General Toxicology (Acute and Repeat Dose Studies), Immunogenicity and Phototoxicity

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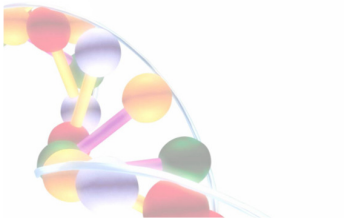
General Toxicology (Acute and Repeat Dose Studies), Immunogenicity and Phototoxicity

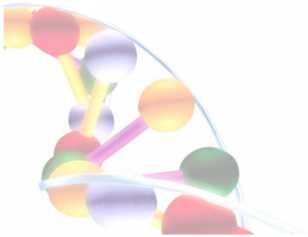
In this presentation we will cover

- Goals of non-clinical safety testing
- Overview of relevant ICH directives and guidelines
- Study conduct - regulatory requirements and GLP
- Design of single and repeat dose studies and duration required to support clinical trials (including exploratory clinical studies)
- Specific investigations – immunotoxicity, phototoxicity
- Special situations – alternative routes (inhalation, ocular) and combination products



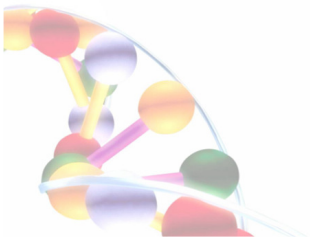
Non-clinical drug safety evaluation – What are we trying to achieve?

- Characterize the nature and extent of injury the drug candidate *could* produce (using non-human models)
- Predict the consequences and probability of similar injury occurring in humans/patients
- Assure the reasonability of the risks entailed in clinical evaluation and use of the drug
- Provide for informed consent of clinical trial subjects



Why is this Important?

- Ethical obligation to minimize risks (i.e., select safest alternative)
- Understand the “risk” side of the risk/benefit equation
- Satisfy legal requirements and mandates
- Find out “worst case scenario” before it occurs



Goals of Non-clinical Safety Testing

Characterisation of toxicity

- Identify target organs
- Dose dependence and relationship to exposure (toxicokinetics)

Risk assessment

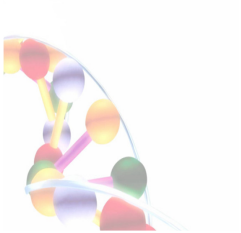
- Safety margins between toxicology and efficacy studies
- Monitorability and reversibility of the observed toxicity
- Mechanism of toxicity
  - Relevance to humans
  - Relationship to pharmacology

Guidance for clinical trials

- Studies designed to characterise potential adverse effects that might occur in the clinical trial to be supported
  - Duration
  - Same route of administration

Estimation of a safe starting dose & guide dose escalation

Parameters for clinical monitoring



Overall Development Path

Bespoke studies throughout (mechanistic, response to clinical findings or regulator requests)

Screening in vitro and in vivo studies

Rat and Rabbit early embryofoetal development (EFD) studies

3 month tox, full EFD studies

Pre-FIH package: All GLP – 1 month in 2 species, safety pharmacology and genetic toxicology

6 or 9 month tox, DRF transgenic mouse, carcinogenicity studies, peri-post natal and fertility studies

International Conference on Harmonisation - Background

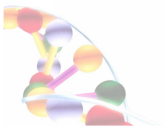
Unique harmonisation project involving the regulatory authorities and pharmaceutical industries of US, EU, and Japan

- Launched in 1990
- WHO, Canada, and EFTA are observers

Objectives:

- To streamline the new drug development and registration process
- To promote public health, prevent duplication of clinical trials in humans, and minimize the use of animal testing without compromising safety and effectiveness

Accomplished through the development and implementation of harmonised guidelines and standards



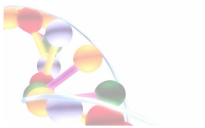
ICH Designation

- Q = Quality topics - *i.e.*, those relating to chemical and pharmaceutical quality assurance (stability testing, impurity testing, *etc.)*

- S = Safety topics - i.e., those relating to *in vitro* and *in vivo* pre clinical studies (eg safety pharmacology, carcinogenicity, genotoxicity and reprotoxicity)

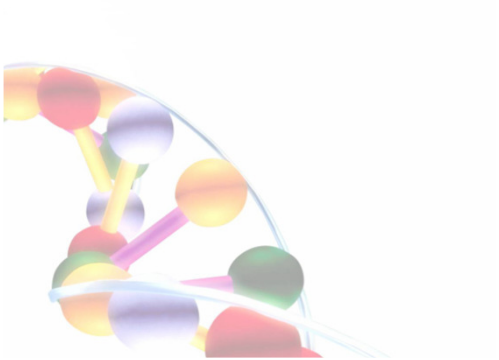
- E = Efficacy topics - i.e., those relating to clinical studies in human subject (dose response studies, good clinical practices, etc.)

- M = Multidisciplinary topics - i.e., cross-cutting topics which do not fit uniquely into one of the above categories



Key ICH safety guidance documents

- Carcinogenicity studies (S1)
- Genotoxicity studies (S2)
- Toxicokinetics and pharmacokinetics (S3)
- Toxicity testing (S4)
- Reproductive toxicology (S5)
- Biotechnological products (S6)
- Safety pharmacology (S7)
- Immunotoxicology (S8)

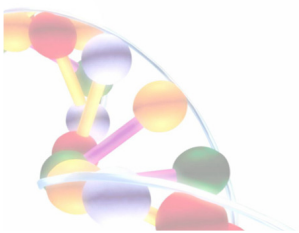


Key ICH safety guidance documents

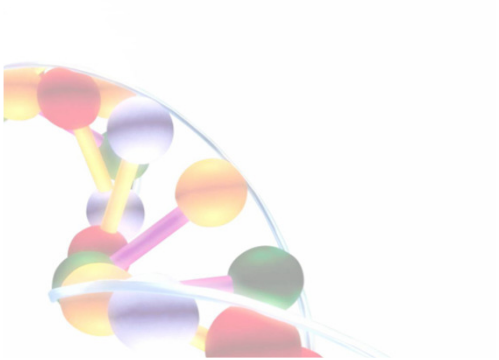
Multidisciplinary (M)

- Original ICH M3 (safety & efficacy) document (R1)
- “Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals” (1997)

- Revision of ICH M3 (R2)
- “Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals”

