PreClinical Safety
CONSULTANTS LIMITED

AGAH Workshop Oktober 2010

ICH M3 (R2) 2009

Auswirkungen auf die präklinische Arzneimittelentwicklung
Auswahl von Dosis und Studiendauer

PCS, for all your outsourced preclinical safety needs

Übersicht

- Auswahl der hohen Dosis in Toxizitätsstudien
  - Definition in ICH M3(R2)
  - Definitionen in anderen Guidelines
    - Ergänzend und/oder widersprüchlich:
      Reproduktion, Kanzerogenese, Genetische Toxizität, Juvenile Toxizität
    - Verschiedene Ansätze in den regulatorischen ICH-Regionen
  - Limit Dose und Exposition
  - Definition Safety Ratio
- Studiendauer in Toxizitätsstudien
  - Definition in der ICH M3(R2)
  - Beispiele aus dem Entwicklungsalltag
- Zusammenfassung und Schlussfolgerungen

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Auswahl der hohen Dosis in Toxizitätsstudien

- Konzept zum ersten Mal in ICH M3 aufgenommen
- Bezug zu anderen Richtlinien
  - Reproduktionstoxikologie (ICH S5)
  - Kanzerogenität (ICH S1)
  - Genetische Toxizität (OECD)
  - EU vs. US – verschiedene Auffassungen sind impliziert

Definitions used in ICH M3(R2)

- "Generally, in toxicity studies, effects that are potentially clinically relevant can be adequately characterized using doses up to the maximum tolerated dose (MTD)"
  - It is not essential to demonstrate the MTD in every study
- Other equally appropriate limiting doses include those
  - that achieve large exposure multiples or saturation of exposure
  - use the maximum feasible dose (MFD)
  - These limit doses *prevent the use of doses in animals that would not add value to predicting clinical safety*
- These recommendations are consistent with those for reproduction and carcinogenicity study designs that already have defined limit doses and/or exposures

Definitions used in ICH M3(R2) (2)

- Limit doses for acute, subchronic, and chronic toxicity studies of **1000 mg/kg/day** for rodents and non-rodents are considered appropriate in all cases except those discussed below
- In the few situations where a dose of 1000 mg/kg/day does not result in a mean exposure margin of 10-fold to the clinical exposure and the clinical dose exceeds 1 g per day, then the **doses** in the toxicity studies should be **limited by a 10-fold exposure margin or** a dose of **2000 mg/kg/day** or the **MFD**, whichever is **lower**
- In those rare situations in which the dose of 2000 mg/kg/day results in an exposure that is less than the clinical exposure, a higher dose **up to the MFD** can be considered

Definitions used in ICH M3(R2) (3)

- Doses providing a 50-fold margin of exposure (usually based on group mean AUC values [see Note 1] of the parent drug or the pharmacologically active molecule of a pro-drug) to the clinical systemic exposure generally are also considered acceptable as the maximum dose for acute and repeated-dose toxicity studies in any species
  - Note 1: In this document “exposure” generally means group mean AUC. In some circumstances (e.g., if the compound or compound class is known to produce acute functional cardiovascular changes or central nervous system-related clinical signs) it might be appropriate to base the exposure margin on group mean Cmax values rather than AUC

Definitions used in ICH M3(R2) (4)

- To support Phase III clinical trials for the United States, dose-limiting toxicity generally should be identified in at least one species when using the 50-fold margin of exposure as the limit dose
- If this is not the case, a study of one-month or longer duration in one species that is conducted at the 1000 mg/kg limit dose, MFD or MTD, whichever is lowest, is recommended
  - However, on a case-by-case basis this study might not be warranted if a study of a shorter duration identifies dose-limiting toxicity at doses higher than those resulting in a 50-fold exposure margin

Definitions used in ICH M3(R2) (5)

- If genotoxicity endpoints are to be incorporated into a general toxicity study, then an appropriate maximum dose should be selected based on a MFD, MTD or limit dose of 1000 mg/kg/day
- *NOTE: no reference is made to OECD guidance which defines appropriate maximum doses in genetic toxicity studies*
- *Standard battery of genotoxicity tests requires:*
  - An *in vivo* test for chromosomal damage using rodent hematopoietic cells
    - OECD 474: Mammalian Erythrocyte Micronucleus Test („MNT in vivo“)
    - The highest dose is defined as the dose producing signs of toxicity such that higher dose levels, based on the same dosing regimen, would bexpected to produce lethality.

