Federal Institute
for Drugs
and Medical Devices

EMA SME Workshop 2016: Focus on non-clincial aspects

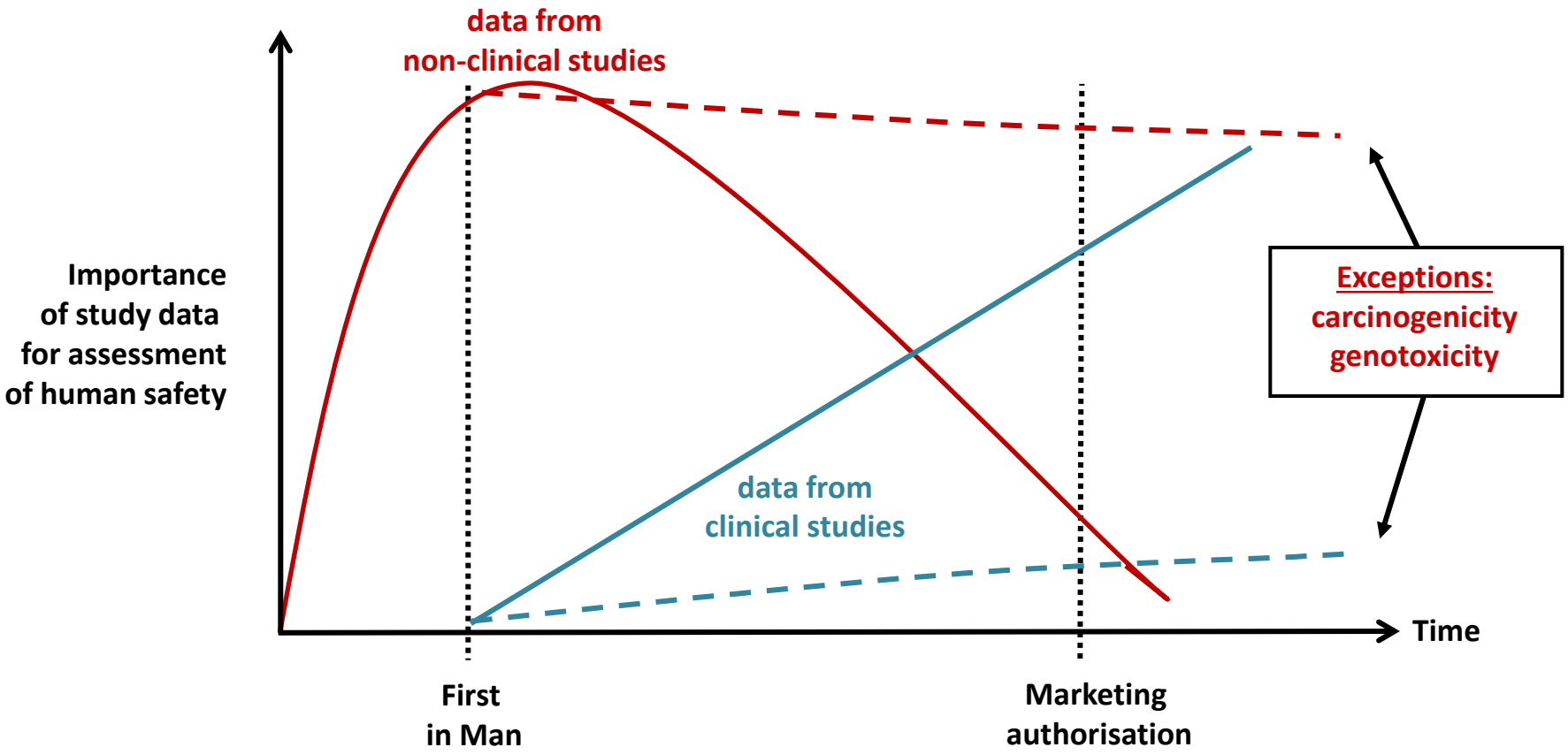
Approaches to genotoxicity and carcinogenicity assessment