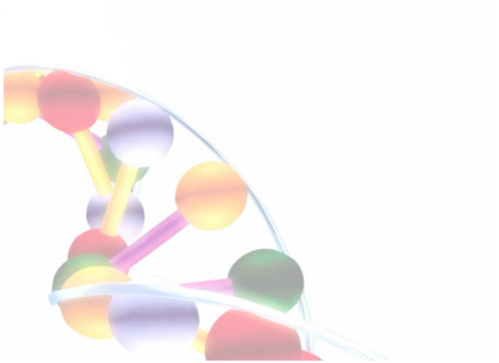


Regulatory Toxicology Studies and Good Laboratory Practice



Regulatory (GLP) studies

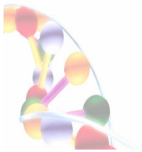
- Mandatory to provide data to the regulatory authorities in support of requesting permission to start human clinical trials
- Study design is heavily standardised
  - Robust with minimal numbers of animals
- International Committee of Harmonization ensures study designs are acceptable across Europe, America and Japan (www.ich.org)



GLP Principles

- Good Laboratory Practice (GLP) is a quality system of management controls to ensure uniformity, consistency, reliability, reproducibility, quality and integrity of non-clinical safety testing
  - Introduced in the US in 1976 following fraud by toxicology CROs resulting in pharmaceutical companies submitting safety data to the FDA
  - GLP has legal ramifications

- Principles of GLP
  - resources (organization, personnel, training, facilities and equipment)
  - rules (protocols and written procedures)
  - characterization (test items and test systems)
  - contemporaneous documentation (raw data, final report and archives)
  - quality assurance



Purposes of Acute and Repeated Dose Toxicology Studies

Acute Studies

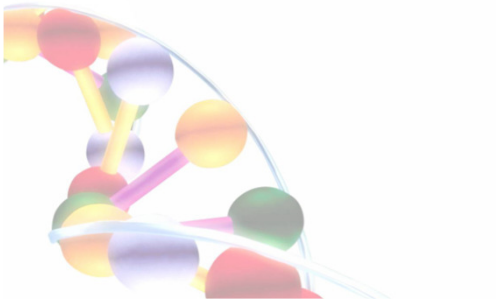
- Single dose or multiple doses within 24hrs
  - Dose selection for repeat dose studies
  - Support exploratory (low dose) clinical trials

Sub-chronic studies

- 2 weeks – 3 months in duration
  - Support clinical trials of same duration
  - Dose selection for chronic studies

Chronic studies

- 6 - 9 months in duration
  - Support clinical trials of similar duration
  - Support registration



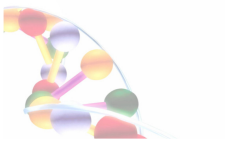
Acute Toxicology Studies

Historically

- ICH S4: single dose studies (1991)
  - LD50 should be abandoned
- Acute toxicity from single dose studies in 2 species via clinical and parenteral routes
- Regulatory requirement for acute studies challenged (NC3Rs workshop (2007); Robinson et al, 2008)

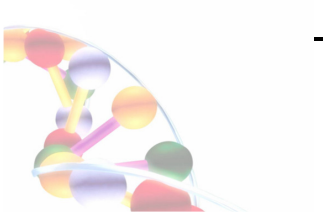
ICH M3 Guidance

- These data typically obtainable from dose range finding or dose escalation repeated dose studies
  - Clinical route only
  - Can be non-GLP
  - Lethality not an intended endpoint
- If these data are available **separate single dose studies not recommended**
- In some specific cases (eg clinical microdose trials) acute toxicity or single dose studies can be the primary support for human studies



General Design of Acute and Repeat Dose Toxicology Studies

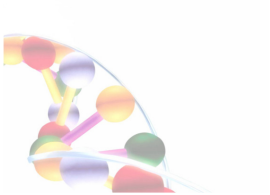
- **Drug administered by relevant route(s)**
  - Same as clinical, possibly another route with higher bioavailability
- **Physical effects monitored**
  - Appearance, behavior, ambulation, cognition
  - Growth, food consumption, neurological exam, water consumption
  - Ophthamoscopy, body temperature, blood pressure and ECGs
- **Diagnostic tests conducted**
  - Clinical chemistry; hematology; urinalysis; biomarkers
- **Exposure to compound documented**
  - Plasma drug kinetics (e.g., Cmax, Cmin, AUC)



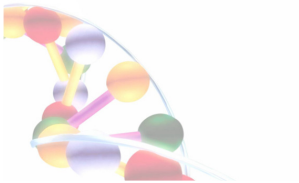
General Design of Acute and Repeat Dose Toxicology Studies (Cont)

- **Pathological change determined**
  - Organ weights
  - Macroscopic examination
  - Histology (~52 tissues per animal)

- **Data Interpretation**
  - Target organs of toxicity
  - Determine dose level/exposures necessary to elicit adverse reactions
    - Maximum Tolerated Dose (MTD)
    - No Observed Effect Level (NOEL)
    - No Observed Adverse Effect Level (NOAEL)
  - Estimate Margin of Safety relative to human exposure



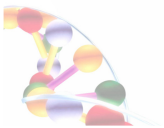
Duration of Repeat Dose Toxicology Studies to Support Clinical Trials



Repeat-Dose Toxicology

Maximum duration of clinical trial	Recommended minimum duration of repeat-dose toxicity studies to support clinical trials	
	Rodent	**Non-Rodent**
Up to 2 weeks	2 weeks (a)	2 weeks (a)
Between 2 weeks to 6 months	Same as clinical trial duration (b)	Same as clinical trial duration (b)
Greater than 6 months	6 months (b,c)	9 months (b,c)

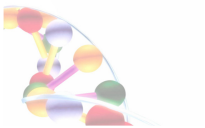
(a) In the US, an extended single dose design can support single dose human trials
(b) Longer trials can be initiated if equivalent duration toxicology studies are available before the duration of existing toxicity studies is exceeded in the trial
(c) Longer term juvenile toxicity studies may be required for pediatric drugs where there is evidence of developmental concerns



Repeat-Dose Toxicology

Duration of indicated treatment	Recommended duration of repeat-dose toxicity studies to support marketing	
	Rodent	**Non-Rodent**
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
Greater than 3 months	6 months (a)	9 months (a)

(a) Longer term juvenile toxicity studies may be required for pediatric drugs where there is evidence of developmental concerns



Points to Consider in Designing a Toxicology Study

- Work backwards from the clinical plan

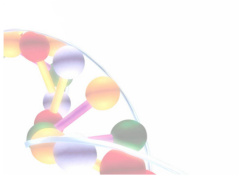
- Initial questions are:
- **What do we want to do in the clinic?**
  - Both now and in the future?

