EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Non-clinical Assessment Requirements

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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

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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)

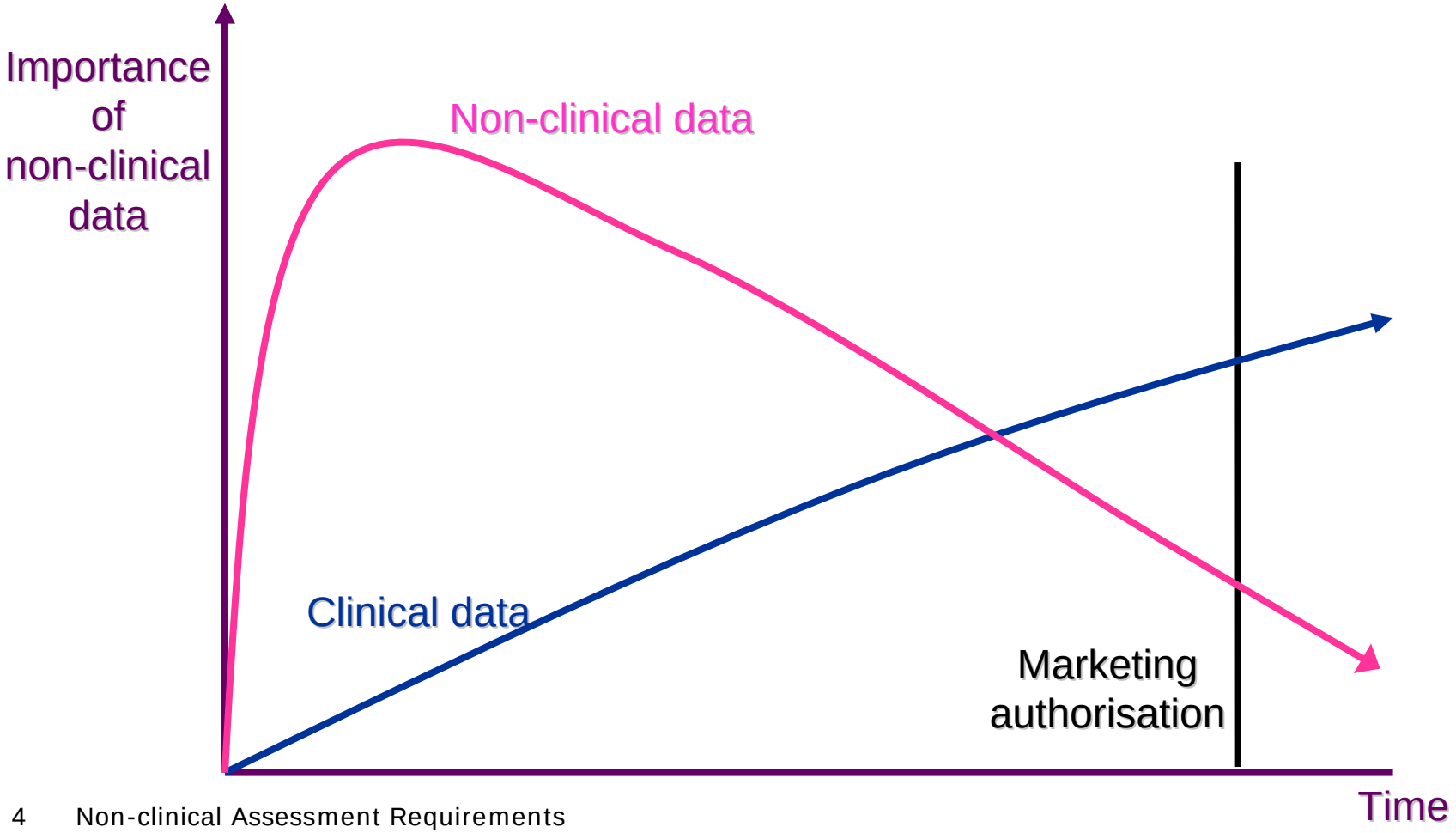
- Understand the toxicological profile