Peter Kasper

Content

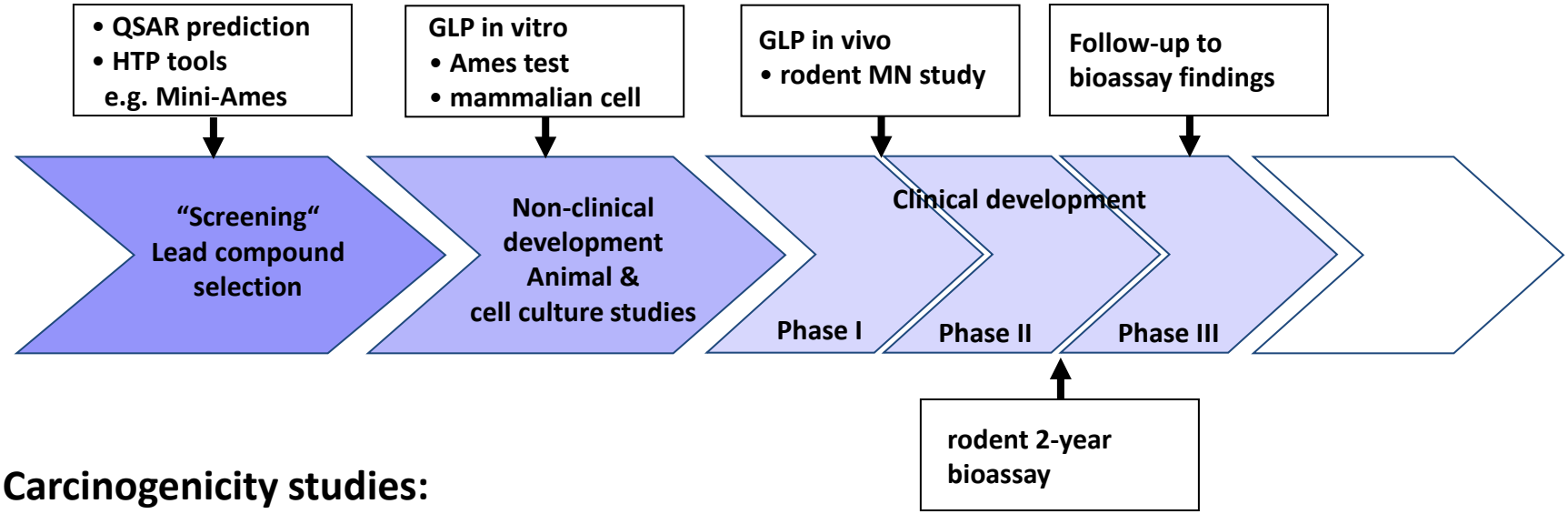
- "Specific non-clinical challenges"?
- Genotoxicity
  - Basics & guideline requirements
  - Test outcome: Potential impact on drug development
  - Role of genotoxicity data for carcinogenicity assessment
- Carcinogenicity
  - Basics & guideline requirements
  - Current problems in carcinogenicity assessment
  - Search for new approaches: ongoing ICH process
- Summary

Role of non-clinical data through the drug development process



Potentially problematic timing:
Carcinogenicity studies during drug development

Genotoxicity studies:



Carcinogenicity studies:

Content

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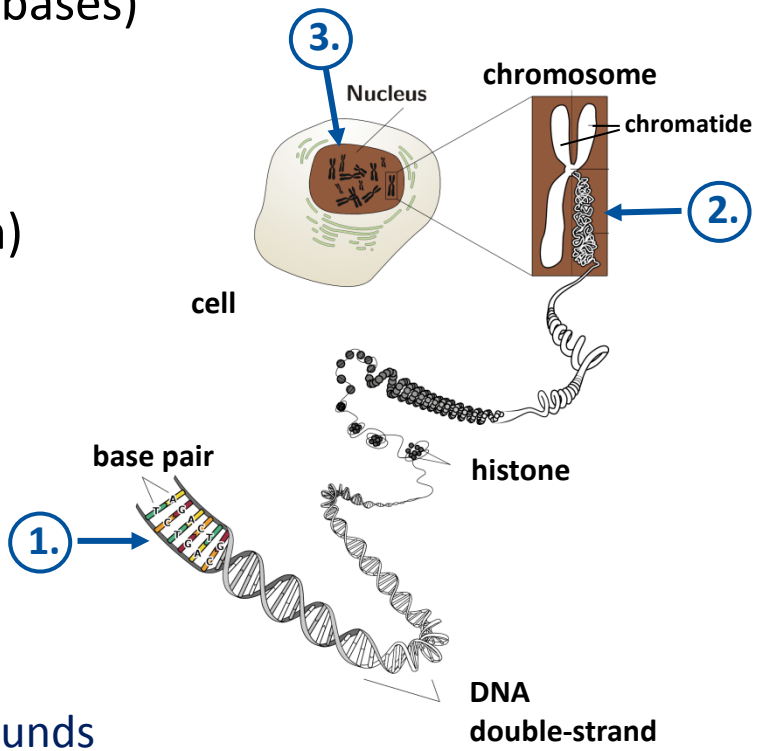
Types of mutations