- **Who do we want to expose, by what route, how often and for how long?**

The Non-clinical Safety Programme

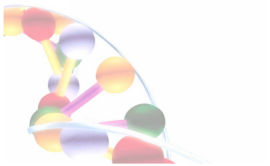
A strategic plan describing the purpose, scope and timing of a series of non-clinical studies that support safe clinical experimentation and application for marketing approval

- Unique to the drug candidate being developed
- Integrated with the overall development plan
- Dynamic, flexible; changes with emerging data
- Consistent with regulations, laws
- Timing and cost for each activity pre-defined
- Results incorporated into regulatory documents



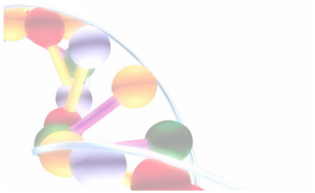
Points to Consider in Designing a Toxicology Study

- Species
- Route of administration (and vehicle)
- Dose levels
- Duration and frequency of dosing
- Investigations for the study
- Consider need for a recovery period



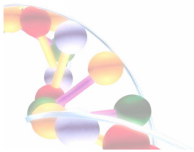
Species Selection

- Generally two species required
  - Rodent and non-rodent
  - Exceptions for some biopharmaceuticals and vaccines
- Species need to be relevant and justifiable
  - Predictive for humans
  - Pharmacology
  - Metabolism
  - Unsuitability of other species

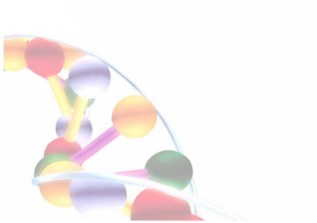


Species Selection

- Rodent
  - Usually the rat as first choice
  - Mice used for carcinogenicity studies (with rat)
- Non-Rodent
  - Dogs – preferred second species
  - Non-Human Primates – where dog is unsuitable or monkey more relevant
  - Minipigs – preferred for dermal programs
  - *Ethically – use the lowest relevant species*
- Rabbits
  - Lagomorphs so neither rodent or non-rodent
  - Preferred for vaccines, assessment of irritancy
  - Honorary non-rodent for reproductive toxicology studies!

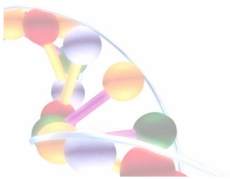


Route of Administration and Formulation



Route of administration

- Clinical route of exposure used where possible
- Common routes are:
  - Oral (bolus)
  - Intravenous (bolus)
  - Inhalation (as close as to clinical as possible)
- Other routes include:
  - Dermal, subcutaneous, intramuscular, intra-vaginal, intra-ocular etc
- Intravenous infusion (intermittent or continuous)
  - Can be used to replicate systemic exposure from other routes of administration
  - Dose volume and solubility may impact dose

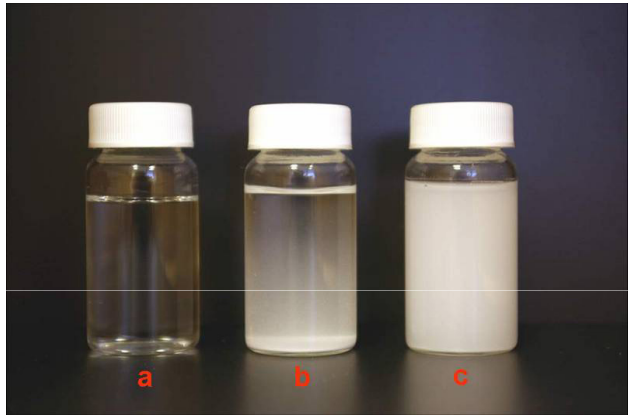


Formulation and Test Material

- Important to use well characterised and suitable batch of active drug substance
  - Pure, but not too pure as want to cover some impurities and degradation products
  - Ideal scenario is to use a common batch to supply both toxicology and Phase 1 clinical trials for ‘automatic’ qualification of any impurities but not mandatory or always possible
- The substance used in the repeated dose toxicity studies should present at least a similar pattern or levels of impurities as the product intended for use in human (clinical trials and marketing), as much as possible (Guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1)

Formulation Selection

- Simplicity – avoid exotic ingredients
  - Oral formulations
    - Predominately suspensions or solutions
    - High dose volumes possible
  - Parenteral formulations
    - IV solutions or emulsions
    - SC solutions, suspensions or emulsions
- Ease of administration
- Sufficiently chemically and physically stable
- Well characterised, with validated analytical techniques



