Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments




New Health Canada Guidances and Notices to Industry on Bioequivalence and Comparative Bioavailability

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Canada

Overview

- Expert Advisory Committee (EAC) on Bioavailability: Report C
- Notice to Industry *Bioequivalence Requirements for Combination Drug Products (2004)*
- Notice to Industry *Bioequivalence Requirements for Long Half-Life Drugs (2005)*
- Notice to Industry *Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs) (2005)*
- Guidance for Industry *Bioequivalence Requirements: Critical Dose Drugs (2006)*
- Guidance for Industry *Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State (2005)*

Introduction

New Guidances and Notices

Bioequivalence Requirements for Combination Drug Products (2004)

Bioequivalence Requirements for Long Half-Life Drugs (2005)

Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs) (2005)

Bioequivalence Requirements: Critical Dose Drugs (2006)

Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State (2005)

Report C

- *Combination Drug Products*
- *Drug Products with an Effective Half-Life > 12 hrs*
- *Drugs for which an Early Time of Onset or Rapid Rate of Absorption is Important*
- *Highly Toxic Drugs*
- *Drugs with a Narrow Therapeutic Range*

Notice to Industry Bioequivalence Requirements for Combination Drug Products (2004)

- Combination drug product - product containing two or more active ingredients
- Report C: Type 1 (independently) and Type 2 (synergistic) products
- Current requirements
  - all combination products requiring comparative bioavailability studies, the PK parameters to be reported and assessed are those which would normally be required of each drug if it were in the formulation as a single entity
  - refer to current TPD guidances, polices, notices for study design and standards

Notice to Industry Bioequivalence Requirements for Combination Drug Products (2004)

- Amoxicillin Trihydrate / Clavulanate Potassium immediate-release combination tablets

- Requirements

Amoxicillin Trihydrate

- 90% confidence interval of the relative mean AUC_T of the test to reference product should be within 80-125%.
- the relative mean measured C_{max} of the test to reference product should be between 80-125%.

Clavulanate Potassium

- 90% confidence interval of the relative mean AUC_T of the test to reference product should be within 80-125%.
- the relative mean measured C_{max} of the test to reference product should be between 80-125%.

Notice to Industry Bioequivalence Requirements for Long Half-Life Drugs (2005)

- Report C
  - effective half-life is greater than 12 hours
  - parallel studies, steady-state studies should be considered when effective half-life is greater than 72 hours
  - the measurement of more than 80% of the expected AUC_{inf} may require an unreasonable long sampling duration
  - absorption generally occurs within 24 hours

- Current requirements
  - the terminal elimination half-life is greater than 24 hours
  - standards for comparative bioavailability/bioequivalence studies will be applied to $AUC_{0\text{-}72h}$
  - alternate designed studies (*e.g.* parallel studies) can be considered

Notice to Industry Bioequivalence Requirements for Long Half-Life Drugs (2005)

- Amlodipine besylate immediate-release tablets
  - terminal elimination half-life of about 30-50 hours (CPS 2005)

- Requirements
  - 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ of the test to reference product should be within 80-125%.
  - the relative mean measured C_{max} of the test to reference product should be between 80-125%.

Notice to Industry Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs) (2005)

- Rapid onset drugs (*e.g.* analgesic for rapid relief of pain)
  - immediate release formulations (Guideline A)
  - time of onset of effect is important because of therapeutic or toxic effects

- Current requirements
  - 90% CI of the relative mean AUC_T of the test to reference should be between 80% and 125%
  - the relative mean measured C_{max} of the test to reference product should be between 80% and 125%.
  - the relative mean $AUC_{Reftmax}$ of the test to reference should be within 80% and 125%

Notice to Industry Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs) (2005)

- Sumatriptan succinate immediate release tablets
  - indicated for the acute treatment of migraine attacks with or without aura
  - if migraine returns or partial response to initial dose, a second dose may be repeated after 2 hours

- Requirements
  - 90% CI of the relative mean AUC_T of the test to reference should be between 80% and 125%
  - the relative mean measured C_{max} of the test to reference product should be between 80% and 125%.
  - the relative mean $AUC_{Reftmax}$ of the test to reference should be within 80% and 125%

Guidance for Industry Bioequivalence Requirements: Critical Dose Drugs (2006)

- Report C
  - Narrow Therapeutic Range drugs (NTR): adverse effects which limit the therapeutic use to doses close to therapeutic range
  - Highly Toxic: therapeutic use may result in dose- or concentration-dependent adverse effects

Previous requirements

- 95% CI of the relative mean AUC_T of the test to reference should be between 80.0% and 125.0%
- 95% CI of the relative mean measured C_{max} of the test to reference should be between 80.0% and 125.0%
- single dose fasted and fed studies

Guidance for Industry Bioequivalence Requirements: Critical Dose Drugs (2006)

- Critical dose drugs: "comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reaction, which maybe persistent, irreversible…life-threatening …hospitalization …disability …death"

- Current requirements
  - Single-dose studies
    - 90% CI of the relative mean AUC_T of the test to reference should be between 90.0% and 112.0%
    - 90% CI of the relative mean measured C_{max} of the test to reference should be between 80.0% and 125.0%
    - fasted and fed states
  - Multiple dose study (if required)
    - in addition, 90% CI of the relative mean measured C_{min} of the test to reference should be between 80.0% and 125.0%

Guidance for Industry Bioequivalence Requirements: Critical Dose Drugs (2006)

- Cyclosporin (Appendix I)
  - immunosuppressive therapy
  - narrow therapeutic range (~50-300 ng/mL)
  - nephrotoxicity associated with trough plasma levels greater than 250 ng/mL

Requirements for immediate release formulation

- two comparative bioavailabiliy studies conducted under fasting and fed conditions
- 90% CI of the relative mean AUC_T of the test to reference should be between 90.0% and 112.0%
- 90% CI of the relative mean measured C_{max} of the test to reference should be between 80.0% and 125.0%

Guidance for Industry Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State (2005)

- Uncomplicated drugs in immediate-release dosage forms (Guideline A)
  - comparative bioavailability studies under fasting conditions
- Complicated drugs in immediate-release dosage from (*e.g*. critical dose drugs, non-linear drugs) (Guideline A)
  - EAC on Bioavailability Report C, Notices to Industry, Guidances
  - comparative bioavailability studies under fasting and fed conditions
- Drugs in modified-release dosage forms (Guideline B)
  - comparative bioavailability studies under fasting and fed conditions
  - steady-state studies (if required)

Guidance for Industry Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State (2005)

- If there is a documented serious safety risk to subjects from single-dose administration of the drug or drug product in either the absence or presence of food, then a study in the indicated condition of use (fed or fasted) may be considered acceptable.

- Comparative bioavailability study conducted in the indicated condition of use to prevent the toxicity may be acceptable for purposes of demonstrating bioequivalence

  Example: immediate-release Drug X capsules
  - recommended that drug product *should/must* be administered with food (labelling)
  - highly variable PK characteristics are observed in subjects being administered Drug X in the absence of food resulting in serious adverse events

  Comparative bioavailability study only under fed conditions may be considered acceptable.

Guidance for Industry Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State (2005)

- Standard Test meal
  - sufficient food is given to allow potential perturbation of systemic bioavailability of the drug from the drug product
  - justification for the meal choice and timing of the food administration

Example: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 120 g of hash browns and 240 mL of milk

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QUESTIONS