1. Gene mutation (changes in the sequence of bases)
   - base-pair substitution (“point mutation“)
   - insertion or deletion of single base-pair
     -> frameshift mutation
2. Chromosome mutation (structural alteration)
   - deletion, insertion, translocation/exchanges
   - “clastogenicity“
3. Genome mutation
   (numerical chromosome alteration)
   - Aneuploidy (e.g., 2n +1, 2n -1)
   - Polyploidy (e.g., 3n, 4n)



All types can be induced by chemical compounds

All types of mutations are involved in cancer development

No single genotoxicity test can detect all types of mutations

Genotoxicity in ICH guidelines

ICH	GuidelineTitel	Comments
S2 (R1) 2012	**Genotoxicity testing and data interpretation**	• **Defines standard testing battery & design of studies** • **data interpretation and follow-up testing** • **Focus on "small molecules"**
S6 (R1)	Preclinical safety evaluation of biotechnology-derived pharmaceuticals	• Genotoxicity tests usually not needed unless there is a cause for concern • Standard genotoxicity tests are not applicable
S9	Nonclinical evaluation for anticancer pharmaceuticals	• Genotoxicity studies not required to support clinical trials for therapeutics intended to treat patients with late stage/advanced cancer • Genotoxicity studies required to support marketing
M3 (R2)	Non-clinical safety studies for the conduct of human clinical trials and marketing authori-zation for pharmaceuticals	• Single dose clinical trials: One assay for gene mutation • Multiple dose clinical trials: Additional assay detecting chromosomal damage in a mammalian cells • Phase II trials: Complete battery of tests for genotoxicity
M7 2014	Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk	• Focus on QSAR-/Ames-positive impurities • Defines acceptable levels of mutagenic impurities that pose negligible carcinogenic risk (TTC concept)

ICH S2 (R1) Recommended test battery
Option 1

1. Test for gene mutations in bacteria (Ames test)

2. Test for chromosomal damage in mammalian cells
   - *in vitro* chromosomal aberration assay or
   - *in vitro* micronucleus assay or
   - *in vitro* mouse lymphoma *TK* gene mutation assay

3. *In vivo* test for chromosomal damage (blood or bone marrow)
   - acute stand-alone test or
   - integrated into repeat dose toxicity study

ICH S2 (R1) Recommended test battery
Option 2

1. Test for gene mutations in bacteria (Ames test)

2. Test for chromosomal damage in mammalian cells
   - *in vitro* chromosomal aberration assay or
   - *in vitro* micronucleus assay or
   - *in vitro* mouse lymphoma *TK* gene mutation assay

3. *In vivo* test for chromosomal damage (blood or bone marrow)
   - acute stand-alone test or
   - (integrated into repeat dose toxicity study)
   - plus comet (DNA strand breakage) assay in liver

combined

Standard battery: all negative

- Sufficient assurance of absence of genotoxic activity, further testing normally not necessary

