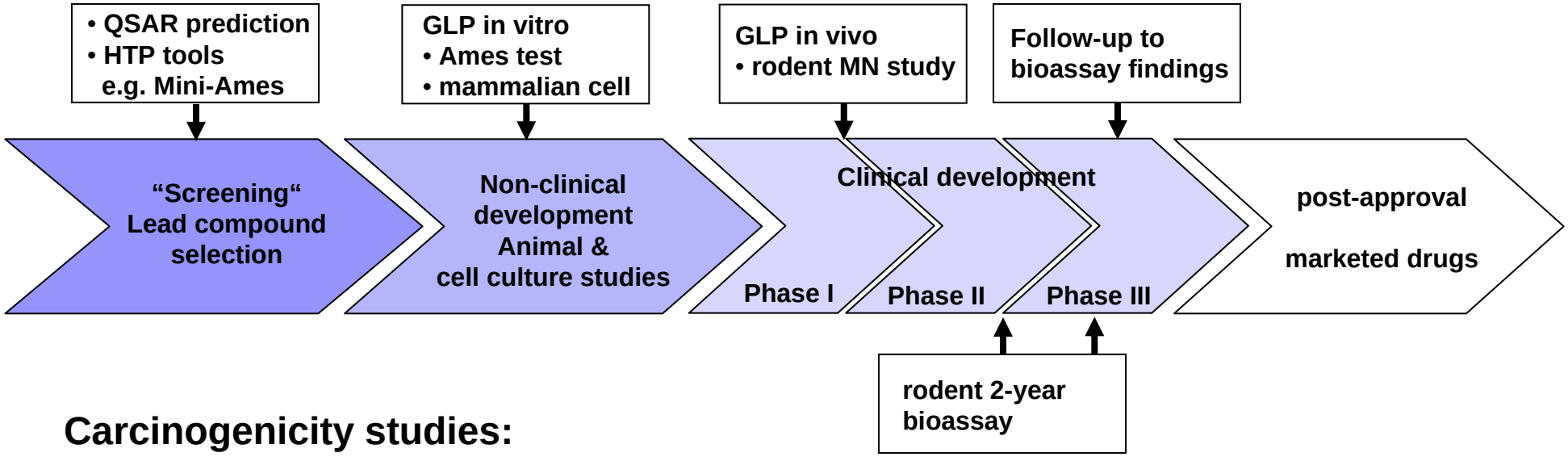
Role of genetic toxicity data in relation to carcinogenicity

- in the absence of carcinogenicity data:
  for prediction of carcinogenic potential
  (e.g. when starting first clinical trials)

- in the presence of carcinogenicity findings:
  as part of the weight of evidence in cancer risk assessment

Timing of genotoxicity / carcinogenicity studies during drug development

Genotoxicity studies:



Carcinogenicity studies:

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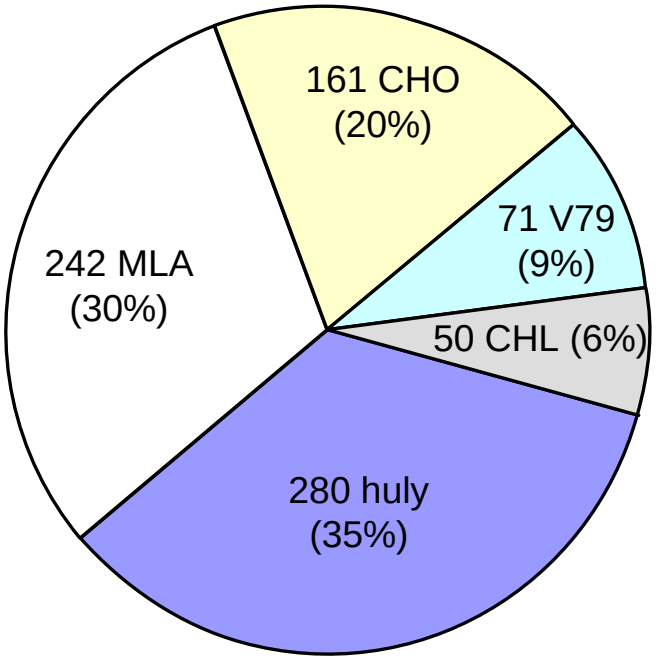
Impact of positive genotoxicity findings

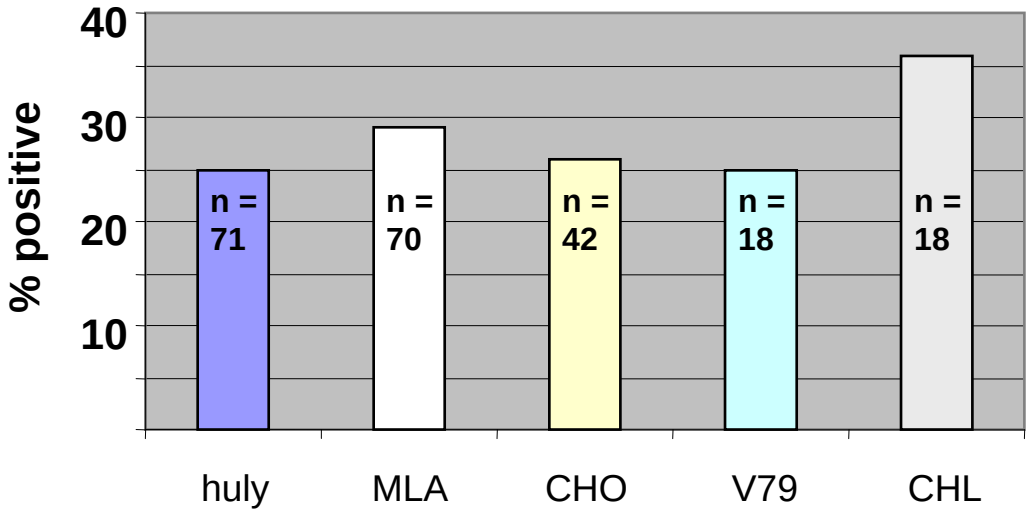
- Ames test
  - rare event; triggers termination of development
- in vivo rodent bone marrow study
  - rare; usually termination of development (or mechanistic data to demonstrate lack of clinical relevance)
- in vitro mammalian cell test
  - frequent; additional studies to clarify relevance