  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



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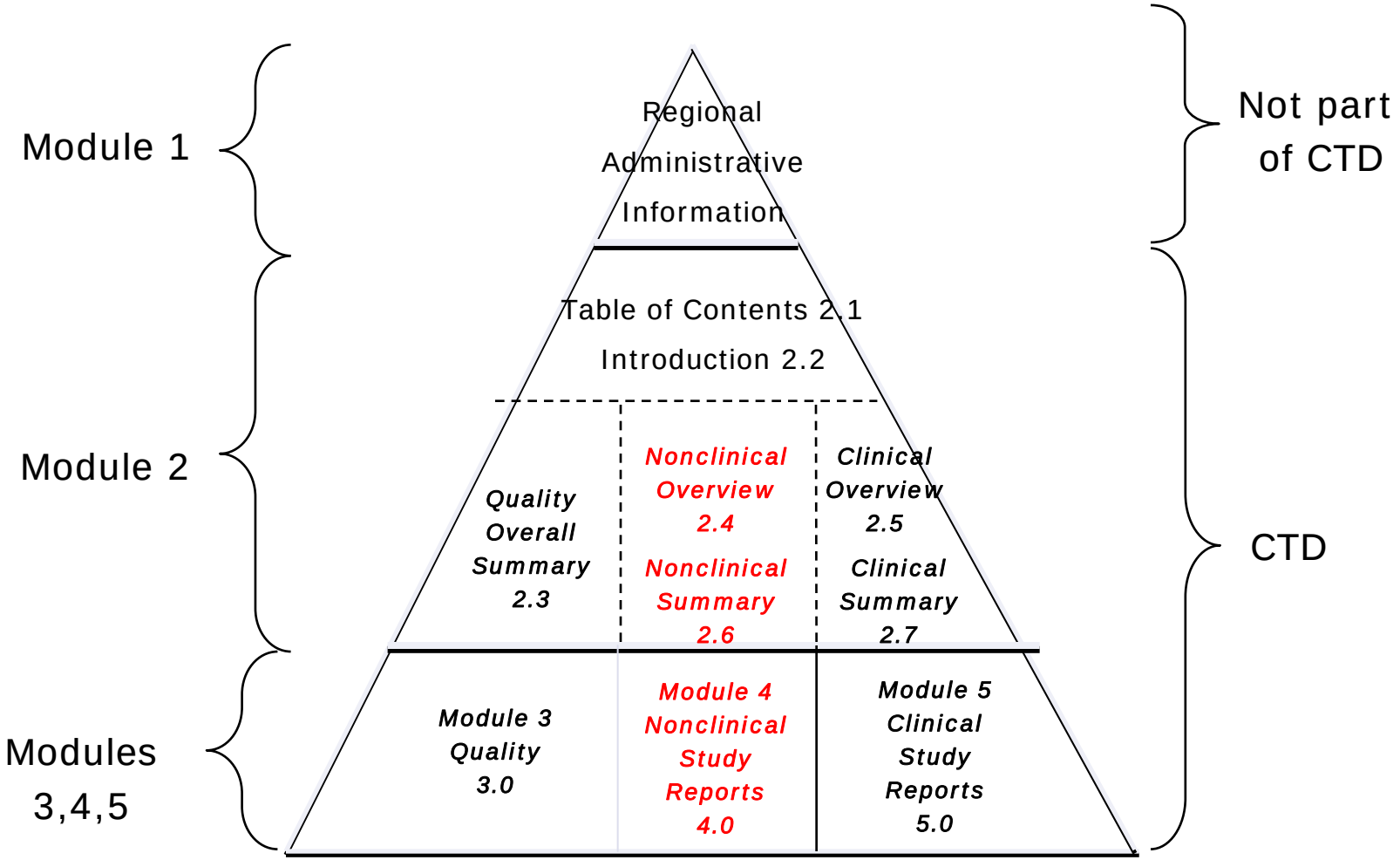
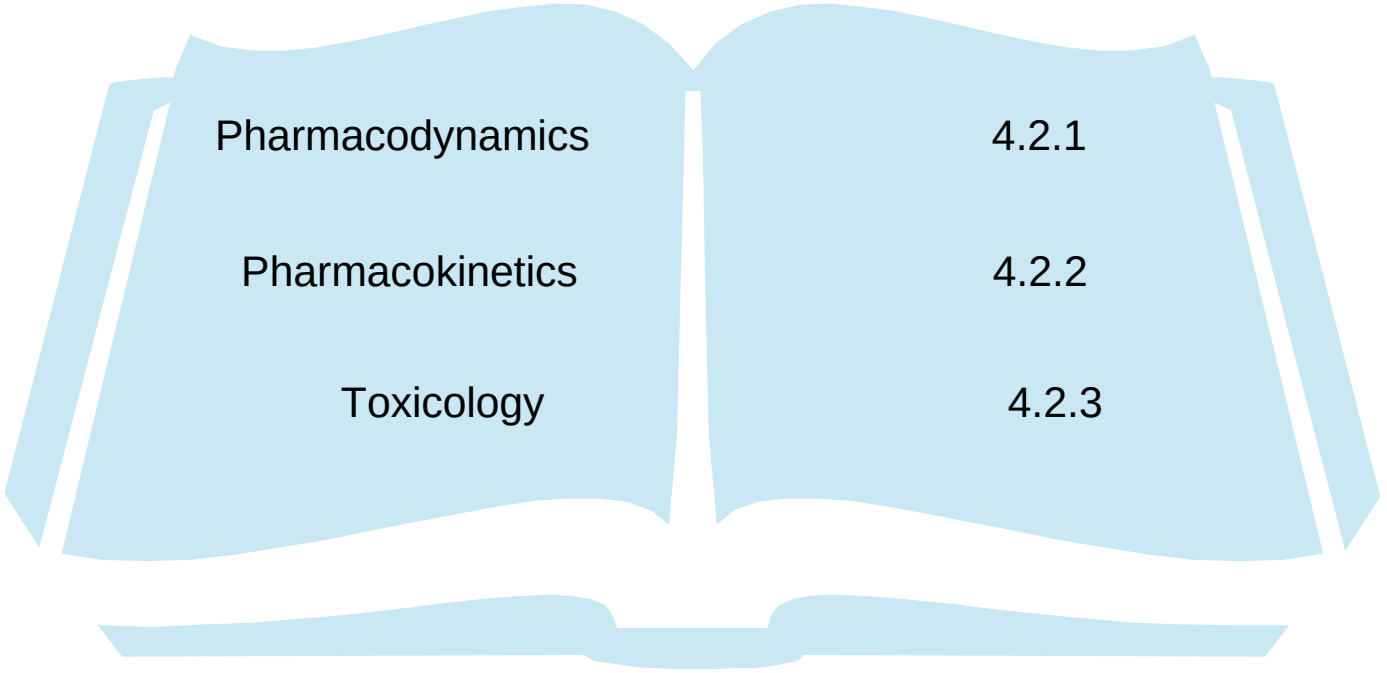