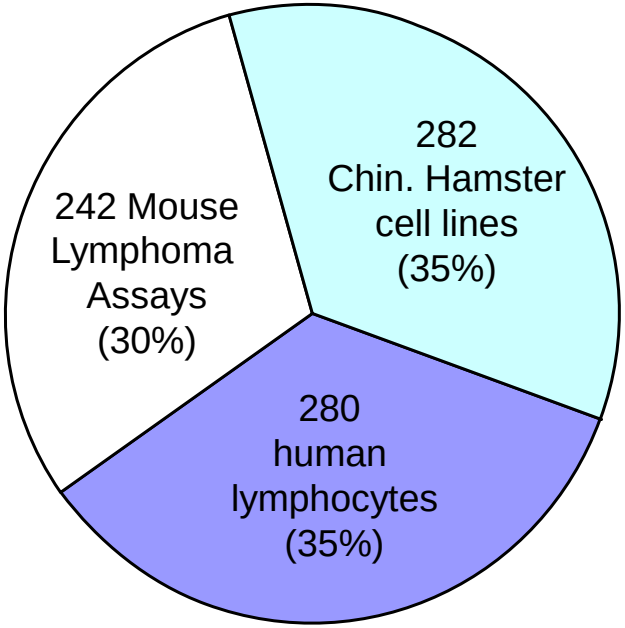
- Factors that may indicate a need for further testing:
  - human metabolite not present in preclinical models
  - carcinogenic activity without clear non-mutagenic mode of action
  - structural alert / class-specific effects

- Additional testing appropriate to concern

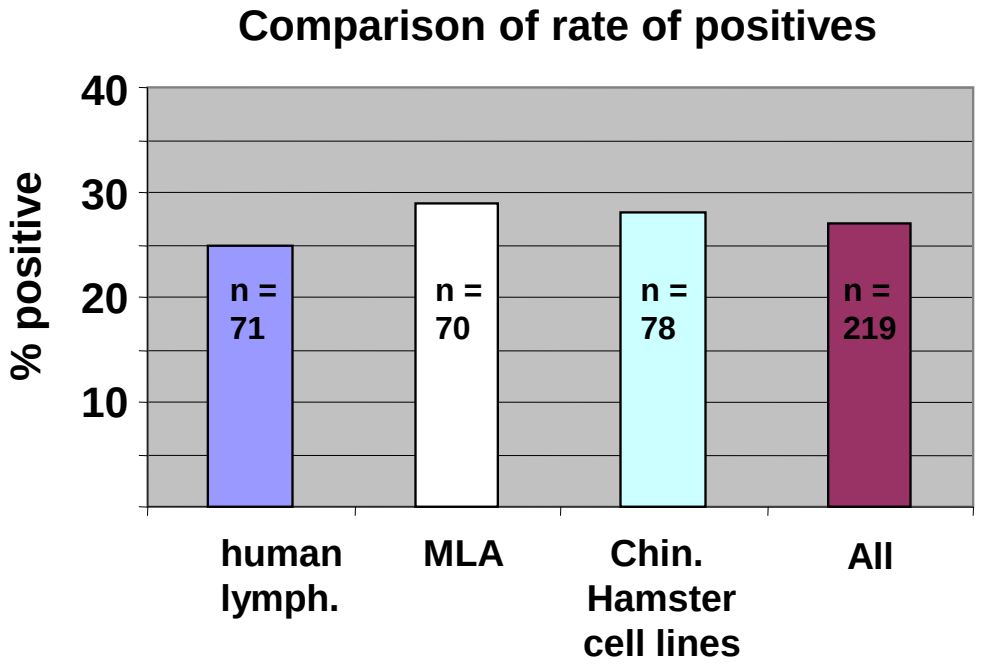
Impact of positive genotoxicity findings on drug development

- *In vitro* mammalian cell test
  - frequent; additional studies to clarify relevance

Incidence of *in vitro* mammalian cell test "positives" in regulatory submissions



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



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

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Avoidance of irrelevant *in vitro* positives

- Do not exceed the recommended top concentration of 1 mM
- Use appropriate measure of cytotoxicity (updated OECD guidelines)
- Do not exceed the requested limits of cytotoxicity
- Do not test into precipitating range
- Use appropriate target cells (p53 proficient)
  - Human lymphocytes
  - Human lymphoblastoid cell line
  - Less appropriate cells (p53 deficient) commonly used:
    Mouse lymphoma, chinese hamster cell lines (CHO, CHL, V79)

Impact of positive genotoxicity findings on drug development

- *In vitro* mammalian cell test
  - frequent; additional studies to clarify relevance
- Ames test
  - rare event; triggers termination of development
  - Special case: Ames-positive metabolite (discovered late in development)
- *In vivo* MN (and/or) other *in vivo* studies
  - rare; usually termination of development
  - or mechanistic data to demonstrate lack of clinical relevance

Role of genotoxicity data in relation to carcinogenicity (and vice versa)

