Prequalification Programme
Bioequivalence Assessment
Update

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World Health Organization

WHO Prequalification of Medicines Programme 3rd Meeting with Manufacturers of FPPs and APIs
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Overview

- Review of commonly used bioequivalence (BE) approaches
  - Updates on recommended approaches

- Review and update
  - Biowaivers
    - Biowaiver documentation
    - Eligible APIs
  - Comparators
  - Analytical method validation

- Sources of up-to-date information
Crossover Design

- Blood samples are collected and assayed
  - Before and several times after drug administration. No need after 72 h
- Prior to period 2, pre-dose levels must be <5% of Cmax of 2nd period
- Wash out period must take into account the slow metabolizers
- Minimum wash out: 7 days (1 week)
Typical *in vivo* BE Design

- Single-dose administration
- Cross-over (within-subject) comparison
- Healthy volunteers
- Administration with or without food
  - Fasted study is the norm
- Thoroughly validated bioanalytical method
- Data from parent compound used for BE decision
- Analysis should be carried out on the logarithmically transformed $AUC_T$ and $C_{max}$ data
In vivo BE Study Design

Administration of products under fasted or fed conditions?

Fasted conditions
- Study conducted under fasted conditions the norm
- Comparator product labeling (SPC)
  • Specifies fasted conditions
  • Does not specify fasted/fed for administration
  • States that either fasted or fed administration

Fed conditions
- If specified in comparator product labeling (SPC)
**In vivo BE Study Design**

Administration of products under fasted or fed conditions?

- **Fed conditions**
  - If specified in comparator product labeling (SPC)
  - Type of meal to be consumed
    - high-fat, high-calorie meal
    - “standard” or typical breakfast

- **Administration under both fasted and fed conditions**
  - Not generally necessary for immediate-release products
  - Required for modified-release products
    - e.g., didanosine enteric coated tablets
Examples
HIV/AIDS Medicines

- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
  - Lamivudine
    - Administration with respect to food not specified
    - Fasted
  - Stavudine
    - Maybe taken with or without food
    - Fasted
  - Zidovudine
    - Administration with respect to food not specified
    - Fasted
Examples
Malaria Medicines

- Artemisinin-based fixed dose oral combination formulations

- Artemether + Lumefantrine
  - Artemether
    • Bioavailability increased when taken with food (x2)
  - Lumefantrine
    • Bioavailability increased when taken with food
      - x16 increase with high fat meal
      - x2 increase with lower fat meal
  - Fed conditions (“standard” breakfast)
  - See specific study advice on website
Drugs with long elimination $t_{1/2}$: Parallel

- Normally wash-out period should not exceed 3-4 weeks
- If a larger wash-out period is necessary a parallel design may be more appropriate
- Variability will be larger, needs higher sample size
  - Parallel design: Total variability (intra+inter)
  - Cross-over: Intra-subject variability
- Sampling: Up to 72 h
In vivo BE Study Design

- Crossover Design
  - Each subject administered both test and comparator
  - Within-subject comparison
  - Preferred

- Parallel Design
  - Each subject administered test or comparator
  - Between-subject comparison
  - Only recommended for extremely long half-life drugs
  - Consult WHO
  - e.g., medroxyprogesterone depot injection
Alternative *in vivo* BE Study Designs

- Unknown variability
  - Estimates of intra-subject CV not available
  - Pilot Study
  - Two-stage group sequential two-way crossover design
    - Details of statistical plan in protocol
    - Overall Type 1 error must be preserved
      - Adjusted level of significance resulting in CIs higher than 90%
  
  - Canadian guidance ‘Conduct and Analysis of Comparative Bioavailability Studies’ (2012)
Alternative *in vivo* BE Study Designs

- **High variability in Cmax**
  - Intra-subject ANOVA-CV of ≥ 30%
  - Replicate design
    - Estimation of variability based on replicate administration of comparator product
    - Widening of acceptance criteria for Cmax based on estimated variability
Biowaivers

- Surrogate approaches for demonstrating safety and efficacy of products in lieu of conducting in vivo bioequivalence studies

- Biopharmaceutics Classification System (BCS) – based biowaivers
  - Suitable for products containing eligible APIs

- Additional strengths biowaivers
  - Suitable for additional strengths in a product line when one of the strengths has been proven bioequivalent to the comparator
BCS-based Biowaivers eligible APIs

- Medicines for HIV/AIDS and related diseases
  - Abacavir sulfate (Class III)
  - Emtricitabine (Class I)
  - Lamivudine (Class III)
  - Stavudine (Class I)
  - Zidovudine (Class I)

- Anti-tuberculosis medicines
  - Ethambutol (Class III)
  - Isoniazid (Class III)
  - Levofloxacin (Class I)
  - Moxifloxacin HCl (Class I)
  - Ofloxacin (Class I)
  - Pyrazinamide (Class III)
BCS-based Biowaivers

- Updated guidance document
  - General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications
    - Unification of requirements into one document
    - Clarification of requirements

- Updated biowaiver application form
  - Biowaiver Application Form: Biopharmaceutics Classification System (BCS)
Additional Strengths Biowaiver

- Updated biowaiver application form
  - Biowaiver Application Form: Additional Strengths
    - Clarification of reference for comparisons
      - Strength with demonstrated in vivo bioequivalence
    - Comparative in vitro dissolution: Studies comparing different strengths of the test product
    - Comparative in vitro dissolution: Studies comparing each strength of the test product to equivalent strength of comparator product
      - ONLY under certain circumstances
    - Better instructions for reporting dissolution procedures
Additional Strengths Biowaiver

Please pay attention to the following:

- Filtration
  - Reporting of methods employed
- Calculation of f2 as per WHO guidance
- Comparative dissolution study protocol & report
- Auditing and monitoring
- Special dissolution study requirements for delayed-release products (enteric-coated products)
Comparator (Reference) Products

Comparator products should be obtained from a well regulated market with stringent regulatory authority *i.e.*, from countries participating in the International Conference on Harmonization (ICH).

Countries officially participating in ICH
- ICH members: European Union, Japan and USA
- ICH observers: Canada and EFTA as represented by Switzerland
- Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.
Comparator Products

- If WHO comparator product cannot be located from ICH-associated markets, consult PQP
  - Assistance identifying pharmaceutical distributors
  - Identification of alternate markets for sourcing particular products

- There are instances when a comparator is not available in the ICH region
  - *e.g.*, Terizidone 300mg
    - Terivalidin 250 mg (Sanofi-Aventis, South Africa)
  - *e.g.*, Artesunate + Amodiaquine 100 mg + 270 mg FDC
    - Coarsucam (Sanofi-Aventis)
Comparator Products

- Complete documentation required as per website
  - Purchase
  - Shipping
  - Storage & handling

- Check website regularly for updated lists
Zinc Sulfate Tablets

- Complicated situation with respect to absorption / bioavailability of zinc

- Posting of updated guidance document
  - Additional Guidance for submission of applications for prequalification of Zinc Sulfate tablets and Zinc Sulfate oral liquid (solution)
  - Expected soon
Analytical Method Validation

• Complete validation is necessary to produce confidence in the data set

• All procedures including handling and storage should be validated

• EMA guidance ‘Guideline on Bioanalytical Method Validation’ (2011)
Conclusions

- Prequalification Programme constantly evolving

- Check website regularly for updates
  - Guidance
    - Including advice on the design of bioequivalence studies for specific APIs
  - Application forms
  - Comparator information

- Consultation with programme
  - Scientific advice
Contact

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Thank you!