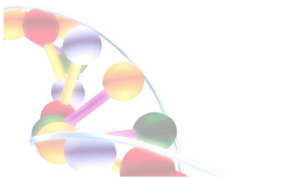
A = solution

B = physically unstable suspension

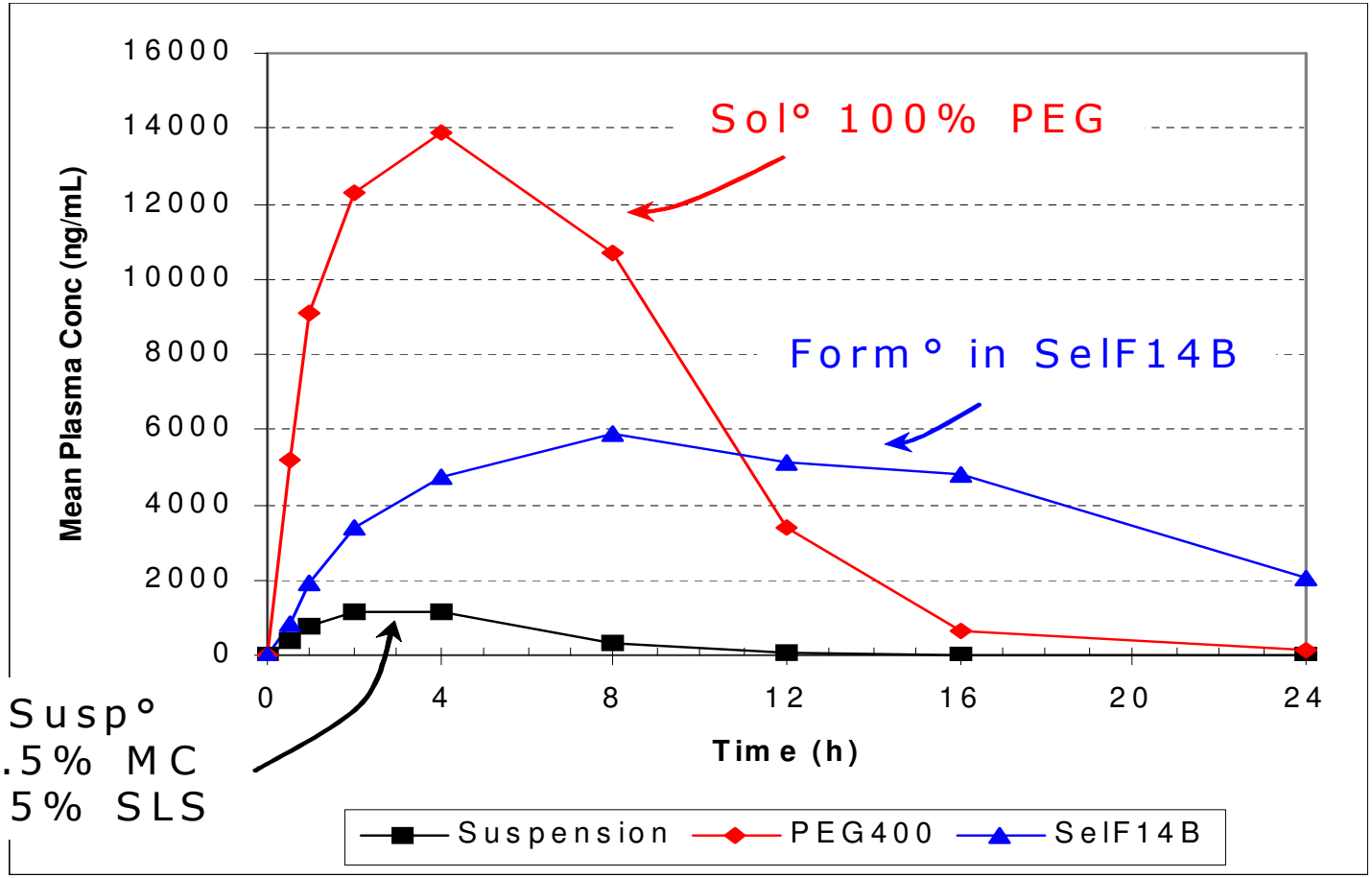
C = physically stable suspension

Enhancing Bioavailability via Formulation Modification

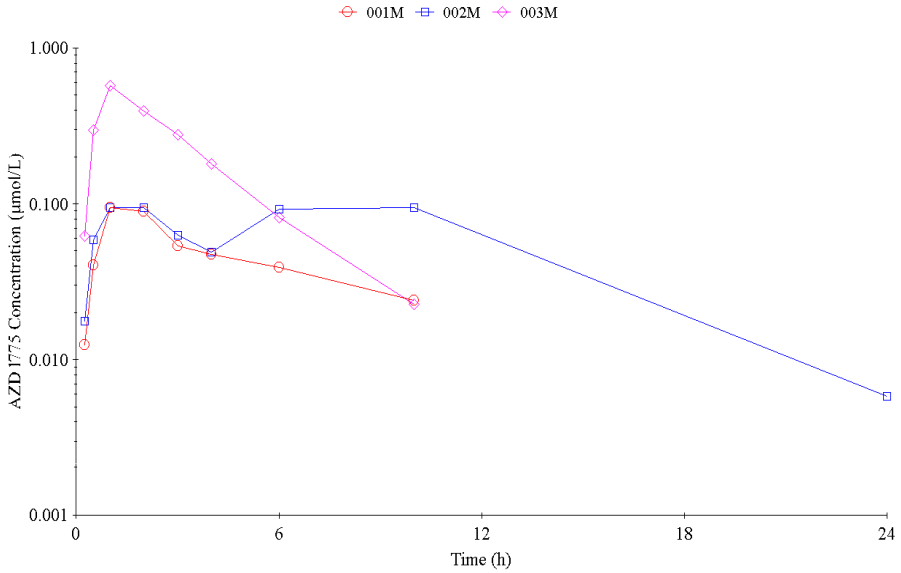
- Solubility - Equilibrium state between a compound in solution and in excess as a solid
  - **Aqueous based systems**
    - pH / Ionic strength adjustment (buffers)
    - Complexes (eg cyclodextrin)
    - Solubilising Agents (eg surfactants / phospholipids, co-solvent systems)
  - **Non Aqueous Systems**
    - Hydrophilic: solution in PEG, micelles
    - Hydrophobic: oils and surfactants
- Dissolution Rate - Related to solubility and to surface area
  - **Increase surface area**
    - Micronisation of drug solid
    - Wet milling of formulated material



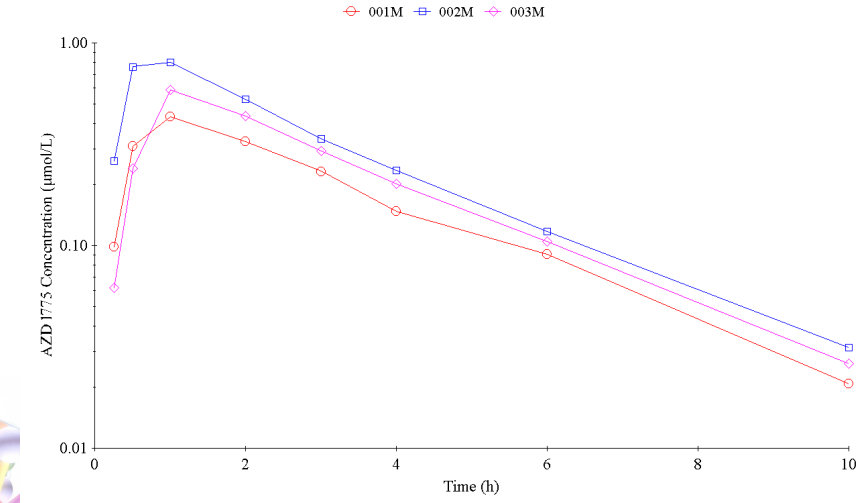
Comparison of Drug Exposure Provided by Suspension Solution and Self-Emulsifying Systems



Comparison of Drug Exposure Provided by Suspension and pH Adjusted Solution

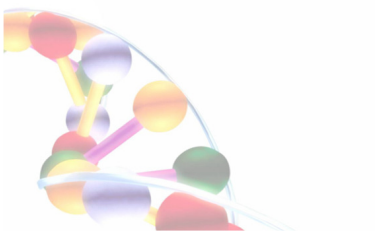


Suspension in 0.5% methyl cellulose



Solution in 0.5% methyl cellulose pH3

Dose Selection and Study Design

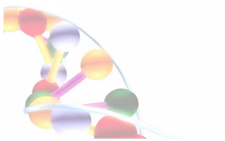


Dose Selection

For regulatory studies, take early toxicology and systemic exposure into account

- High Dose:
  - Maximum tolerated dose
  - Limit dose – usually 1000 mg/kg/day for rodents and non-rodents
  - Saturation of exposure (eg dose limited absorption)
  - Maximal feasible dose - volume/route restrictions
  - Dose giving 50-fold exposure margin vs clinical*
- Low dose:
  - Low multiple of expected therapeutic dose (2-3 x)
  - Expected to be non-toxic
- Intermediate dose:
  - Some evidence of toxicity
  - Establish a dose response relationship