- In the absence of carcinogenicity data:
  - for prediction of carcinogenic potential
    (e.g. when starting first clinical trials)
  - positive genotoxicity may lead to request for assessing possible cancer risk before continuing clinical trials

- In the presence of carcinogenicity findings:
  - as part of Mode-of-Action (MOA) evaluation in cancer risk assessment
  - provide insight whether the dose-response curve is likely to be linear or non-linear at low doses

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Current carcinogenicity testing approach (ICH S1)

two-year rat study

+

two-year mouse study

or

6- or 9-month transgenic mouse study

… the most expensive, time- and resource consuming studies in toxicology.
Yet, the results are often of doubtful human relevance!

Regulatory Toxicology and Pharmacology 60 (2011) 225–248

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Evaluation of carcinogenicity studies of medicinal products for human use authorised via the European centralised procedure (1995–2009)

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Active substances with carcinogenicity data	Number	%
All compounds	144	100
- Negative in mice and/or rats	50	35
- **Positive** in mice and/or rats	94	65

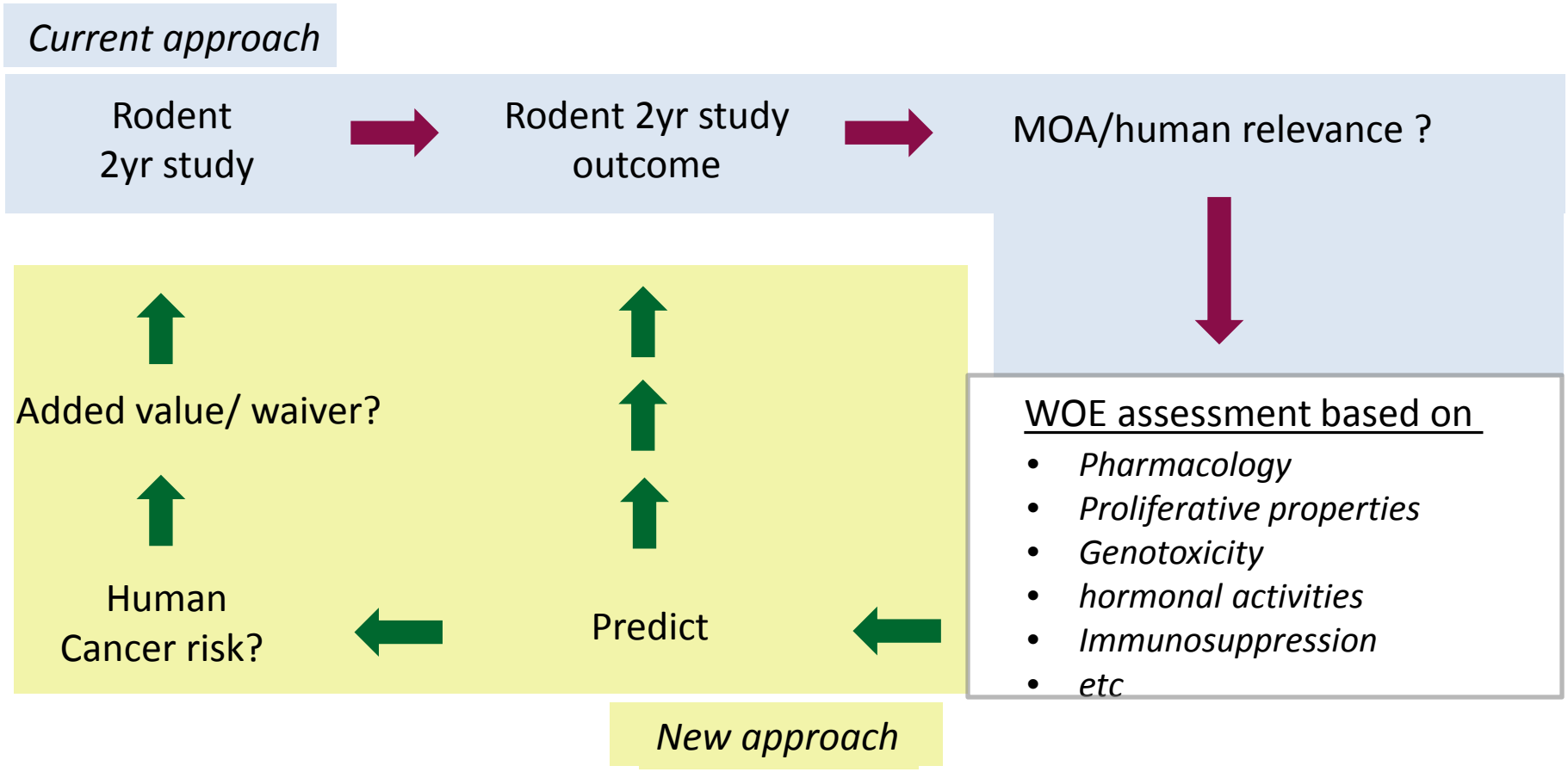
Key steps in evaluating the human relevance of rodent tumors:

1. Is the **weight of evidence (WOE)** sufficient to establish a **mode of action (MOA)** in animals

2. Is this MoA relevant to humans

3. Is the MoA relevant to the conditions of (much lower) human exposure

Current approach vs new proposal



Revised March 2016

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

September 2013
EMA/CHMP/ICH/752486/2012
Committee for Medicinal Products for Human Use (CHMP)

ICH guideline S1
Regulatory notice on changes to core guideline on rodent carcinogenicity testing of pharmaceuticals

Transmission to CHMP	December 2012
Adoption by CHMP for release for consultation	December 2012
End of consultation (deadline for comments)	April 2013
Final adoption by CHMP	September 2013
Release for information	September 2013

Proposed Hypothesis

- Carcinogenicity assessment could be completed for certain pharmaceuticals without conducting a 2-yr rat carcinogenicity study.
- Pharmacological and toxicological data from numerous sources can be integrated to predict that a pharmaceutical will fall into one of 3 categories:

ICH S1 Regulatory notice on changes to core guideline on rodent carcinogenicity

Category	Description	
1	• likely to be **tumorigenic in humans** • product would be labeled as such • rodent carc studies would **not add value**	
2	• **tumorigenic potential for humans is uncertain** • rodent carc studies are likely to **add value** to human risk assessment	
3a	• likely to be **tumorigenic in rats but not in humans** • a 2-yr rat study would **not add value**	
3b	• likely **not to be tumorigenic in both rats and humans** • no 2-yr rat study is needed	

Proposed Hypothesis

- Carcinogenicity assessment could be completed for certain pharmaceuticals without conducting a 2-yr rat carcinogenicity study.
- Pharmacological and toxicological data from numerous sources can be integrated to predict that a pharmaceutical will fall into one of 3 categories.
- Sponsors can provide a **Carcinogenicity Assessment Document (CAD)** which could justify a ‘waiver request‘ to omit the conduct of 2-yr rat studies.

ICH S1 Regulatory notice on changes to core guideline on rodent carcinogenicity

Category	Description	Waiver Request
1	• likely to be **tumorigenic in humans** • product would be labeled as such • rodent carc studies would **not add value**	Yes
2	• **tumorigenic potential for humans is uncertain** • rodent carc studies are likely to **add value** to human risk assessment	No
3a	• likely to be **tumorigenic in rats but not in humans** • a 2-yr rat study would **not add value**	Yes
3b	• likely **not to be tumorigenic in both rats and humans** • no 2-yr rat study is needed	Yes

Weight-of-Evidence (WOE) Elements

- The CAD would address the overall carcinogenic risk of the investigational drug as predicted by WOE elements
  - Knowledge of intended drug target and pathway pharmacology, secondary pharmacology, & drug target distribution in rats and humans
  - Histopathological Evaluation of Repeated Dose Rat Toxicology Studies
  - Genetic Toxicology Study Results
  - Evidence of Hormonal Perturbation
  - Immune Suppression
  - Special (Mechanistic) Studies and Endpoints
  - Results of Non-Rodent Chronic Study
  - Transgenic Mouse Study

Weight-of-Evidence (WOE) Elements

- The CAD would address the overall carcinogenic risk of the investigational drug as predicted by WOE elements
  - Knowledge of intended drug target and pathway pharmacology, secondary pharmacology, & drug target distribution in rats and humans
  - **Histopathological Evaluation of Repeated Dose Rat Toxicology Studies**
  - **Genetic Toxicology Study Results**
  - **Evidence of Hormonal Perturbation**
  - Immune Suppression
  - [illegible]
  - [illegible]
  - [illegible]