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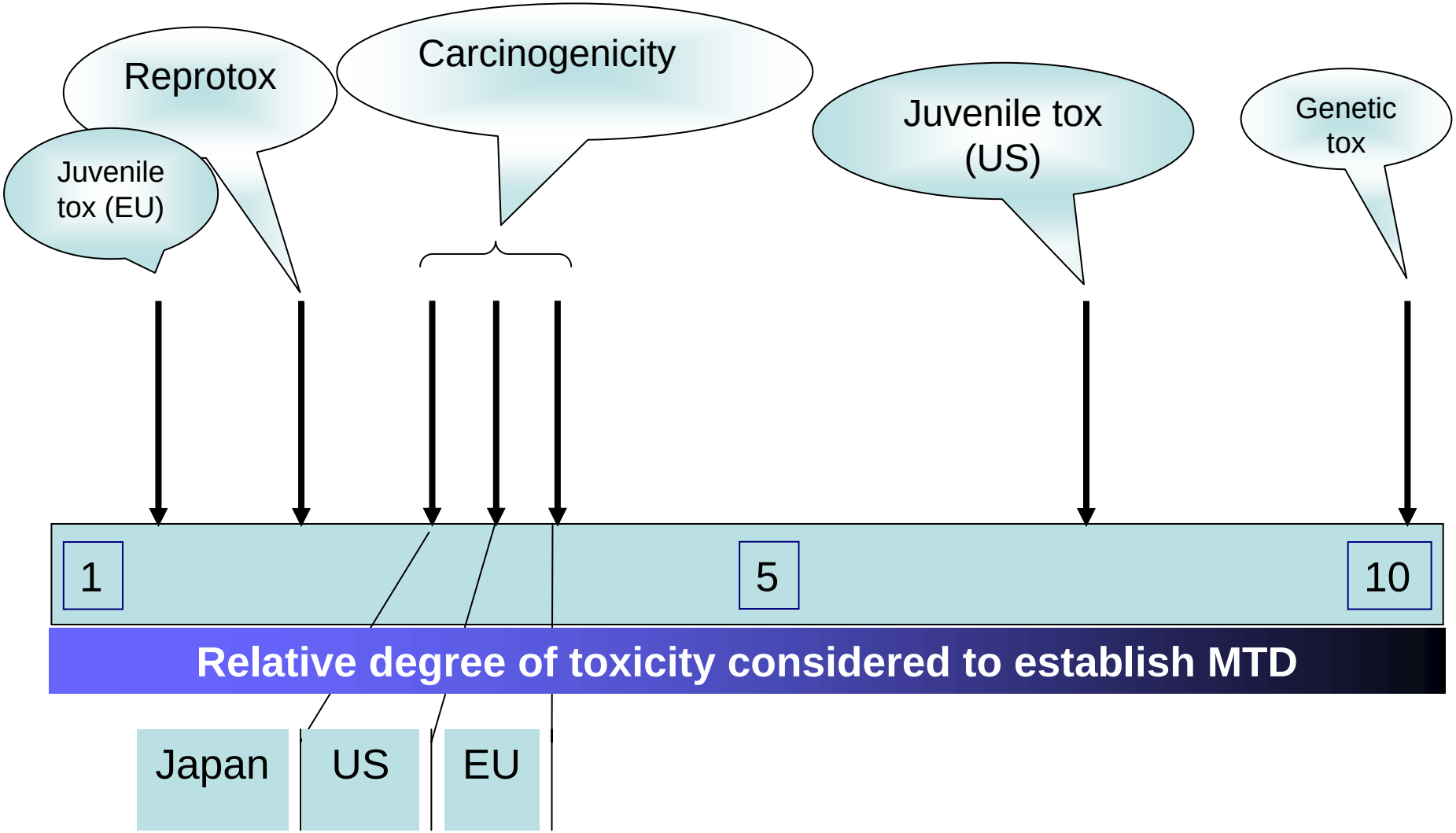
What is tolerance?