* To support phase III trials in the United States using the 50× exposure margin criteria, dose-limiting toxicity should be identified in at least one species. If this is not the case, an additional study of ≥1 month duration in one species at maximum tolerated dose (MTD), maximum feasible dose (MFD), or a limit dose may be needed



Study Design

- Standardized over the years to optimize design and use minimum numbers of animals
- Recovery period as appropriate
  - Maintain separate group of animals for treatment free period
  - Can be very important in assessing delayed toxicity or reversibility of any effects seen during the dosing period

	Rodent	Non-rodent
Number of dose groups	4 (control plus 3 dose levels)	4 (control plus 3 dose levels)
Number of animals per dose group	10 -15 per sex	3 per sex
Recovery animals	5 per sex in control and high dose	2 per sex in control and high dose
Satellite animals?	Often for TK*	No

Impact of Eliminating Satellite Animals

Table 1: Example of a study design for a six month rat study with assessment of recovery and satellite animals

Dose group	Low	Medium	High	Control
No. of animals	15M + 15F	15M + 15F	15M + 15F	15M + 15F
No. of TK satellites	9M + 9F	9M + 9F	9M + 9F	3M + 3F
No. of recovery**			5M + 5F	5M + 5F
Maximum total for one study				200*

Table 3: Example of minimised study design for a six month rat study with assessment of recovery without separate satellite animals

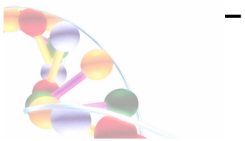
Dose group	Low	Medium	High	Control
No. of animals	15M + 15F	15M + 15F	15M + 15F	15M + 15F
No. of recovery			5M + 5F	5M + 5F
Typical total for one study				140*

* This design includes toxicokinetic sampling from main study animals rather than the use of toxicokinetic satellite animals

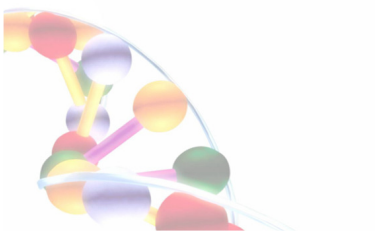
From Sparrow et al (2011) Reg Tox Pharmacol 61: 222 -229

Assessment of Reversibility

- Required when severe toxicity observed in a non-clinical study with potential adverse clinical impact
  - Study on reversibility
  - Scientific assessment
- Demonstration of full reversibility not essential
  - Trend towards reversibility (eg reduced incidence / severity) and scientific assessment generally sufficient
- Toxicity study with terminal non-dosing period generally warranted if scientific assessment can't predict and:
  - Severe toxicity at clinically relevant exposures (eg <10x clinical) or
  - Toxicity only detectable at an advanced stage of pathophysiology and significant reduction in organ function expected
- Terminal non-dosing period generally not warranted if toxicity:
  - Can be readily monitored at an early stage
  - Known to be irrelevant to humans
  - Is only observed at high exposures not clinically relevant
  - Is similar to that induced by related agents for which prior clinical experience indicates risk is manageable

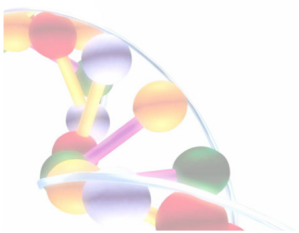


Non-clinical Requirements to Support Exploratory Clinical Studies



Exploratory First in Man (FIM) Studies – ICH M3 Guideline

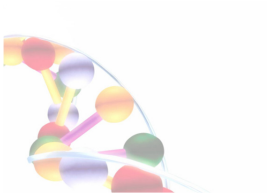
- Involve limited human exposure, no therapeutic intent, and are not intended to examine tolerability
- Can be used to investigate PK, PD, biomarkers e.g. PET studies
- Subjects can be selected patients or volunteers
- Five different approaches to exploratory FIM studies are outlined in the M3 Guideline; however, other approaches can be adopted
- Exploratory FIM studies generally supported by a reduced program of non-clinical safety studies because of the limited human exposure



TOPRA

Exploratory First in Man (FIM) Studies
ICH M3 Guideline Approaches

- **Micro-dose (single dose) – Approach 1**: P S
  - <1/100th pharmacological and NOAEL dose and maximum 100µg
- **Micro-dose (multiple dose) – Approach 2** P 7
  - Up to 5 micro-doses with washout of >x6 half lives
- **Mini-dose (single dose) – Approach 3** P sp S A
  - Sub-therapeutic dose or into anticipated therapeutic range
  - Maximum dose up to ½ NOAEL if toxicity is monitorable & reversible
- **Mini-dose (repeat dose) – Approach 4** P sp 14 AC
  - Up to 14 doses at sub-therapeutic or into anticipated therapeutic range
  - Maximum dose up to 1/10th AUC exposure in most sensitive species
- **Mini-dose (repeat dose) – Approach 5** P sp 14 AC
  - Up to 14 doses into therapeutic range
  - Maximum dose < AUC at NOAEL in non-rodent & < ½ AUC at NOAEL in rodent



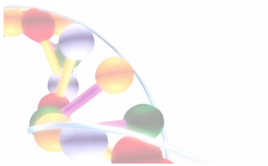
Exploratory Clinical Trial Guidance (ICH M3(R2))
Example 1:

Clinical:		**Non clinical:**		
Dose to be Administered	Start and Maximum Doses	Pharmacology	General Toxicity Studies	Genotoxicity / Other
Approach 1: **Total dose ≤ 100 µg; maximum of 5 administrations (no inter-dose interval limitations)** **AND** **Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (scaled on mg/kg for i.v. and mg/m^2 for oral)**	**Maximal and starting doses can be the same but not exceed 100 µg**	***In vitro* target/ receptor profiling should be conducted Appropriate characterization of pharmacology in a pharmacodynamically relevant species should be available to support human dose selection.**	**Extended single dose toxicity study in one species, usually rodent, by intended route of administration with toxicokinetic profile or via the i.v. route. A limit dose of 10 mg/kg in rats (~6000 times the 100 µg clinical dose on a mg/ kg comparison basis) can be used.**	**Genotoxicity studies are generally not conducted, but any studies or SAR assessments conducted should be included in the clinical trial application.** **For highly radioactive agents, appropriate pharmacokinetics and dosimetry estimates should be submitted**

