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Health Canada Santé Canada

Therapeutic Products Directorate

Direction des produits thérapeutiques

Health Products and Food Branch

Direction générale des produits de santé et des aliments

2.4 – Regulations & Guidelines: CMC and Non-Clinical

Presentation to APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

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Slide 1

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop

Objectives

Regulations and guidelines for:

Chemistry, manufacturing, and controls

Non-clinical data requirements

Canadian CMC Regulations

- Schedule B compendial monographs (e.g., USP, Ph.Eur., BP)
- Division 5: drugs for clinical trials
  - Medicinal and non-medicinal ingredients and dosage form
  - Physical, chemical, and pharmaceutical properties of the drug
  - C&M information in respect of the drug, including its site of manufacture
  - Manufactured, handled, and stored in accordance with applicable GMPs
  - Labelling requirements

Canadian CMC Guidelines

- Good manufacturing practices (GMPs): general guideline and Annex 2 for the manufacture of drugs used in clinical trials
- Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications
- Preparation of the Quality Information for Drug Submissions in the CTD Format:
  - Conventional Biotherapeutic Products
  - Vaccines
  - Blood Products
  - Biotechnological Products

CMC ICH Guidelines (1)

Q1A(R2): Stability Testing of New Drug Substances and Products

Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products

Q1C: Stability Testing: Requirements for New Dosage Forms

Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q1E: Evaluation of Stability Data

Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

Q2A: Text on Validation of Analytical Procedures

Q2B: Validation of Analytical Procedures: Methodology

CMC ICH Guidelines (2)

Q3A(R): Impurities in New Drug Substances

Q3B(R): Impurities in New Drug Products

Q3C: Impurities: Guideline for Residual Solvents

Q5A: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological / Biological Products

Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological / Biological Products

Q7A: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients

CMC Requirements from Guidelines

- At the clinical trial stage:
  - Do not require that sponsors follow ICH guidelines
  - Do not inspect manufacturing sites against the Annex 2 of the GMP
  - Expect that sponsors work towards meeting the guidelines by improving the manufacturing and control of the drug substance and drug product as the product progresses through clinical development
- Guidelines are applied at the marketing stage

Canadian Non-Clinical Regulatory Requirements

- Division 5: drugs for clinical trials, the investigator's brochure must include
  - The pharmacological aspects of the drug, including its metabolites in all animal species tested
  - The pharmacokinetics of the drug and the drug metabolism, including the biological transformation of the drug in all animal species tested
  - Any toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study in respect of the drug
  - Any results of carcinogenicity studies in any animal species tested in respect of the drug

Non-Clinical ICH Guidelines (1)

S1A: Need for Carcinogenicity Studies of Pharmaceuticals

S1B: Testing for Carcinogenicity of Pharmaceuticals

S1C: Dose Selection for Carcinogenicity Studies of Pharmaceuticals

S1C(R): Addendum to "Dose Selection for Carcinogenicity Studies of Pharmaceuticals" Addition of a Limit Dose and Related Notes

S2A: Guidance on Specific Aspects Of Regulatory Genotoxicity Tests For Pharmaceuticals

S2B: Genotoxicity: A Standard Battery for Genotoxcity Testing of Pharmaceuticals

S3A: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies

S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

Non-Clinical ICH Guidelines (2)

S4A: Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)

S5A: Detection of Toxicity to Reproduction for Medicinal Products

S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

S7A: Safety Pharmacology Studies for Human Pharmaceuticals

S7B: The Nonclinical Evaluation of the Potential for Delayed ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

M3: Timing of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Non-clinical Requirements from Guidelines

- Generally require that sponsors follow all applicable ICH guidelines for the non-clinical program

References

Annex 2: Manufacture of Drugs Used in Clinical Trials	www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/cln_trials-essais_cln_e.pdf
Pharmaceutical Quality Guidance	www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/qual_cta_dec_e.html
Biologics Quality Guidances	www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/index_e.html
ICH CMC and Non-clinical guidelines	www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/index_e.html