MTD definitions in related guidances cited in ICH M3(R2) – Reproductive toxicity ICH S5(R2)

- ICH S5(R2) Guideline: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility; June 1993 (Addendum dated 9 November 2000 incorporated in November 2005)
- Selection of dosages:
  - Using similar doses in the reproductive toxicity studies as in the repeated dose toxicity studies will allow interpretation of any potential effects on fertility in context with general systemic toxicity
  - Some minimal toxicity is expected to be induced in the high dose dams
  - Having determined the high dosage, lower dosages should be selected in a descending sequence, the intervals depending on kinetic and other toxicity factors. Whilst it is desirable to be able to determine a "no observed adverse effect level", priority should be given to setting dosage intervals close enough to reveal any dosage related trends that may be present.

MTD definitions in related guidances cited in ICH M3(R2) – Reproductive toxicity ICH S5(R2) (2)

- According to the specific compound, factors limiting the high dosage determined from repeat dose toxicity studies or from preliminary reproduction studies could include:
  - reduction in bodyweight gain or increased bodyweight gain, particularly when related to perturbation of homeostatic mechanisms
  - specific target organ toxicity
  - haematology, clinical chemistry
  - exaggerated pharmacological response, which may or may not be reflected as marked clinical reactions (e.g. sedation, convulsions)
  - the physico-chemical properties of the test substance or dosage formulation which, allied to the route of administration, may impose practical limitations in the amount that can be administered. Under most circumstances 1 g/kg/day should be an adequate limit dose.
  - kinetics, they can be useful in determining high dose exposure for low toxicity compounds. There is, however, little point in increasing administered dosage if it does not result in increased plasma or tissue concentration
  - marked increase in embryo-fetal lethality in preliminary studies

MTD definitions in related guidances cited in ICH M3(R2) – Carcinogenicity ICH S1C(R2)

- ICH S1C(R2) Guideline: Dose Selection for Carcinogenicity Studies of Pharmaceuticals; March 2008.
- Ideally, the doses selected for rodent bioassays for non-genotoxic pharmaceuticals should provide an exposure to the agent that
  - (1) allow an adequate margin of safety over the human therapeutic exposure
  - (2) are tolerated without significant chronic physiological dysfunction and are compatible with good survival
  - (3) are guided by a comprehensive set of animal and human data that focus broadly on the properties of the agent and the suitability of the animal
  - (4) and permit data interpretation in the context of clinical use

MTD definitions in related guidances cited in ICH M3(R2) – Carcinogenicity ICH S1C(R2) (2)

Toxicity endpoint in high dose selection

- The top dose or maximum tolerated dose is that which is predicted to produce a minimum toxic effect over the course of the carcinogenicity study.
- Such an effect may be predicted from a 90-day dose range-finding study in which minimal toxicity is observed. Factors to consider are alterations in physiological function which would be predicted to alter the animal's normal life span or interfere with interpretation of the study.
- Such factors include
  - no more than 10% decrease in body weight gain relative to controls
  - target organ toxicity
  - significant alterations in clinical pathological parameters.

ICH S1C(R2) Carcinogenicity: NOTE 1 DEFINITION (1)

Equivalent definitions of the toxicity based endpoint describing the MTD

- The US Interagency Staff Group on Carcinogens has defined the MTD as follows:
  - "The highest dose currently recommended is that which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity without significantly altering the animal's normal lifespan due to effects other than carcinogenicity. This dose, sometimes called the maximum tolerated dose (MTD), is determined in a subchronic study (usually 90 days duration) primarily on the basis of mortality, toxicity and pathology criteria.
  - The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study. […]."

ICH S1C(R2) Carcinogenicity: NOTE 1 DEFINITION (2)

Equivalent definitions of the toxicity based endpoint describing the MTD

- "The MTD was initially based on a weight gain decrement observed in the subchronic study; i.e., the highest dose that caused no more than a 10% weight gain decrement.
  - More recent studies and the evaluation of many more bioassays indicate refinement of MTD selection on the basis of a broader range of biological information.
- Alterations in body and organ weight and clinically significant changes in haematologic, urinary, and clinical chemistry measurements can be useful in conjunction with the usually more definitive toxic, pathologic or histopathologic endpoints." (Environmental Health Perspectives, Vol. 67, pp. 201-281, 1986)

ICH S1C(R2) Carcinogenicity: NOTE 1 DEFINITION (3)