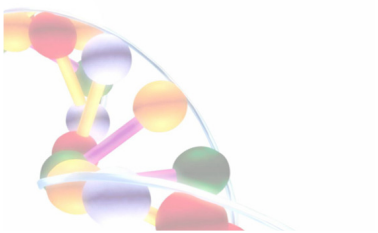
Exploratory Clinical Trials – Extended Single Dose Toxicity Studies

- Evaluation of haematology, clinical chemistry, necropsy and histopathology data after a single administration with further evaluations conducted two weeks later (delayed toxicity / recovery)

- Design
  - Rodents
    - 10/sex/group for Day 2 assessment
    - 5/sex/group for Day 14 assessment
  - Non-rodents
    - 3/sex/ group for Day 2 assessment
    - 2/sex/group for Day 14 assessment



Immunotoxicity

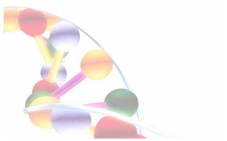


ICH S8 - Immunotoxicity

- Routine testing is not necessary but all new pharmaceuticals should be evaluated for potential to produce immunotoxicity

- Weight of evidence approach:
  - Findings from standard toxicology studies
  - Drug pharmacology
  - Patient population
  - Structural similarity to known immunomodulators
  - Drug disposition
  - Clinical information

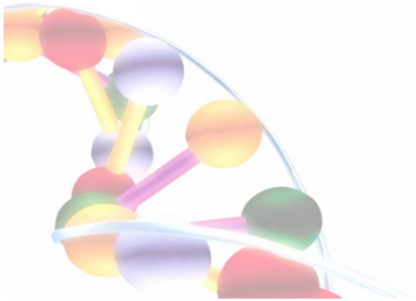
- Investigation into unintended effects is required (immunosuppression / immunoenhancement)



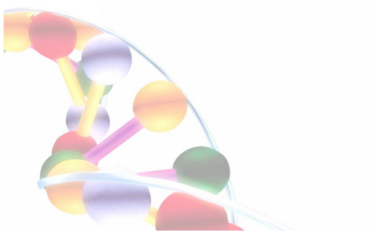
ICH S8 - Immunotoxicity

- Functional endpoints derived from standard toxicity studies
  - Organ weights (thymus, spleen, lymph nodes)
  - Histopathology (macroscopic vs. microscopic)
  - Haematology (whole blood cell count, white blood differentials, flow cytometry)
  - Clinical observations: urticaria (skin rash), core body temperature, susceptibility to infection, pulmonary issues

- If cause for concern identified, consider additional specific immunotoxicity assays
  - » T cell dependent antibody response
  - » Immunophenotyping
  - » Natural killer cell assays
  - » Host resistance studies
  - » Macrophage / neutrophil function
  - » Cell mediated immunity

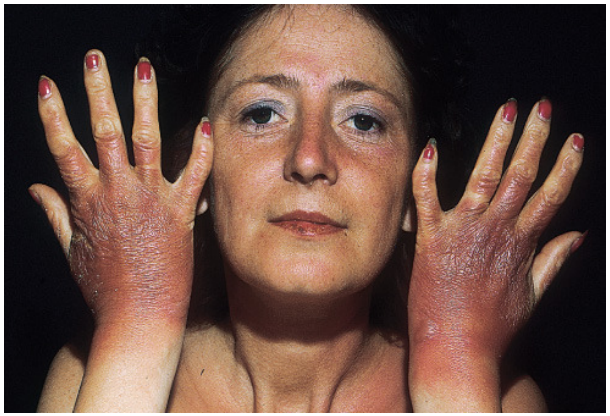


Phototoxicity



Phototoxicity

- Phototoxicity is any light induced adverse reaction
- Chemically induced photoxicity is a light induced change to a chemical that elicits an exaggerated toxic response
  - Most phototoxicities involve light induced release of free radicals
- Phototoxic reactions can be seen in any light exposed tissue (skin)

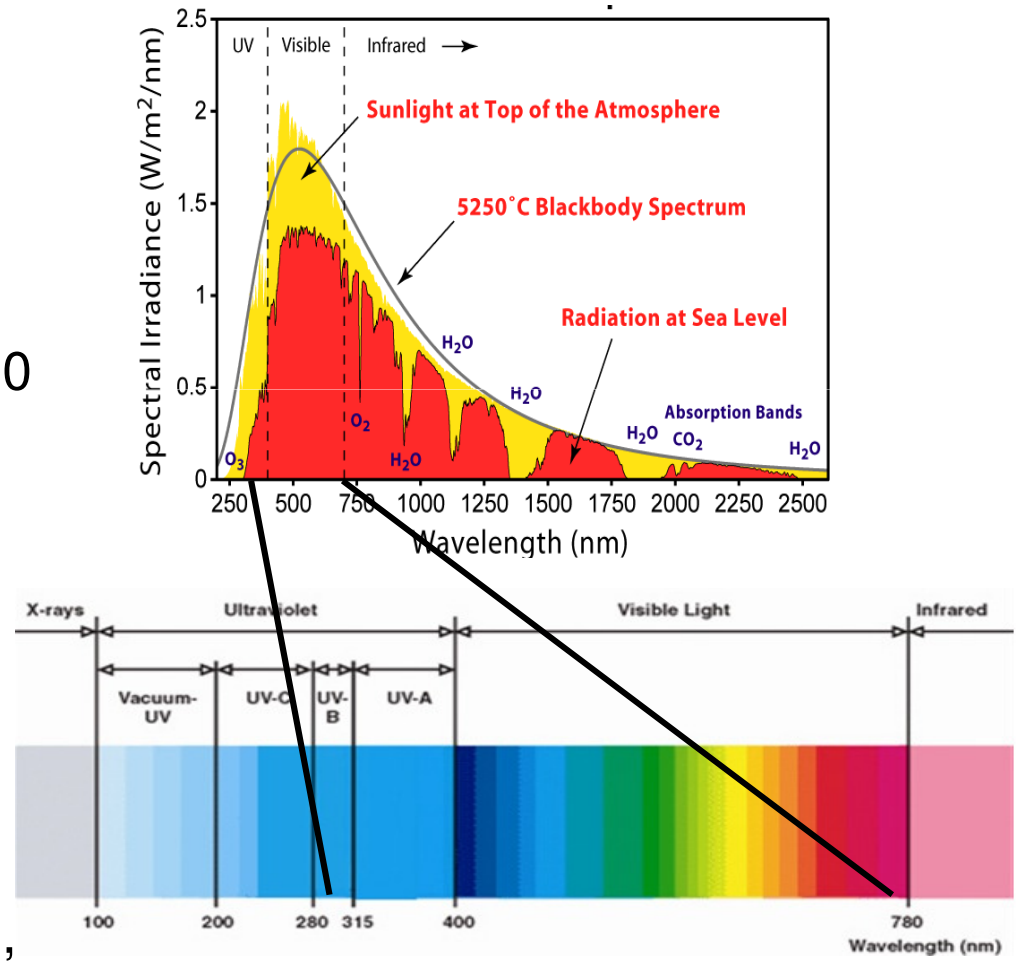


Doxycycline phototoxic reactions

General Principles for Phototoxicity Testing

Criteria required to present a concern (ICH S10)