Retrospective analysis in:

Sistare FR et al (2011) *An analysis of pharmaceutical experience with Decades of rat carcinogenicity testing: Support for a proposal to modify current regulatory guidelines.* ***Toxicol Pathol 39, 716-744.***

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  - E
  - In
  - Sp
  - Results of Non-Rodent Chronic Study
  - Transgenic Mouse Study

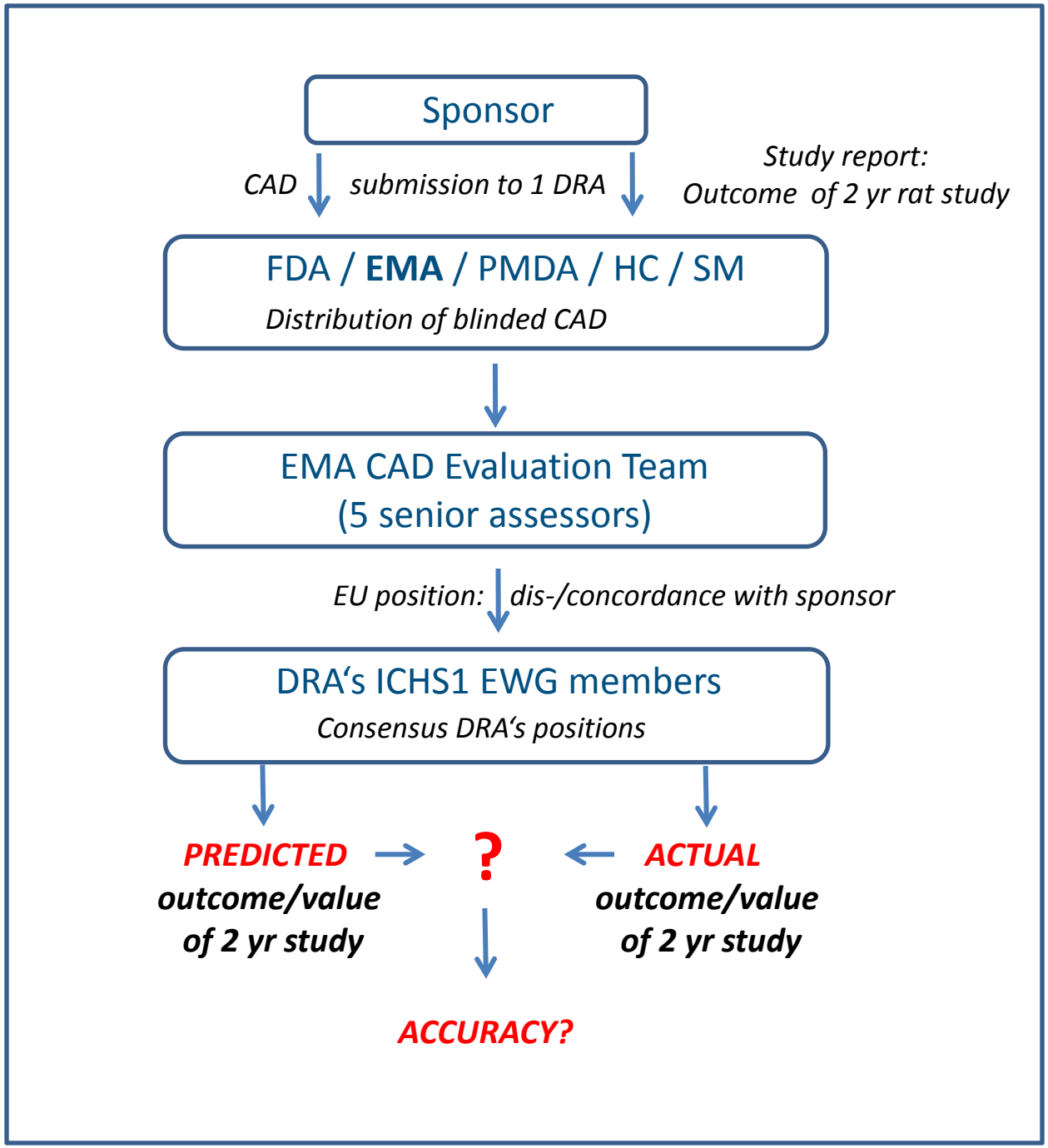
Retrospective analysis in:
van der Laan JW et al (2016) *Critical analysis of carcinogenicity outcomes. Relationship with pharmacological properties.* ***Critical Reviews in Toxicology 46, 587-614.***

Prospective evaluation of the proposed hypothesis…

- … to justify proceeding with the revision of the ICH S1 guidance.

