Non-clinical Assessment Requirements

Presented by: Maria Nieto-Gutierrez
Safety and Efficacy of Medicines/Human Medicines Development and Evaluation
Non-clinical Assessment Requirements

Contents:

• Relevance of non-clinical studies in drug development

• Non-clinical requirements in the EU pharmaceutical legislation

• Non-clinical guidelines

• Non-clinical assessment within the centralised procedure

• Support on non-clinical matters - Safety Working Party
Non-clinical Assessment Requirements

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Relevance of Non-clinical Studies in Drug Development

Basic Goals:

- Identify the pharmacological properties
  
  \(PD\) (mode of action)
  
  \(PK\) (metabolism)

  Comparative physiology (extrapolation of animal data to humans)

- Understand the toxicological profile

  Establish a safe initial dose level of the first human exposure

  Identify parameters for clinical monitoring of potential adverse effects

  Special toxicity (e.g. genotoxicity, carcinogenicity, reproduction toxicity)
Relevance of Non-clinical Studies in Drug Development

Importance of non-clinical data

Non-clinical data

Clinical data

Marketing authorisation

Time

Non-clinical Assessment Requirements
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Non-clinical Requirements

Module 1
- Nonclinical Overview
- Nonclinical Summary

Module 2
- Regional Administrative Information
- Introduction

CTD
- Table of Contents
- Clinical Overview
- Clinical Summary

Module 3
- Quality Overall Summary
- Nonclinical Overview
- Nonclinical Summary

Module 4
- Module 4 Clinical Study Reports
- Module 4 Nonclinical Study Reports

Module 5
- Module 5 Clinical Study Reports

Not part of CTD
- Not part of CTD

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Non-clinical Requirements
Annex 1 to Directive 2001/83/EC

Module 4. Non-Clinical Reports

Pharmacodynamics  4.2.1
Pharmacokinetics    4.2.2
Toxicology          4.2.3
Non-clinical Requirements

Module 4

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions
Non-clinical Requirements

Module 4

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports
4.2.2.2 Absorption
4.2.2.3 Distribution
4.2.2.4 Metabolism
4.2.2.5 Excretion
4.2.2.6 Pharmacokinetic Drug Interactions
4.2.2.7 Other Pharmacokinetic Studies
Non-clinical Requirements

Module 4

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity

4.2.3.2 Repeat-Dose Toxicity

4.2.3.3 Genotoxicity

4.2.3.4 Carcinogenicity

4.2.3.5 Reproductive and Developmental Toxicity

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies
Non-clinical Requirements: Environmental Risk Assessment

• In Article 8(3) of Directive 2001/83/EC the evaluation of the potential environmental risks posed by the medicinal product is required

Module 1. Administrative Information

Environmental Risk Assessment (ERA)

1.6

» It is not part of the risk-benefit assessment
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Non-clinical Assessment: Guidelines

**Guidelines**: “Community documents intended to fulfil a legal obligation laid down in the Community pharmaceutical legislation”

- Guidelines are state of the art documents that describe the specific recommendations on how to fulfil the requirements stated by the law
- Guidelines are useful for:
  - Harmonisation
  - Consistency
  - Transparency
  - Guidance to industry and assessors
- Justifications are needed if going beyond framework
Non-clinical Guidelines

Non-clinical guidelines introduction

The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines, in consultation with the competent authorities of the EU Member States, to help applicants prepare marketing-authorisation applications for medicinal products for human use.

Guidelines are intended to provide a basis for practical harmonisation of the manner in which the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. They also help to ensure that applications for marketing authorisation are prepared in a manner that will be recognised as valid by the Agency.

Non-clinical guidelines are provided for:

- Pharmacology
- Pharmacokinetics
- Toxicology
- General guidelines

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Non-clinical Guidelines

Pharmacology

• Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3[R2]) Dec 2009

• Guideline on Strategies to Identify and Mitigate Risks for First-in Human Clinical Trials with Investigational Medicinal Products (CHMP/SWP/28367/07) Sep 2007

• Safety pharmacology studies for human pharmaceuticals (ICH S7A) Jun 2001
Non-clinical Guidelines

Pharmacokinetics

- Pharmacokinetics: Guidance for repeated dose tissue distribution studies (ICH S3B) Jun 1995
- Toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A) Jun 1995
- Pharmacokinetics and metabolic studies in the safety evaluation of new medicinal products in animals (3BS11A) Apr 1994
Non-clinical Guidelines

Toxicology

Single dose

• Q&A on the withdrawal of the “Note for guidance on single dose toxicity” EMA/CHMP/SWP/81714/2010 Jun 2010

Repeated-dose

• Guideline on Repeated dose toxicity CPMP/SWP/1042/99 Rev. 1 Corr Nov 2010
Non-clinical Guidelines

Toxicology

Genotoxicity

• Draft Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human use (ICH S 2 [R1]) – Under discussion

