



Dose Selection for Carcinogenicity Studies of Pharmaceuticals

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Outline

- Scope of the Guideline **ICH S1C**
- General considerations for the conduct of dose-ranging studies
- Choice in endpoints in high dose selection
- Criteria for the use of AUC in high dose selection
- Other endpoints
- Summary



Introduction

Carcinogenicity studies for chemical agents

- Dose selection based on Maximal Tolerated Dose (MTD)
- MTD based on 3 months study

For Pharmaceuticals

- Dose selection based on several approaches including “high multiple” approach in case of low toxicity compounds in some regions



Scope

Pharmaceuticals for which carcinogenicity studies are needed

- S1A The need for carcinogenicity studies
- S1B Selection of species
- S1C Dose selection for Carcinogenicity Studies



Dose selection in carcinogenicity studies

Situation in the past

Endpoints for high dose selection

Default: Maximum Tolerated Dose

With compounds of low toxicity:

Europe/ Japan

High dose selection > 100 times Maximum recommended
human daily dose (in mg/kg)

USA

Maximum Tolerated Dose

All areas: maximum feasible dose (if applicable)



Dose selection in carcinogenicity studies

Ideally

High Doses selected should provide an exposure

1. Allows an adequate margin of safety over the human therapeutic dose
2. Is tolerated without significant chronic physiological dysfunction and is compatible with good survival
3. Is guided by a comprehensive set of animal and human data
4. Permits data interpretation in the context of clinical use.



Dose selection in carcinogenicity studies

Rational approach

Consider all relevant animal and human data available.

Including

pharmacodynamics

pharmacokinetics

toxicity data



Dose selection in carcinogenicity studies

Rational approach

General considerations

1. Carcinogenicity studies in limited number of rat and mouse strains. Ideally the same metabolic profile
2. Dose range studies for males and females
3. Dose selection determined from \geq 90-day studies
4. Appropriate dosing schedule based on clinical use and exposure patterns
5. Ideally toxicity profile and dose-limiting toxicity to be defined
6. Changes in metabolic profiles over time should be understood



Toxicity endpoints harmonized definition of MTD

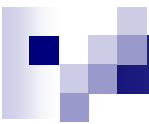
Operational definition

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 can 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.



Pharmacokinetic endpoints criteria based on AUC comparison

- Systemic exposure representing large multiple of human exposure at Maximum Recommended Human dose
- Unbound plasma concentration most relevant measure and AUC most comprehensive parameter
- Selection of a high dose representing a 25- to-1 exposure ratio of rodent to human plasma AUC of parent compound and/or metabolites pragmatic proposal



Pharmacokinetic high dose endpoint (ratio 25)

- Old situation
 - Only to be used in case of nongenotoxic compounds
i.e. strictly no positive signals in battery
- New situation after revision
 - To be used in case of all human pharmaceuticals, also
if positive genotox signals are present

Note: Real genotoxic compounds are not expected to be tested
(see ICH S1A)



Pharmacokinetic endpoints criteria based on AUC comparison

- Strains used in carcinogenicity studies: route of compound administration and dose ranges planned for the carcinogenicity study
- Pharmacokinetic data from studies of sufficient duration: potential time-dependent changes in pharmacokinetic parameters
- Similarity of metabolism between rodents and humans
- Scientific judgement to determine whether the AUC comparison is based on parent, parent and metabolite(s), or metabolite(s) only
- Interspecies differences in protein binding are taken into consideration
- Human pharmacokinetic data from studies encompassing the maximum recommended human daily dose



Other endpoints

- **Saturation of absorption in high dose selection**
- **Pharmacodynamic endpoints in high dose selection**
- **Maximum feasible dose**
- **Limit Dose**
- **Additional endpoints in high dose selection**



Saturation of absorption in high dose selection

- If saturation of absorption measured by systemic availability occurs
- Mid and low doses should take into account metabolic and elimination pathways (might be different from the high dose)



Pharmacodynamic endpoints in high dose selection

- Utility of pharmaceuticals depend on their pharmacodynamic selectivity.
- Pharmacodynamic response might lead to disturbances in physiology or homeostasis
e.g. hypotension, inhibition of blood clotting, diabetes (?)



Maximum feasible dose

- Currently: 5% of the diet in case of oral administration via the diet.
- When other routes of administration (e.g. dermal) are appropriate the limit might be based on practicality and local tolerance.

It is to be expected that because of the introduction of the pharmacokinetic endpoint, the maximum feasible dose will be used less as an endpoint.



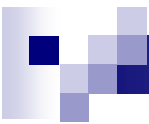
Limit Dose

- As a general guidance the high dose should not be higher than 1500 mg/kg/day.
The limit is applicable in all cases where the maximum human dose does not exceed 500mg/day.
- Exposure in animals should be compared to humans and should be an order of magnitude higher.
- If the human dose is higher than 500 mg/day the dose might be increased to the maximum feasible dose.



Additional endpoints in high dose selection

- Other endpoints might be used based on a scientific rationale
- Such designs should be evaluated based on their individual merits.



Selection of middle and low doses in carcinogenicity studies

- Linearity of pharmacokinetics and saturation of metabolic pathways.
- Human exposure and therapeutic dose.
- Pharmacodynamic response in rodents.
- Alterations in normal rodent physiology.
- Mechanistic information and potential for threshold effects.
- The unpredictability of the progression of toxicity observed in short-term studies.



Conclusion

- Use of ***multiple criteria***
- Results in ***greater flexibility***
- in optimising the design of carcinogenicity studies for therapeutic agents.