Non-clinical documentation
Overview of Requirements

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Outline

- Overview of Legal and Regulatory requirements
- Structure of the dossier (CTD)
- Overview of Scientific Non-clinical Guidelines
- Useful Links
Legal Framework

  – *Article 8(3)* - *Particulars and documents, submitted in accordance with Annex I* (full dossier)
    • (i) Results of pharmaco-toxicological tests.
    • (ca) Evaluation of the potential environmental risks posed by the medicinal product.
Legal Framework

  - *Introduction and General principles*
    - (9): GLP conduct of non-clinical studies
    - (10): Animals tests are conducted in accordance with Council Directive 86/609/EEC
  - *Part I - Modules 1 to 5*
    - 1.6 Environmental Assessment (Module 1)
    - 2.4 Non-clinical overview (Module 2)
    - 2.6 Non-clinical Summaries (Module 2)
    - Module 4: Non-clinical Reports
  - *Part IV: Advanced Therapy Medicinal Products* (update June 2009)
Regulatory Framework

- **Eudralex Vol. 2 - Notice to Applicants (NTA)**
  - Vol. 2A: Procedures for Marketing Authorisation
  - **Vol. 2B: Presentation & Content of the dossier**
    (CTD/ICH M4)
  - Vol. 2C: Regulatory Guidelines
- **Eudralex Vol. 3**: Scientific guidelines for medicinal products for human use (EMEA)
- **ICH Guidelines Safety and Multidisciplinary topics**
  “S” and “M”
Diagrammatic Representation

Module 2
(Summaries)

Module 3
Quality
Overall Summary
2.3

Module 4
Non-clinical Study Reports
4.0

Module 5
Clinical Study Reports
5.0

1.0 Regional Administrative Information

Non-clinical Overview
2.4

Non-clinical Written & Tabulated Summaries
2.6

Clinical Overview
2.5

Clinical Written Summary
2.7

Module 1 not part of CTD
Non-clinical Summaries

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics (ADME)
- Toxicology
- Integrated overview and conclusions
- List of literature citations
Structure of the Dossier (CTD)

The Non-clinical Summaries

- Annex to module 4 in CTD (NTA Vol. 2B):
  - List of references to non-clinical guidelines
- Annexes to ICH M4 (S)
  - A. Examples of Tables and Figures for Written Summaries
  - B. Nonclinical Tabulated Summaries: Templates
  - C. Nonclinical Tabulated Summaries: Examples
The Written and Tabulated Summaries

• Order of presentation:
  – *In vitro* before *in vivo*.
  – By species.
  – By route.
  – By duration.

• In general, not more than 100 to 150 pages.
Overview (Module 2.4)

- Same structure as CTD, cross-references to data
- Introduction and rationale for non-clinical development
- Critical assessment with supportive data e.g. mechanistic studies (if appropriate)
- Sound justifications for any deviations from guidelines or missing data
- Integration across studies including quality and clinical data if appropriate
- Conclusion with benefit-risk aspects, labelling recommendations
Benefits of the CTD

- Clear, well-structured dossier
- Reduces variability of presentation of dossier
- Helps Validation, Navigation, Evaluation
- Higher quality of Assessment reports
- Allows use of e-CTD tools
eCTD Implementation Strategy at EMEA: Key Milestones

• From 1 July 2008:
  – The EMEA accepts electronic-only submissions,

• From 1 January 2009:
  – The EMEA strongly recommends electronic-only submissions,

• From 1 January 2010:
  – The EMEA will mandate the use of the eCTD format for all electronic-only submissions for all applications (new and existing) and all submission types.
Scientific Guidelines

- Guidelines recently discussed at ICH (Brussels Nov. 2008)
  - “Non-clinical Evaluation of Anticancer Pharmaceuticals” (S9)  
    - Scope limited to development of anticancer pharmaceuticals intended to treat cancer in patients with late stage or advanced disease.
  - “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals” (S6 addendum)
    - Topics will include: species selection, study design, reproductive/developmental toxicity, carcinogenicity, and immunogenicity.
  - “Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” (M3 revision)
    - New sections: Estimation of the First Dose in Humans, Clinical Trials in Paediatric Populations, Immunotoxicology, Phototoxicity, and Nonclinical Abuse Liability. The guideline is expected to be finalised (ICH Step 4) in June 2009
Scientific Guidelines

• Guidelines on Specific topics
  – Reproductive toxicity
    • Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling EMEA/CHMP/203927/05
    • Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications CHMP/SWP/169215/05
    • Points to consider on the Need for assessment of reproduction toxicity of human insulin analogues (CPMP/SWP/2600/01)
  – Genotoxicity
    • Guideline on Genotoxic Impurities (CPMP/SWP/5199/02)
    • Reflection Paper on the assessment of the Genotoxic Potential of Antisense Oligodeoxynucleotides (CHMP/SWP/199726/04)
Scientific Guidelines

• Guidelines on Specific topics
  – Carcinogenicity
    • Carcinogenicity Evaluation of Medicinal Products for the Treatment of HIV Infection (EMEA/194898/2006)
    • Points to consider on the Non-clinical assessment of the carcinogenic potential of human insulin analogues (CPMP/SWP/372/01)
Scientific Guidelines

- Guidelines on Specific topics
  - Non-clinical guideline on drug-induced hepatotoxicity
    CHMP/SWP/150115/06 – Draft
  - Environmental risk assessment
  - Non-Clinical Investigation of the Dependence Potential of Medicinal Products
    CHMP/SWP/94227/04
  - Need for revision of the Note for Guidance on photo-safety testing
    (CPMP/SWP/398/01)
  - Strategies to identify and mitigate risks for first-in-human clinical trials
    with investigational medicinal products
    CHMP/SWP/28367/07
  - Fixed dose combinations
Scientific Guidelines

• Guidelines on Specific topics (cont.)
  – *In vitro and local tolerance*
    • Replacement of animal studies by *in-vitro models* CPMP/SWP/728/95
    • *In Vitro* investigation of *mitochondrial toxicity of anti-HIV* nucleoside reverse transcriptase inhibitors CHMP/SWP/8212/07 – Draft
    • Non-clinical *local tolerance* testing of medicinal products (CPMP/SWP/2145/00)
  – *Gene therapy* medicinal products guidelines
    • Inadvertent germ-line transmission of gene transfer vectors
    • Environmental risk assessment (draft)
    • Non-clinical requirements before 1st Clinical Trial (draft)
  – *Biosimilar* guidelines (Non-clinical Annex)
    • Recombinant erythropoietin
Ongoing and Future Challenges

- **Advanced Therapy Medicinal Products**: New guidelines and Non-clinical certification in 2009.
- **Biomarker Qualification** and other Innovative methods of safety testing, Joint EMEA/FDA evaluation
- **New technologies** and their use in risk assessment (e.g. -omics)
- **Safety of Nano-Medicines**: Collaboration with other EU Agencies (food, chemicals..) and Commission.
- **“Translational” aspects of medicines**: CHMP multidisciplinary group (planned)
- **Reduction of animal testing** (3R’s): Acute toxicity (ICH M3), EU collaboration (EPAA, IMI, FP7 etc.)
Commission WEBSITE for EC documents
“Latest news on Pharmaceuticals”
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

EUDRALEX:
NTA documents
EC Regulations
EC Guidelines
Useful Links

- ICH-website: http://www.ich.org