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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

Session 7 – Clinical Trial Assessment Bioequivalence Studies

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

Overview

- Regulations & Guidance
- Objective & characteristics of bioequivalence studies
- Data requirements
- Study designs
- Essential components in the review

Regulations & Guidance

- Comparative bioavailability studies fall under Division 5 and a CTA is required (regulations apply as for other clinical trials)
- 7 day administrative review target; 30 day default if target is not met
- Non-Canadian reference products used to support an Abbreviated New Drug Submission (ANDS) must meet the criteria defined in the HPFB guidance *Canadian Reference Product* (December 4, 1995)
- Guidance for clinical trial sponsors on how to file an application for a comparative bioavailability study is available

Guidance for Registration (1)

- Conduct and analysis of bioavailability and bioequivalence studies

  Part A: Oral Dosage Formulations Used for Systemic Effects

  Part B: Oral Modified Release Formulations

- Report C: Report on Bioavailability of Oral Dosage Formulations, not in Modified Release Form, of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics

- Notice to Industry - Bioequivalence Requirements for Long Half-life Drugs

Guidance for Registration (2)

- Bioequivalence Requirements: Critical Dose Drugs
- Notice to Industry - Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs)
- Guidance for Industry: Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State
- Draft Guidance for Industry: Use of Metabolite Data in Comparative Bioavailability Studies
- Notice to Industry - Bioequivalence Requirements for Combination Drug Products

Data Requirements

- Format is the same as for a CTA
  - HC form 3011 with signed attestation
  - Clinical package
  - CMC package
- QOS-BE template to be filled-out by sponsor and submitted
- Clinical package to include the protocol, informed consent form and Canadian Product Monograph (or similar document for a comparator product not marketed in Canada)

Objective & Characteristics

Objective of Comparative Bioavailability Studies:

- To test the formulation of a subsequent-entry pharmaceutical product as compared to a reference

Characteristics

- Healthy adult volunteers
- Canadian reference product or product that is marketed in US, EU, Australia, or Switzerland
- Single or total daily dose does not exceed that specified in the labelling of the reference drug product
- The study does not include the simultaneous administration of a radioactive labelled and unlabelled drug product

Study Designs

- Single dose with a two period cross-over design
- Conducted in fasted and fed state (if indicated to be taken with food)
- Three and four-period cross-over for modified-release formulations
- Some studies involve parallel group designs
- Steady-state studies for formulations likely to accumulate (e.g., delayed release drug products)

Endpoints

- Pharmacokinetic parameters (e.g., AUC_t, C_{max}, T_{max}, elimination $t_{1/2}$, AUC_{tau}, C_{min})

- Safety of the new formulation as compared to the reference

Quality Review

- Information on Canadian Reference Product or Non-Canadian Reference Product
- Drug substance:
  - Attestations (GMP, ICH organic solvents, TSE/BSE)
  - Batch analyses
- Drug product:
  - Composition of dosage form
  - Attestation (non-medicinal ingredients consistent with reference product, prohibited excipients, GMP)
  - Batch analyses
  - Excipients of human or animal origin (information may be submitted later, but 2 days prior to starting the study)

Clinical Review (1)

- Use a Reviewer's check-list
- Dose as labelled
- Choosing the dose for drugs that need to be titrated ("critical dose" drugs)
- Dose tapering at end of dosing (abrupt discontinuation can lead to withdrawal symptoms)
- Wash-out period should consist of at least 10 terminal elimination half-lives; should not exceed 3 to 4 weeks

Clinical Review (2)

- Sample size usually >12 and depends on the estimated intra-subject variability
- Eligibility criteria
  - should take into consideration the contraindications, warnings and precautions for the drug
  - TB screening for immunosuppressants or drugs with immunosuppressant properties (medical history and TST)
- Pregnancy testing if females of child-bearing potential included; acceptable contraceptive methods defined

Clinical Review (3)

- Total blood volume collected should not exceed 500 mL within a 4 week period (minimum time between donations according to the Canadian Blood Services and International Red Cross is 56 days)
- Intravenous catheter for multiple blood draws in early time points
- Risks related to the drug are listed in the informed consent form and acceptable contraceptive methods defined

Summary

- Some studies are not for Canadian registration
  - allow use of non-Canadian reference product from another ICH region, Australia, or Switzerland
- Health Canada has several guidance documents on the requirements for registration
- Review of comparative bioavailability studies focuses on safety

References

Guidance for Industry on Clinical Trial Applications for Comparative Bioavailability Studies for Pharmaceuticals	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/ctabio_decbio_e.html
Quality Overall Summary Template for Comparative Bioavailability Studies	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qoscectaba_sgqecdeceb_e.pdf
Quality Guidance for Clinical Trial Sponsors – Clinical Trial Applications	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/qual_cta_dec_e.html
Notice for TB screening	http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/tuberc_notice_avis_e.html