Non-clinical Requirements

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

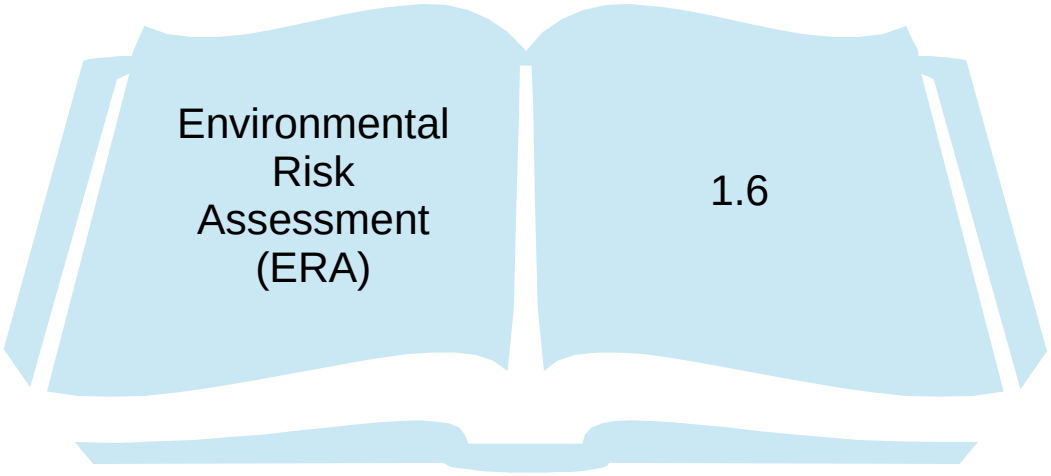
4.2.3.6. Local Tolerance

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



» 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

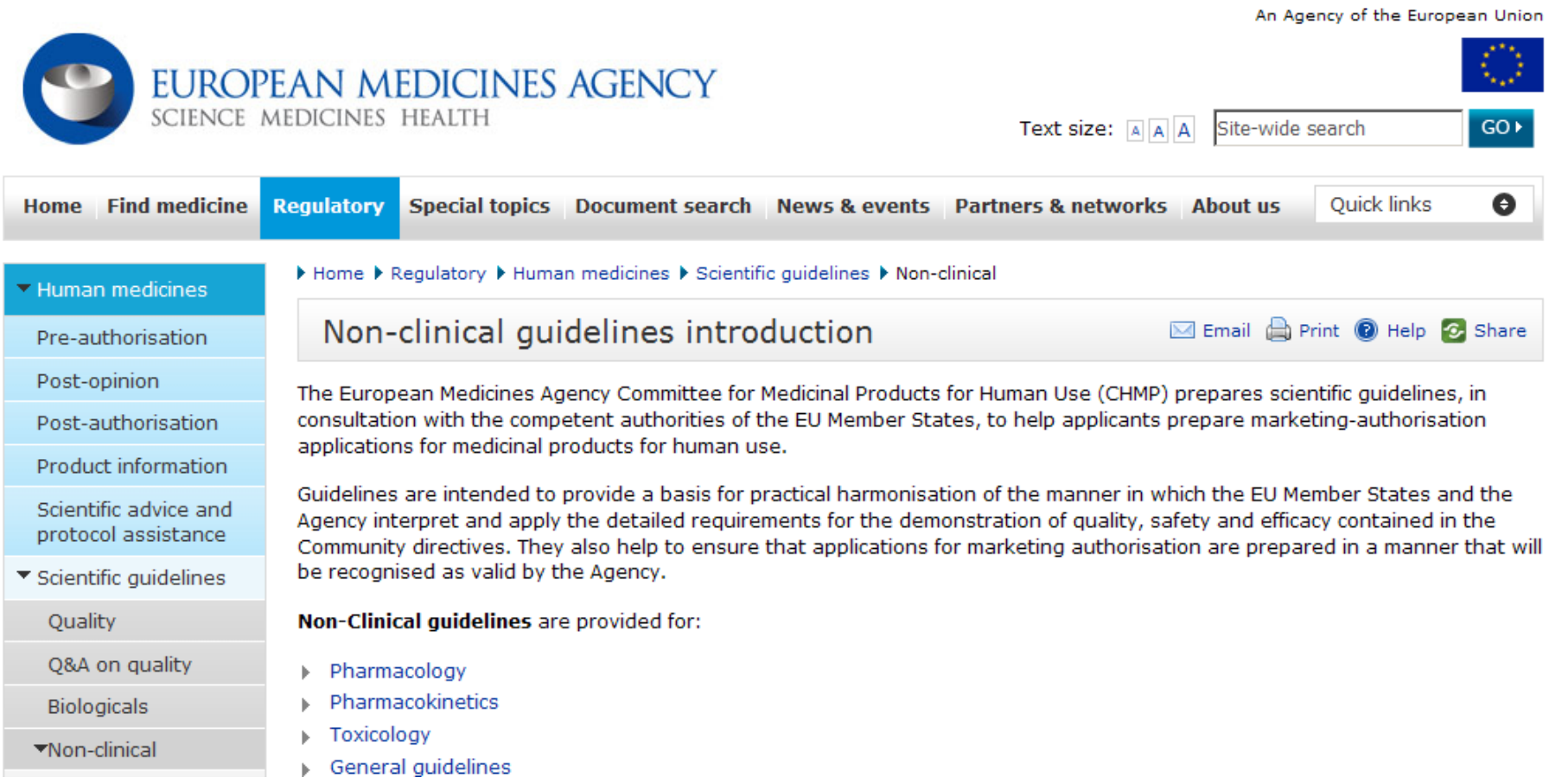
  Consistency

  Transparency

  Guidance to industry and assessors

- Justifications are needed if going beyond framework

Non-clinical Guidelines



Non-clinical Guidelines