- Absorbs light in the range of natural sunlight (290-700 nm)
- Generates a reactive species following absorption
- Distributes **sufficiently** to light-exposed tissues (e.g., skin, eye)



ICH M3 – Timing of Photosafety Testing Relative to Human Exposure

Assessment of:

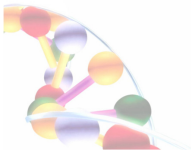
- Photochemical properties
- Information on phototoxic potential of related compounds
- Tissue distribution
- Clinical or non-clinical findings indicative of phototoxicity

If phototoxic potential identified:

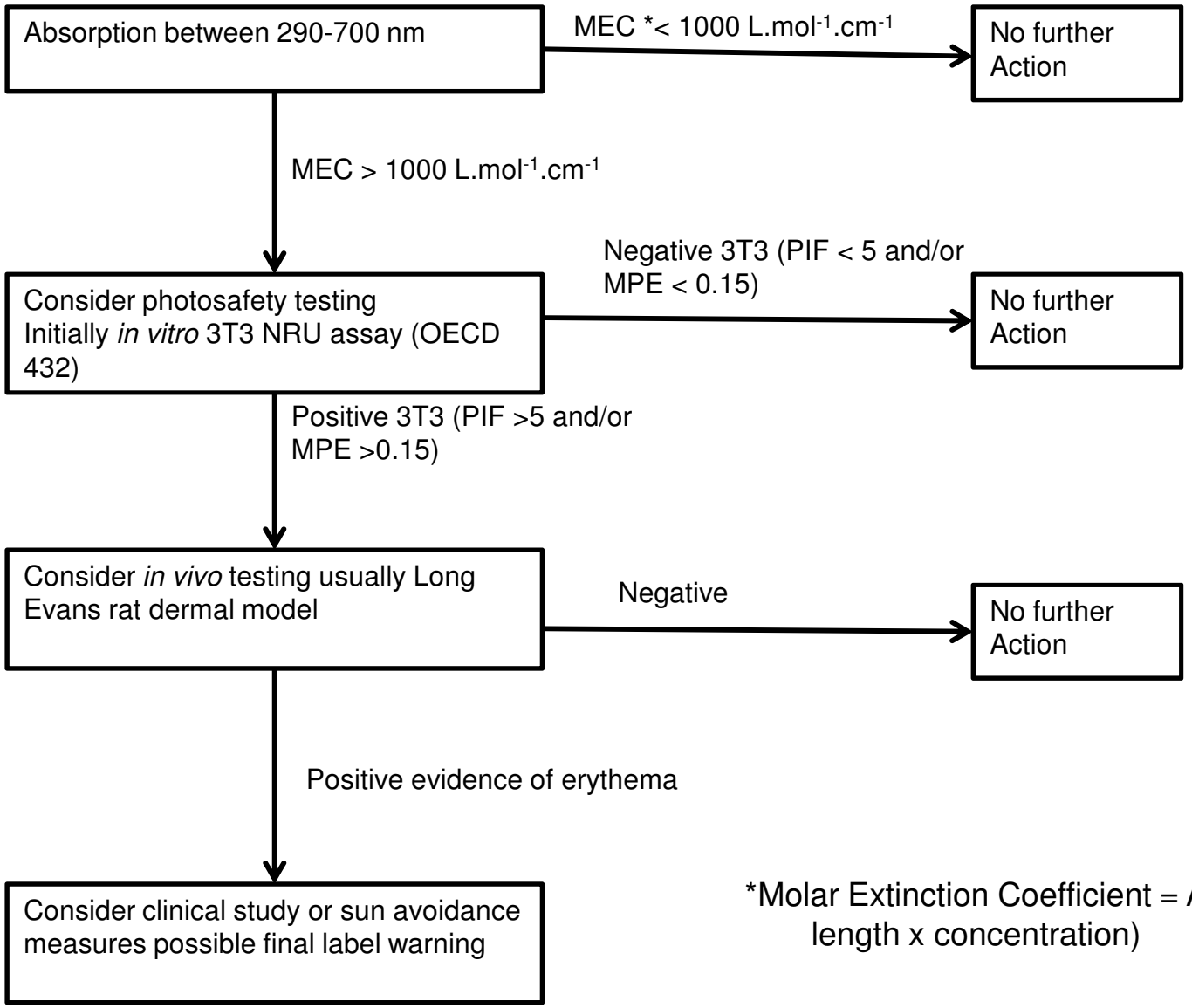
- Undertake protective measures during clinical studies
- Conduct non-clinical distribution studies to eye and skin

OR

- Directly assess phototoxic potential in non-clinical or clinical studies



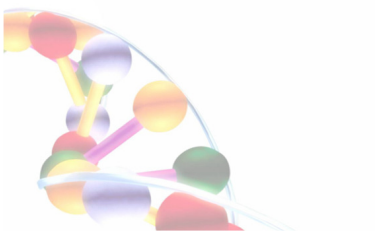
AZ Photosafety Flow Chart



*Molar Extinction Coefficient = Absorbance / (path length x concentration)

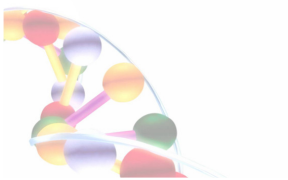
Additional ICH M3 Guidance - Special Situations

- Local Irritation
- Combination Products
- Novel routes of administration eg inhalation, ocular



Additional ICH M3 R2 Guidance - Local Tolerance

- Preferably part of standard toxicology studies – stand alone studies not recommended
- Single dose study in a single species suitable to support limited human administration by non-therapeutic routes
  - Formulation similar but not necessarily identical to clinical
- IV microdosing
  - If novel IV vehicle used then its local tolerance should be assessed
- Parenteral products
  - Evaluation of unintended sites before exposure of large number of patients (eg Phase III)
    - E.g. single-dose paravenous study for the i.v. route in EU/JPN
    - Normally not for US



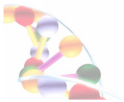
Additional ICH M3 R2 Guidance – Fixed Combination Drugs

Combination drugs co-packaged or in a single dosage form

≥2 late stage entities (e.g. ≥Phase III):

