Key Output of Programme

- A list of prequalified medicinal products used for treatment of HIV/AIDS, malaria, tuberculosis, influenza, and for reproductive health

- To get a product included on the list, a manufacturer provides a comprehensive set of data about the quality, safety and efficacy of its product

- For most products (multisource or generic), this data set will include the results of *in vivo* bioequivalence tests (clinical trials conducted in healthy volunteers) as evidence of safety and efficacy
Bioequivalence

Possible Differences
- Drug particle size, ...
- Excipients
- Manufacturing process
- Equipment
- Site of manufacture
- Batch size ....

Documented Bioequivalence = Therapeutic Equivalence
Establishing Bioequivalence

- Comparative pharmacokinetic studies
  - *In vivo* comparative bioavailability studies
  - Comparison of performance of products based rate and extent of absorption of drug substance from each formulation
    - Area under the concentration-time curve (AUC)
    - Maximal concentration (Cmax)
    - Time to maximal concentration (Tmax)

- Comparative pharmacodynamic studies

- Comparative clinical trials

- Comparative *in vitro* methods
  - Biopharmaceutics Classification System (BCS)-based biowaivers
BCS-based Biowaiver

- Eligibility for BCS-based Biowaiver
  - General Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications

- Requirements for BCS-based Biowaiver
  - General Notes on BCS-based Biowaiver Applications
  - Biopharmaceutics Classification System (BCS)-based Biowaiver Applications: Anti-Tuberculosis Medicines
In vivo BE Study Design

Products being tested

- Comparator product
  - WHO provides recommendations
  - To be discussed by Dr. Welink

- Test product
  - Biobatch of sufficient size
  - Consistent with product proposed for market
In vivo BE Study Design

- Single-dose administration

- Multiple-dose administration
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
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)
**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
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

Randomization to treatments

Group 1: Treatment A

Group 2: Treatment B
**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
Examples
HIV/AIDS Medicines

- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
  - Lamivudine
    - Administration with respect to (wrt) food not specified
    - Fasted
  - Stavudine
    - Maybe taken with or without food
    - Fasted
  - Zidovudine
    - Administration with respect to (wrt) food not specified
    - Fasted
  - Note: as monocomponent products: BCS-based biowaiver
Examples
HIV/AIDS Medicines

- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
  - Didanosine (enteric-coated)
    - Delayed-release formulation
    - Two studies required: Fasted and fed conditions
  - Tenofovir disoproxil fumarate
    - US labeling of comparator: “The dose is one 300 mg tablet once daily taken orally, without regard to food.”
    - European labeling of comparator: “...(one tablet) once daily taken orally with food.”
    - Either accepted
Examples
HIV/AIDS Medicines

- Non-Nucleoside Reverse Transcriptase Inhibitors
  - Efavirenz
    - Fed administration increases bioavailability but also increases adverse events
    - Comparator labeling recommends administration on an empty stomach
    - Fasted
  - Nevirapine
    - Administration with respect to (wrt) food not specified
    - Fasted
Examples
HIV/AIDS Medicines

Protease Inhibitors

- Atazanavir
  - Administration with food increases bioavailability and decreases variability
  - Fed

- Ritonavir
  - Administration with food improves absorption
  - Fed

- Atazanavir / ritonavir combination
  - Fed
  - Standard breakfast
Examples
Tuberculosis Medicines

- First-line treatments
  - Ethambutol
    - Administration not affected by food
    - Fasted
  - Isoniazid
    - Administration on an empty stomach
    - Fasted
  - Pyrazinamide
    - Administration preferably without food
    - Fasted
  - Note: as monocomponent products: BCS-based biowaiver
Examples
Tuberculosis Medicines

- First-line treatments
  - Rifampicin
    - "It is recommended that oral rifampin be administered once daily, either 1 hour before or 2 hours after a meal with a full glass of water."
    - Fasted

- Second-line treatments
  - Cycloserine
    - Maybe taken with or without food
    - Fasted
Examples
Tuberculosis Medicines

- **Second-line treatments**
  - Levofloxacin
    - Administration with respect to (wrt) food not specified
    - Fasted
    - Eligible for BCS-based biowaiver
  - Ofloxacin
    - “…should not be taken within two hours of magnesium/aluminium containing antacids, sucralfate, zinc or iron preparations…”
    - Administration with respect to (wrt) food not specified
    - Fasted
    - Eligible for BCS-based biowaiver
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)
Examples Malaria Medicines

- Artemisinin-based fixed dose oral combination formulations

- Artesunate + Amodiaquine
  - Artesunate
    - Bioavailability decreased when taken with food
  - Amodiaquine
    - Bioavailability increased when taken with high fat meal
  - Labeling states “should not be taken with a high-fat meal”
  - Fasted
Examples
Malaria Medicines

- Artemisinin-based fixed dose oral combination or co blister formulations

- Artesunate + Mefloquine
  - Artesunate
    - Bioavailability decreased when taken with food
  - Mefloquine
    - Bioavailability increased when taken with food (40%)
    - Labeling states “Should not be taken on an empty stomach”
  - Fed
  - “Standard” breakfast, not high-fat meal
Examples
Reproductive Health Medicines

- Oral hormonal contraceptives
- Ethinyl estradiol + levonorgestrel
  - Administration with respect to (wrt) food not specified
  - Fasted
Typical Design

- Single-dose administration
- Cross-over (within-subject) comparison
- Administration with or without food
  - Fasted study is the norm
  - Labeling of the comparator product is the guide
    - Bioavailability / pharmacokinetics
    - Adverse events
- Consultation with Programme encouraged