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 Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/05) Jan 2009

• 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 EMA/CHMP/SWP/336670/2010 Mar 2011 – New ICH topic S10

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

• Q&A on the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/44609/2010) Mar 2011

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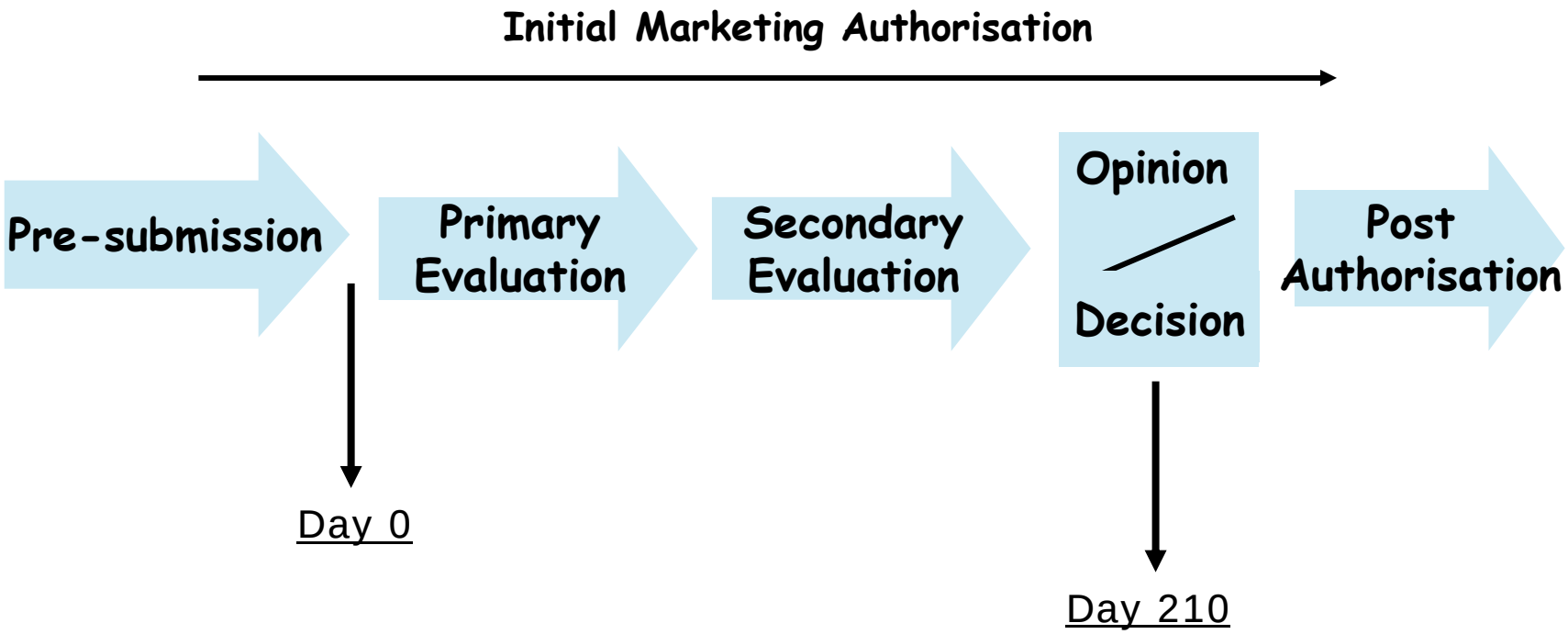
Non-clinical Assessment within the Centralised Procedure