Carcinogenicity

• Possible ICH topic in 2012 – Discussion ongoing

• Carcinogenic potential CPMP/SWP/2877/00 Jan 2003

• ICH S1A Jul 1996, S1B Mar 1998 and S1C(R2) Oct 2008
Non-clinical Guidelines

Toxicology

*Reproductive and Development Toxicity*


- Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications (CHMP/SWP/169215/05) Aug 2008

- Detection of toxicity to reproduction for medicinal products including toxicity to male fertility (ICH S5A[R2) Nov 2000
Non-clinical Guidelines

Toxicology

Local Tolerance

• Non-clinical local tolerance testing of medicinal products
CPMP/SWP/2145/00 Feb 2001 – Under revision

Other toxicity

• Reflection paper on non-clinical evaluation of drug induced liver injury (DILI) EMEA/CHMP/SWP/150115/2006 Jun 2010

• Question & answers on the note for guidance on photosafety testing
Non-clinical Guidelines

**Toxicology**

*Other toxicity (cont)*

- Immunotoxicity studies for Human Pharmaceuticals (ICH S8) **May 2006**

- Replacement of animal studies by in vitro models CPMP/SWP/728/95 **Feb 1997** – Under Revision to include 3Rs developments
Non-clinical Guidelines

General Guidelines

• Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 R1) – Under revision to include addendum – Finalised pending publication

• Non-clinical studies for generic nanoparticle iron medicinal product applications EMA/CHMP/SWP/100094/2011 Apr 2011

• Nonclinical evaluation for anticancer pharmaceuticals (ICH S9) May 2010

• Pre-clinical pharmacological and toxicological testing of vaccines CPMP/SWP/465/95 Jun 1998
Non-clinical Guidelines

Environmental Risk Assessment

• Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00) Dec 2006

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Non-clinical Assessment within the Centralised Procedure

Initial Marketing Authorisation

- Pre-submission
- Primary Evaluation
- Secondary Evaluation
- Opinion/Decision
- Post Authorisation

Day 0

Day 210
Non-clinical Assessment Reports

<C0> Rapporteurs’ Day 80 Critical Assessment Report

Non-Clinical Aspects

Applicant:

» Last updated September 2010

Non-clinical Assessment Reports

<Co-> Rapporteurs’ Day 80 Critical Assessment Report

Non-Clinical Aspects

- GUIDANCE DOCUMENT -

» Last updated September 2010


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Non-clinical Concerns

Applications 2000-2009 with non-clinical concerns after first round: 27% (129/482)

» Non-clinical concerns (MO) after second round: 4% (21/482) - 8 positive opinions
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Safety Working Party

Recommendations to CHMP on all matters relating to the non-clinical safety part of drug development.

1- Guidelines
2- Support to product evaluation
3- Ad hoc issues

Who are the Safety Working Party (SWP) stakeholders?

Internal - CHMP, CMD(h), PDCO, CAT
- SAWP and other working parties

External - Industry
- Learned societies/academia
- Patients/consumers associations
Safety Working Party

Guidelines
- 31 guidelines as per 2011 work plan
- Comments on documents under external consultation
  First in man guideline: 58 organisations provided comments
- Workshops
  Workshop on In Vitro Cytokine Release Assays To Predict Cytokine Release Syndrome (2009)
- Interactions with interested parties
  Annual meetings with EFPIA

Support to product evaluation
- Product specific queries: CHMP, SAWP, CMD(h), PDCO, CAT
- Trainings (1 per year): Non-Clinical Requirements to Support Clinical Trials: ICH-M3(R2) and ICH S9 (2010)
Updating Safety Requirements

Safety Working Party – In the pipeline for 2012

• ICH topics: Q&As for M3R2, genotoxicity S2R1, genotoxic impurities M7, carcinogenicity, photosafety S10, heavy metal impurities Q3D, QT prolongation E14

• Application of 3Rs (reduce/refine/replace)

• Non-clinical local tolerance testing

• Environmental risk assessment

• Non-clinical requirements for biosimilars
Updating Safety Requirements

Safety Working Party – In the pipeline for 2012 (cont)

- Guideline on excipients in the package leaflet
- Toxicological assessments for dedicated facilities (GMP)
- Preclinical requirements for vaccines
- Pharmacokinetics and metabolic studies in safety evaluation
- Contribution to new guidelines for gene therapy and cell products
- List of available qualified biomarkers
Questions?

Thanks!
Guideline ICH M3(R2) (Dec 2009)

Phase I
- Repeated dose toxicity (2W)
- Safety pharmacology
- Local tolerance
- Genotoxicity in vitro
- Male reproductive organs

Phase II
- Repeated dose toxicity (2W-6M)
- Genotoxicity in vivo

Phase III
- Repeated dose toxicity (1M – chronic)
- Reprotoxicity
  - Male and female fertility
  - Embryofetal
  - Peri-post natal
- ADME
Reproductive and Development Toxicity

Importance of Non-clinical data

Developmental toxicity studies

Clinical data

Marketing Authorisation

Time