Mammalian cell assays:
Use in regulatory testing and rates of positives



804 mammalian cell studies submitted between 1995 and 2005 to BfArM
(testing of 596 compounds)

Comparison of rate of positives among the cell systems currently in use



219 of 804 studies positive = 27%
181 of 596 compounds positive in at least 1 in vitro clastogenicity test = 30%

Proposed ICH S2 revisions

Avoidance of non-relevant in vitro positives

- *In vitro* mammalian cell assay
  - top concentration: reduced from 10 to 1 mM
  - cytotoxicity limits: more clearly defined
  - testing into precipitating range: no longer required
- option to avoid *in vitro* mammalian cell test in standard testing battery

Revised testing battery: 2 Options!

Current (S2B)	Revised S2	
	Option 1	**Option 2**
Bacterial gene mutation (with repeat)	**Bacterial gene mutation (no repeat)**	**Bacterial gene mutation (no repeat)**
In vitro mammalian cell test: Chromosome aberrations OR: mouse lymphoma assay ➔ 10 mM top conc ➔ > 50/80 % cytotoxicity	**In vitro mammalian cell test: Chromosome aberrations OR: mouse lymphoma assay OR: micronucleus assay** **➔ 1 mM top conc** **➔ at most 50/80 % cytotoxicity**	**NO in vitro assay in mammalian cells!**
In vivo micronucleus test (acute stand alone test)	**In vivo micronucleus test** **(preferably integrated into rodent toxicity study)**	**In vivo micronucleus test 2nd in vivo endpoint/tissue (preferably integrated into rodent toxicity study)**

Dose acceptance criteria in general toxicity study for genotoxicity evaluation (ICH S2 R1)

- Maximum feasible dose
- Limit dose (2000 mg/kg for ≥ 14 days)
- Maximal possible exposure:
  - plateau/saturation in exposure
  - compound accumulation
- Top dose is ≥ 50% of top dose that would be used for acute administration
- If none of the criteria are met do study with acute administration

Proposed ICH S2 revisions
Follow-up of *in vitro* positives

positive result in mammalian cell assay
(insufficient weight of evidence to indicate lack of relevance)

↓ **either**

in vitro studies to provide mechanistic information

↓ **or**

two appropriate *in vivo* assays,
usually with different tissues,
and with supporting demonstration of exposure

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Impact of positive carcinogenicity findings (from rodent bioassays)

Two important questions

1. What is the carcinogenic mode of action (MoA) in animals
2. Is this MoA relevant to humans / to the conditions of (much lower) human exposure

Carcinogenic MoA analysis

- additional mechanistic studies may be needed
- if data are insufficient to characterize MoA, animal findings are assumed to be relevant to humans by default
- presence of positive genotoxicity findings can be critical (often divergent interpretations of inconsistent data sets)
- mutagenic MoA = linear extrapolation at low doses

positive genotoxicity finding

+

positive rodent carcinogenicity

=

genotoxic carcinogen (mutagenic MoA)??

Carcinogenicity/genotoxicity results with pharmaceuticals

(Snyder & Green, 2001: Review of data of marketed pharmaceuticals in the Physician's Desk Reference and published literature)

	Carcinogenicity positive	Carcinogenicity negative
Genotoxic	26	24
Non-genotoxic	51	100
Totals	77	124

High probability of positive genotoxicity and/or carcinogenicity findings during drug development process!

Correlation of carcinogenicity/genotoxicity results

Outcome of testing	Carcino-genicity	Geno-toxicity	
	negative	negative	
	negative	positive	mostly related to positive findings in *in vitro* mammalian cell tests
	positive	positive	may indicate a mutagenic MoA or both events occur without any causal relation
	positive	negative	carc finding with non-mutagenic MoA or false-negative genotoxicity??

non-genotoxic carcinogenic MoA

- chronic cell injury with regenerative cell proliferation
- immunosuppression
- increased secretion of trophic hormones
- receptor activation
- other (e.g. CYP 450 induction)

- In many cases rodent-specific or high-dose specific effects (no relevance for clinical conditions)

Is the rodent lifetime bioassay really a “golden“ standard?

- Clear lack of accuracy for predicting human carcinogenicity (high number of false positives)
- Transgenic models haven’t improved the situation
- Hot research topic:
  - Biomarker for non-genotoxic carcinogenesis
  - US C-Path PSTC
  - EU Improved Medicine Initiative IMI
- Need revision of ICH S1B – But when??

Summary

- Data from genotoxicity and carcinogenicity studies are a pivotal part in MAA
- Assessment of gentox & carc is based solely on non-clinical data
- (Some) test models currently in use have poor specificity (high rate of irrelevant positives)
- Positive findings need usually extensive follow-up work
- Improvements expected with revision of ICH S2 (genotoxicity)
- Carcinogenicity testing approach (ICH S1B) needs revision too!
- For the time being WE have to interprete (the human relevance of) the frequent rodent tumor findings with great caution