Non-clinical Assessment Reports

<Co>Rapporteurs' Day 80 Critical Assessment Report

Non-Clinical Aspects

<Invented Name>
<(Active Substance)>

EMEA/H/C/{nnnn}/{nnn}/{nnn}

Applicant:

» Last updated September 2010

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000121.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022719&jsenabled=true

Non-clinical Assessment Reports

<Co-> Rapporteurs' Day 80 Critical Assessment Report

Non-Clinical Aspects

- GUIDANCE DOCUMENT -

<Invented Name>

<(Active Substance)>

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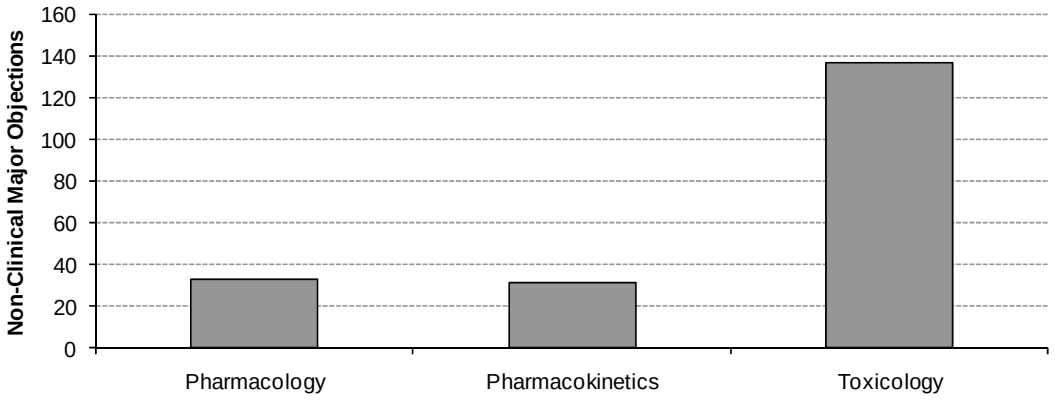
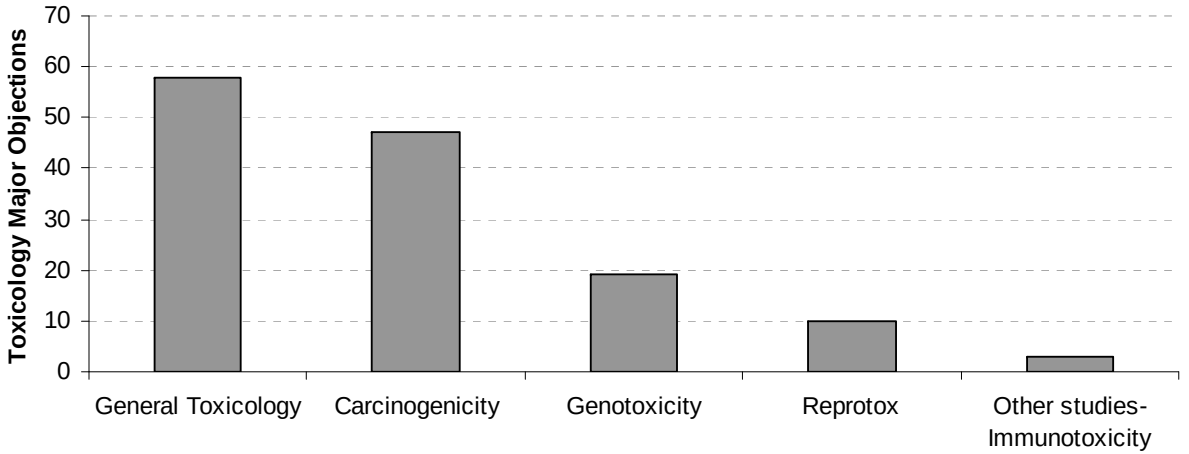
Non-clinical Concerns

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)

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

Phase I

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

Phase II

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

Phase III

Reproductive and Development Toxicity