Equivalent definitions of the toxicity based endpoint describing the MTD

- The Ministry of Health and Welfare in Japan prescribes the following:
  - "The dose in the preliminary carcinogenicity study that inhibits body weight gain by less than 10% in comparison with the control and causes neither death due to toxic effects nor remarkable changes in the general signs and laboratory examination findings of the animals is the highest dose to be used in the full-scale carcinogenicity study." (Toxicity test guideline for pharmaceuticals, Chapter 5, pg. 127, 1985)
- The Committee on Proprietary Medicinal Products of the European Community prescribes the following:
  - "The top dose should produce a minimum toxic effect, for example a 10% weight loss or failure of growth, or minimal target organ toxicity. Target organ toxicity will be demonstrated by failure of physiological functions and ultimately by pathological changes." (Rules Governing Medicinal Products in the European Community, Vol. III, 1987)

Other dose selection criteria in related guidances cited in ICH M3(R2) – Carcinogenicity ICH S1C(R2): Pharmacokinetics

Pharmacokinetic endpoint in high dose selection

- A systemic exposure representing a large multiple of the human AUC (at the maximum recommended daily dose) can be an appropriate endpoint for dose selection for carcinogenicity studies for pharmaceuticals which have similar metabolic profiles in humans and rodent and low organ toxicity in rodents (high doses are well tolerated in rodents)
- There is, as yet, no validated scientific basis for use of comparative drug plasma concentrations in animals and humans for the assessment of carcinogenic risk to humans
- However, for the present, and based on an analysis of a database of carcinogenicity studies performed at the MTD, the selection of a high dose for carcinogenicity studies which represents a 25-fold ratio of rodent to human plasma AUC of parent compound and/or metabolites is considered pragmatic
- *Saturation of absorption is a possible limiting factor for the selection of the high dose*

FDA: Guidance for Industry 2006
Nonclinical Safety Evaluation of Pediatric Drug Products

- It is important to establish a clear dose-response relationship for adverse effects in juvenile animals, when possible.
- The high dose should produce identifiable toxicity (either developmental or general).
- The intermediate dose should produce some toxicity so that a dose-response relationship can be demonstrated if one exists.
- The low dose should produce little or no toxicity, and a NOAEL should be identified, if possible.
- We recommend evaluating and potentially modifying intermediate and low doses in relation to those that produce the desired pharmacodynamic effect in the test species.

Other guidelines defining the MTD: Juvenile toxicity (2)

EMA: 2008
Guideline on the Need for Non-clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications

- The primary purpose of juvenile animal studies is to assess whether juvenile animals have a different sensitivity to a medicinal product compared with adult animals, and to identify effects on developing organs.
- It is recommended that doses in the lower part of the dose response curve established in adult animals are selected. To bridge to the existing adult animal data, a common dose, preferably resulting to similar systemic exposure, and preferably in the low dose range (NOAEL or NOEL), should generally be included in the juvenile animal studies.
- The high dose should achieve some identifiable toxicity, but not result in marked toxicity which may complicate the assessment.
- The low dose should preferably result in exposure levels similar to the anticipated clinical exposure in the intended population. An intermediate dose level might not be necessary in juvenile animal studies if the differences between the low and high doses are relatively small.
- In the absence of a NOAEL in the general toxicology studies, a dose range finding study in juvenile animals is advocated together with toxicokinetic evaluations to support dose selection.

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Limit dose und Exposition – Vergleich

Guidance	Limit Dose (human)	Limit dose (rodent & non-rodent)	Multiples in exposure	Other
	[mg/person/day]	[mg/kg/day]		
ICH M3(R2)	≤ 1000	1000	≥ 10	n/a
	≥ 1000	up to 2000	≤ 10	MFD
	n/a	2000	< human exp	**Up to MFD***
	n/a	n/a	50	n/a
ICH S1C(R2) Carcinogenicity	≤ 500	1500	≥ 10	n/a
	> 500	n/a	25	**Up to MFD**
ICH S5(R2) Reproduction	n/a	1000	n/a	n/a

*MFD = Maximum feasible dose

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Definition Safety Ratio

- Verhältnis von
  - Systemischer Exposition in der Toxspezies bei der Dosis, die als NOAEL identifiziert wurde
  - zur
  - Systemischen Exposition des Menschen nach Gabe der MRHD (maximal empfohlenen menschlichen Dosis)
- In der Regel basierend auf AUC
  - In bestimmten Fällen ist die Cmax relevanter
  - ICH M3(R2) nennt ausdrücklich ZNS- und kardiovaskuläre Toxizität
- „Magische Grenze“: Vielfaches zur menschlichen Exposition = 10
  - Nicht ganz klar definiert, auf welche Dosis sich dieser Wert jeweils bezieht
  - Wird herangezogen, um die maximale Dosis zu bestimmen