- Adequate clinical experience of co-administration- no toxicology study unless cause for concern

- Inadequate experience but no causes for concern
  - No toxicology study for small scale / short duration clinical trials
  - Toxicology combo study recommended before large scale / longer term clinical studies



Additional ICH M3 R2 Guidance - Combination Drugs (cont)

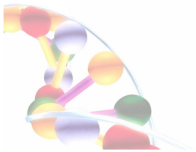
Combination drugs co-packaged or in a single dosage form

Late + early stage entities (e.g. ≤Phase II) or ≥2 early stage entities:

- Repeated dose combination studies recommended with timing as for new active ingredients

- Provided complete nonclinical development programmes conducted on individual entities:
  - Toxicology combo study ≤90 days to support clinical trials (same timing in development)
  - Single relevant species only

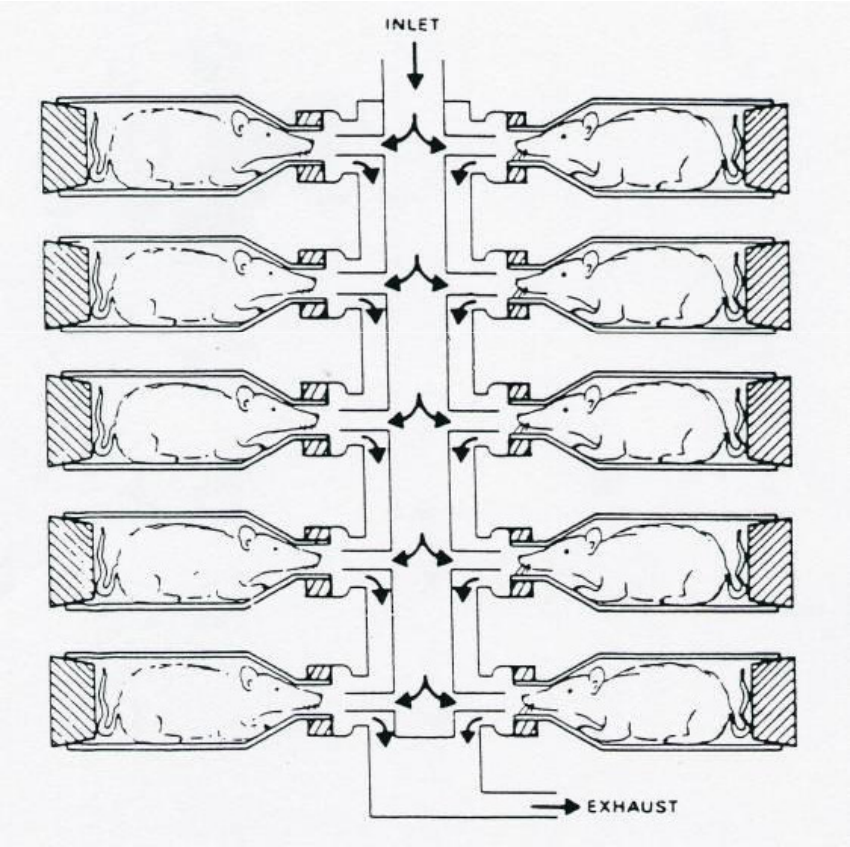
- No genotox, safety pharmacology or carcinogenicity studies of combination if individual compounds have been tested



Inhalation Studies

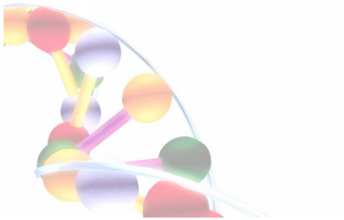
Specific considerations:

- More extensive histopathology of respiratory tract
- Adequate characterisation of dose administered
- Top-up dosing via alternative routes if systemic exposure low
- Respiratory function assessment



In this presentation we have covered

- Goals of non-clinical safety testing
- Overview of relevant ICH directives and guidelines
- Study conduct - regulatory requirements and GLP
- Design of single and repeat dose studies and duration required to support clinical trials (including exploratory clinical studies)
- Specific investigations – immunotoxicity, phototoxicity
- Special situations – alternative routes (inhalation, ocular) and combination products



References

- Note for guidance on Non-clinical Safety Studies for the Conduct of Human Clinical trials for Pharmaceuticals (CPMP/ICH/286/95; ICH M3 (R2)):
- Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and non-rodent toxicity testing)) (CPMP/ICH/300/95, S4B)
- Note for Guidance on Immunotoxicity Studies of Human Pharmaceuticals (CHMP/ICH/SWP/167235/2004; ICH S8)
- OECD Guidance Document 19 on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation
- National Centre for the Replacement, Refinement and Reduction of Animals in Research. Challenging Requirements for Acute Toxicity Studies: Workshop Report; May 2007.
- Robinson S et al. A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. Regul Toxicol Pharmacol. 2008 Apr;50(3):345-52
- Sparrow S. et al Opportunities to minimise animal use in pharmaceutical regulatory general toxicology: A cross-company review. Regul Toxicol Pharmacol 2011 61: 222-229

EMA Guidelines

– CHMP/SWP/302413/08	Need for revision of the guideline on single dose toxicity (3BS1A)
– CHMP/SWP/488313/07	Repeated dose toxicity
– CPMP/SWP/1042/99	Repeated dose toxicity
– CPMP/SWP/5199/02	Limits of genotoxic impurities
– CPMP/SWP/2145/00	Non-clinical local tolerance testing of medicinal products
– CHMP/SWP/150115/06	Non-clinical guideline on drug-induced hepatotoxicity
– CPMP/SWP/398/01	Need for revision of the Note for Guidance on photosafety testing
– CPMP/SWP/728/95	Replacement of animal studies by *in vitro* models
– CHMP/SWP/28367/07	Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
– EMEA/CHMP/SWP/91850/06	Development of a CHMP Guideline on the Non-Clinical Requirements to Support Early Phase I Clinical Trials with Pharmaceutical Compounds
– CHMP/SWP/258498/05	Non-Clinical Development of Fixed Combinations of Medicinal Products
– CPMP/SWP/2599/02	Position Paper on the non-clinical safety studies to support clinical trials with a single micro dose

CDER Guidelines

- Animal Models - Essential elements to Address Efficacy under the Animal Rule
- Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
- Immunotoxicology Evaluation of Investigational New Drugs
- Nonclinical Safety Evaluation of Drug or Biologic Combinations
- Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route
- Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
- Photosafety Testing
- Safety Testing of Drug Metabolites
- Single Dose Acute Toxicity Testing for Pharmaceuticals
- Exploratory IND Studies
- Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination

Any Questions?