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

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Legal Framework

- Parliament and Council Directive 2001/83/EC establishes the Community code relating to medicinal products for human use (pharmaceutical legislation)
  - *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.

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Legal Framework

- Commission Directive 2003/63/EC or **Annex I** to Directive 2001/83/EC, as amended, contains detailed scientific and technical requirements
  - *Introduction and General principles*
    - (9): GLP conduct of non-clinical studies
    - (10): Animals test 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)

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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"

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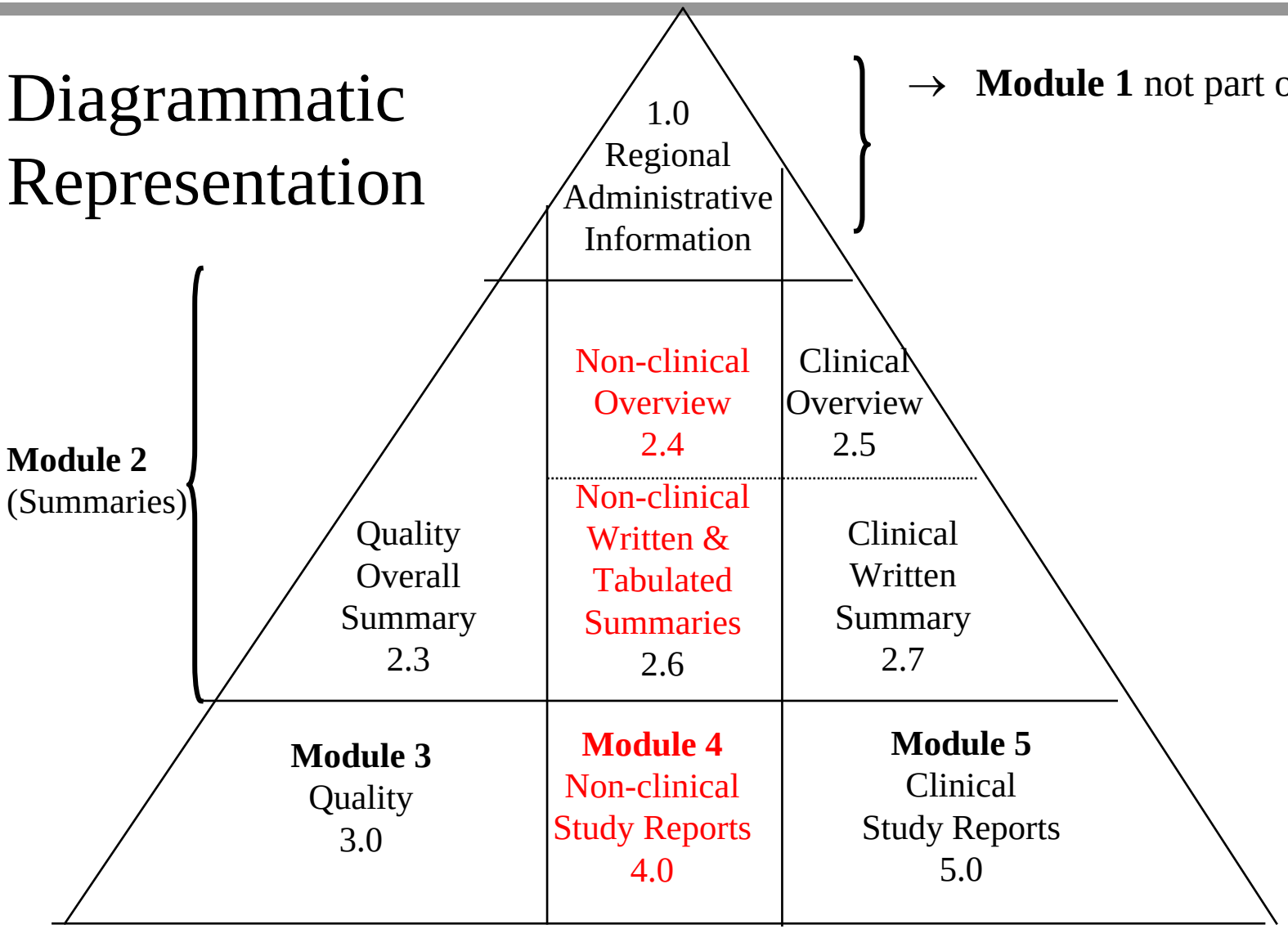
Diagrammatic Representation



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Non-clinical Summaries

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

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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

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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.

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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

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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

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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.

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Scientific Guidelines

- Guidelines recently discussed at ICH (Brussels Nov. 2008)
  - "Non-clinical Evaluation of Anticancer Pharmaceuticals" (S9) *Step 3*
    - 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

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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)

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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)

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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

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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
    - Inadvertant 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

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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.)

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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

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Useful Links

- ICH-website: http://www.ich.org
- Eudralex Vol 2 - NTA (human): http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm
- Vol 2B presentation and content (CTD) http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/update_200805/ctd_05-2008.pdf
- EMEA: scientific guidelines non-clinical: http://www.emea.europa.eu/htms/human/humanguidelines/nonclinical.htm