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Studiendauer ICH M3(R2)

„In principle, the duration of the animal toxicity studies conducted in two mammalian species (one non-rodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies.“

ICH M3(M): Festgelegte Studiendauer

Beispiel 1: Single extended dose

- Single extended dose Studien sind jetzt auch in EU möglich
- Akzeptiertes Konzept in USA
- ICH M3(M) Akutindikationen: 14-Tage Studien waren vorgeschrieben
- Oft irrelevante Toxizität und limitierte Exposition
  - Oft keine wirklich relevante Risikoabschätzung möglich
  - Entweder beide Studientypen oder nur 14-Tage Studie
  - Neues Konzept ermöglicht auch 3R‘s
    - „Replacement“

Beispiel 2: Adaptierte Studiendauer

- Tierstudien können an die Dauer der klinischen Studie angepasst werden
- Möglicherweise relevantere Risikoabschätzung
  - Bei kürzerer Dauer höhere Dosierung möglich
  - Bildet die klinische Realität besser ab
- Caveat: Historische Daten in den Labors werden variabler
- Standardisierung nimmt ab

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Zusammenfassung (1): MTD

- ICH M3(R2)
  - Addressiert die Dosiswahl für die hohe Dosis in toxikologischen Studien zum ersten Mal
  - Macht den Versuch, andere Guidelines zu integrieren
  - Impliziert die unterschiedlichen Auffassungen in den verschiedenen Regionen
  - Bildet in gewissem Ausmaß die Realität ab

Zusammenfassung (2): MTD und NOAEL

- Praktischer Alltag
  - ~~MTD US = MTD EU = MTD Japan~~?
  - Definition der MTD variiert von Guideline zu Guideline
  - Exposition spielt für US FDA eine untergeordnete Rolle
    - Toxizität wird höher bewertet
    - Am unteren Ende der Dosiswirkungskurve (NOAEL) wird überschießender Pharmakodynamik höhere Bedeutung beigemessen
      - **Erniedrigt das NOAEL und erhöht die MTD**
- Dosisselektion für klinische Studien basiert daher auf z.T. erheblich unterschiedlichen Toxizitäten (Schwere)

Schlussfolgerungen (1): 3 R's und globale Entwicklungsstrategie

- **Wie kann man ICH M3(R2) nutzen, um die 3R's zu verwirklichen und die Entwicklung zu erleichtern (Ref 1.1: Objectives of the guideline)?**
  - **MTD früh und eindeutig bestimmen durch**
    - ***Intelligente Dosisfindungsstudien***
      - Machen Akuttoxstudien überflüssig
      - Erlauben fundierte Dosiswahl für die pivotalen GLP-Studien
      - Spätestens die 4-Wochen Studien sollten die MTD über diesen Zeitraum zweifelsfrei festlegen
      - Spätere länger dauernde Studien können entsprechend geplant werden
    - ***Ausreichend ausgelegte pivotale Studien***
      - Unbedingt genügend Tiere einschließen, um klare Aussagen treffen zu können!
        - Zu wenige Tiere erlauben keine klare Aussage
        - Studien müssen dann oft wiederholt werden – Tiere und andere Ressourcen werden verschwendet
      - Wenn nötig: zusätzliche Dosisgruppen
        - Abweichend vom klassischen 4-Gruppen Design (control, low, mid, high)

- **Spart Tiere und Wiederholung von Studien in späteren Phasen der Entwicklung**
- **Stimmt überein mit der Auffassung aller Guidelines und dem Verständnis der verschiedenen Regionen**

Schlussfolgerungen (2): Globale Entwicklungsstrategie

- **ICH kreativ nutzen**
  - **Globale Entwicklung von vornherein anstreben**
- **Frühzeitig den proaktiven Dialog mit den Behörden suchen und alle Möglichkeiten ausschöpfen:**
  - **“Offizielle” Meetings und formale Abläufe (z.B. SPA)**
  - **Dynamische Interaktion**
  - **Entwicklungsplan fortlaufend diskutieren und abstimmen**
  - **Art der Studien, Spezies, Risikobewertung, Risikomanagement**
  - **Unterschiede als Chance begreifen**
  - **Grundlage für Entscheidungen schaffen**

Vielen Dank für Ihre Aufmerksamkeit!

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