- Sponsors are encouraged to submit the CAD to Drug Regulatory Authorities (DRAs) for all investigational pharmaceuticals with ongoing or planned 2-yr rat carcinogenicity studies
- explaining and justifying their position that a waiver decision is, or is not, appropriate prior to knowing the outcome of carcinogenicity testing.

Prospective evaluation: The (EU) process



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Template for use in submitting a CAD: Mock Case

Directions to Sponsor: *Complete the left-side column for prediction of rat tumor outcome, value to overall carcinogenicity assessment and human risk implications, and categorical assignment/waiver request. The reviewing DRA will complete the 'DRA Concurrence' cell after review of the CAD, and will complete the right-side column after review of the 2yr rat carcinogenicity study report.*

Tumor Outcome from 2yr Rat Carcinogenicity Study

Prediction by Sponsor	**Actual Outcome According to Sponsor**
(positive/negative; and target organs) (consider "uncertain prediction" only for Category 2) **No tumors related to treatment are expected based on WOE assment**	(positive/negative; and target organs) **Negative**
	Actual Outcome According to DRA (positive/negative; and target organs) **Negative**

Value to carcinogenicity assessment and human risk implications

Projected Value	**Actual Value**
Low to none	**None**

Categorical Assignment and Waiver Request

Predicted Category by Sponsor	**DRA Concurrence (Y/N)** **Predicted Category**	**Actual Category**
Category 3b	**Category 2**	**Category 3b**
Waiver requested (Y/N) **YES**	Waiver supported (Y/N) **NO**	Waiver supported (Y/N) **YES**

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Number of CADs received and reviewed

Status Dec 2015: **25 CADs**

ICH S1 Report March 2016

	Sponsor	DRAs
Category 1	2	1
Category 2	7	15
Category 3A	8	5
Category 3B	8	1
Partial DRAs Alignement	-	3

Status Aug 2016: **plus 10 CADs**

	Sponsor	DRAs
Category 1	1	?
Category 2	3	?
Category 3A	2	?
Category 3B	4	?
Partial DRAs Alignement	-	?

DRA-sponsor disagreement on category 3a/b

… that prompted DRAs to choose category 2 (6 cases)

- Differences in scientific interpretation of the data presented
  - Relevance of toxicity or hormonal findings from chronic studies
  - Implications of pharmacological complexity and/or off target activity
  - Importance of prior experience with other compounds in the same/similar pharmacological class

- Deficiencies in the CAD write-ups
  - Relevant literature was missing
  - Comparative exposure data for human metabolites was missing
  - Assessment of target selectivity not well described

Conditions & timeline for interim/final evaluation

- **Category 3** most important as such cases dictate the conditions under which a 2 yr rat study waiver is feasible

- **Interim analysis** (November 2016):
- ≥ 6 *category 3* cases (i.e. CAD + study report) & ≥ 10 *category 2* cases
- Category 3 cases = CADs where at least one DRA concurs with sponsor

- **<u>Decisional</u> analysis (end of 2019):**
- ≥ 20 *category 3* cases & X number of total cases
- **<u>Outcome to define the scope of potential modification to S1 Guidelines</u>**

Summary: Take home messages

- Genetic toxicity & carcinogenicity testing is a pivotal part of preclinical testing package of new chemical entities
- Standard testing approaches are well defined in ICH guidelines but interpretation of study outcome can be a challenge
- Assessment of positive findings needs expert knowledge
  - Weight-of-evidence
  - Mode-of-action
- Relevant non-clinical findings can have a severe impact in overall benefit/risk assessment (usually not over-ruled by clinical data)
- An ongoing ICH S1 project is testing the ability of sponsors and DRAs to prospectively predict the outcome of carcinogenicity studies based on a weight-of-evidence approach

Thank you very much for your attention!

Contact

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