Regulatory perspective on drug development from a Non-clinical assessor’s point of view

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Regulatory agencies play a critical role in drug development

- **As reviewers and approvers** of applications to conduct clinical trials and market authorisation approvals:
  - Studies must be documented appropriately
  - Development programmes has to meet regulatory expectations

- **Guidelines** describe requirements for various aspects of drug development programmes:
  - Quality (Chemistry, manufacturing, and controls (CMC))
  - Safety and Efficacy (Non-clinical and Clinical)
  - In addition Multi-disciplinary guidelines
Phases in Drug Discovery

Discovery

Pre project
Screen & Lead Generation
Screen
Lead Optimization
Optimization
PreGLP Tox
Preclinical
Pre GLP Tox
Clinical Development
FIH
Ph IIa
Ph IIb
Ph III
Regulatory input
- Scientific Advice
- Clinical Trials
- MAA
- Pharmacovigilance
Pre Clinical & Clinical Development
Launch
Reg
Primary goals of non-clinical evaluation

• Pharmacological **rational** – mode of action (MOA)
• To identify an **initial safe dose** and subsequent dose escalation schemes in humans
• To identify **potential target organs** for toxicity and for the study of whether such toxicity is **reversible**
  – Genotoxicity
  – Carcinogenicity
  – Reproductive toxicity
• To identify safety parameters for clinical **monitoring**
Basic requirements prior to FIH study

• Pharmacology
  – MOA/effects on intended target, D/R
  – Interaction with the intended target & related targets
  – Specificity and selectivity

• Safety pharmacology (ICH S7A and S7B)
  – Standard core battery (cardiovascular, CNS, respiratory)

• Pharmacokinetics
  – In vitro metabolism & plasma protein binding

• Repeat dose toxicology
  – Minimum 2 week study in two species (toxic dose & NOAEL)
  – Toxicokinetics - Exposure

• Genotoxicity
  – Gene mutation & chromosome aberrations in vitro (ICH S2 b)
“Basic” Guidelines to consider

• Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

• ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals

• ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals

• ICH S9 Non-clinical evaluation for anticancer pharmaceuticals
Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

- Non-clinical issues for consideration prior to the first administration of an investigational medicinal product in humans
- Also addresses the design and conduct of trials in the initial phase of single and ascending doses during the clinical development.

Present Guideline adopted 2007

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DL Comments 28 February 2017
Adoption XXXXX
Factors of risk - risk mitigation strategies

• Mode of action
  – Novel?
  – Steepness of the dose response – linear or non-linear?
  – Multiple signalling pathways affected?
  – Amplification - biological cascade or cytokine release induced?
  – Irreversible or long lasting binding to the primary target?
  – Potential risk of serious pharmacologically-mediated toxicity?
  – Novelty of the molecular structure of the active substance(s)
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• Nature of the target
  – Extent of the available knowledge (structure, tissue distribution, cell specificity, disease specificity, regulation, polymorphism, off-target effects)

• Relevance of animal models
  – Target: structural homology, distribution, signal transduction pathways

• Quality aspects
  – GLP/GMP/Impurities
ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals

- Pharmacology studies
  - Safety Pharmacology (ICH S7A, ICH S7B)
- Toxicology studies
  - Toxic dose (MTD), NOAEL, exposure margins, MFD
- Estimation of the first dose in human
- Exploratory clinical trials
  - Microdose trials (100 µg)
- Local tolerance (specific GL)
  - Stand-alone studies are generally not recommended
- Genotoxicity (ICH S2 (R1))
  - Complete battery of tests before Phase II trials
- Carcinogenicity (ICH S1 A, B, C)
- Reproduction toxicity studies (ICH S5 (R2))
  - Should be conducted as is appropriate for the population that is to be exposed
- Photosafety
  - If appropriate, an experimental evaluation should be undertaken before exposure of large numbers of subjects (Phase III)
ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals

- Conventional approaches to toxicity testing of pharmaceuticals may not be appropriate
  - species specificity
  - immunogenicity

ICH S9 Non-clinical evaluation for anticancer pharmaceuticals

- GL for pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies
“Take home message”

• Know your target
• Scrutinize possible risks
  – Target related, Off target related, Compound related
• Identify possible risk mitigation measures
• Perform studies in line with regulatory expectations and requirements
  – Sufficient documentation important
• Read Guidelines
• Ask for Scientific Advice
  – To clarify “expectations and requirements”
The Medical Products Agency gives the industry and other interested parties e.g. academic institutions, advice concerning the development of medicinal products based on the applicant’s documentation. Advice may be requested for all medicinal products, irrespective of subsequent choice of procedure for approval.

The scope of the scientific advice meeting is to facilitate an open dialogue concerning the development work in relation to applications for marketing authorization or for clinical testing.

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