Australian Government
Department of Health
Therapeutic Goods Administration

Bioequivalence

Regulator's Perspective

Dr Uta Mbere-Nguyen
Pharmaceutical Chemistry Section
Scientific Evaluation Branch
Medicines Regulation Division, TGA
2017 ARCS Annual Conference
August 2017

TGA Health Safety Regulation

Overview

- Bioequivalence, recap
- Evaluation procedure from evaluator's perspective
- Common issues observed in bioequivalence dossier
- Some examples
- Conclusion

Bioequivalence

*CPMP/EWP/QWP/1401/98 Rev. 1/Corr **-Guideline on the investigation of bioequivalence*

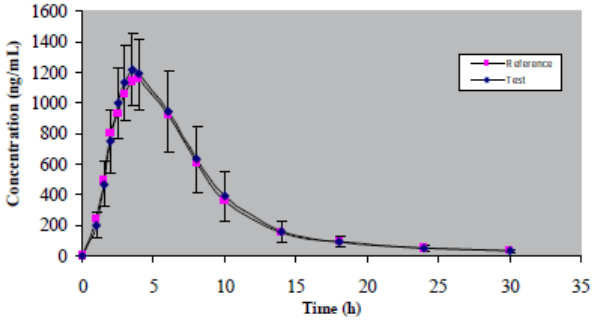


Figure 2: Plasma concentration-time versus of metformin HCl after oral administration of two different formulations containing 750 mg of metfromin HCl. Data are shown as`mean ± SD for 12 subjects.

Journal of Bioequivalence and Bioavailability, 2011, issue 3, volume 1, 016-019

Parameter	Test Formulation	Reference Formulation
$AUC_{0-30\,h}$ (ng x h/mL) Geometric mean Range	9425.41 6230.64 – 13717.76	9248.57 6859.31 – 12387.35
$AUC_{0-\infty}$ (ng x h/mL) Geometric mean Range	9810.29 6568.96 – 13887.61	9664.95 7114.34 – 12623.70
C_{max} (ng/mL) Geometric mean Range	1251.27 884.95 – 1623.95	1181.23 702.42 – 1448.87
T_{max} (h) mean ± SD	3.58 0.36	3.96 1.12
$t_{1/2}$ (h) Geometric mean Range	7.67 3.86 – 11.47	7.96 5.40 – 19.97

Parameter	$AUC_{0-30\,h}$	$AUC_{0-\infty}$	C_{max}
T/R point estimate 90% CI	101.88	101.50	105.93
Lower Limit	94.78	93.77	97.00
Upper Limit	109.54	109.87	115.98

Table 2: Statistical evaluation of comparison of 12 subjects $AUC_{0-30\,h}$, $AUC_{0-\infty}$, and C_{max} of two formulations.

For most cases, bioequivalence is concluded if 90% CI geometric mean ratios of test/reference product for C_{max} and AUC_{0-t} are within 80.00-125.00%

Evaluation Procedure

Study Overview
Published pharmacokinetic data
In-house relevant PK data

Clinical Aspect
- Administrative data
- Study design
- Formulations compared
- Subject sampling time, procedures and storage
- Subject dropout

Analytical Aspect
- Assay method
- Validation of Assay method
- Subject Sample Analysis and results

Statistical Analysis
- Pharmacokinetic calculations
- Statistical analyses

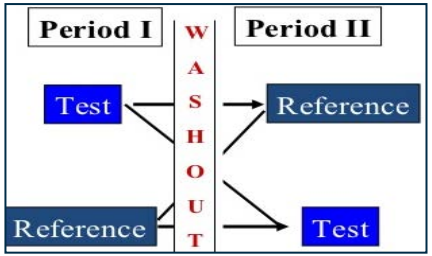
Study overview (Published and in-house pharmacokinetic data)

- Insight into the pharmacokinetic properties of the drug product
  - Tmax, Cmax, Absolute Biovailability, Steady State (level and time)
  - Metabolism, Clearance, Terminal Half-Life (short or long)
  - Effect of age and gender
  - Food Effect? Time of food intake?
  - Linear/Non-Linear Pharmacokinetics

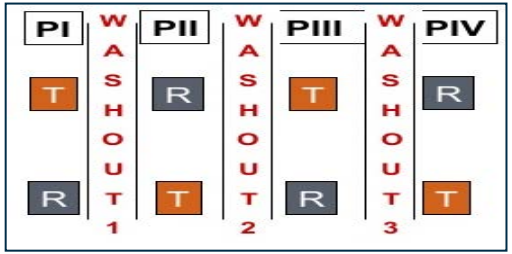
- Other properties of the drug product
  - Narrow Therapeutic Index
  - Highly Variable drug

Clinical aspects (study design)

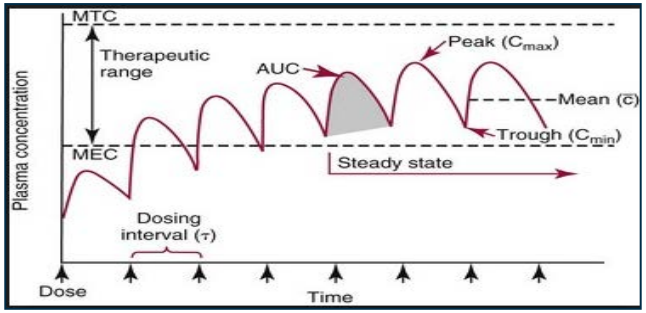
Single-dose, two sequence two-period, crossover



Single-dose, two sequence, four-periods crossover



Multi-dose, two sequence , two period cross over [steady state]



- Single dose, fasted study is most commonly required.
  - Usually in healthy volunteers. Washout period: at least 5 x half-life.
- Food effect study required? Time of food intake as directed in innovator's PI?
- Steady state study required?
- Study conducted on all strengths?
  - If not, has the appropriate strength been chosen to conduct the study
    (as specified in *CPMP/EWP/QWP/1401/98 Rev. 1/Corr **-Guideline on the investigation of bioequivalence*)

Clinical aspects (formulations compared)

- Australian Reference Product whenever possible
  - Certificates of Analysis (Reference + Test) must be provided→ Assay (T vs R): ± 5% difference
  - Do not use an expired reference product

- Other properties
  - Biobatch of Test Product: usually from at least pilot scale
  - Tablet size (T vs R): similarity/difference
  - Dissolution of Test Biobatch: 90% dissolved in 30 minutes→ Dissolution limit: NLT“80% (Q) in 30 minutes”

    EMA/332805/2016 “*Reflection paper on the dissolution Specification for generic oral immediate release product*”.

Clinical aspects (others)

- Subject sampling time, procedures and storage
  - Sampling time adequate to construct a meaningful plasma concentration vs time graph?
  - AUC_{0-t} is at least 80% AUC_{0-inf}
  - Sample processing and storage acceptable?

- Subject drop-out
  - For personal reasons, non-compliance or adverse events (AEs)?
  - For AEs, are they similar between intake of test and reference product?
    - If significantly more AEs observed in one product over the other → seek clinical advice on the relevance of this difference

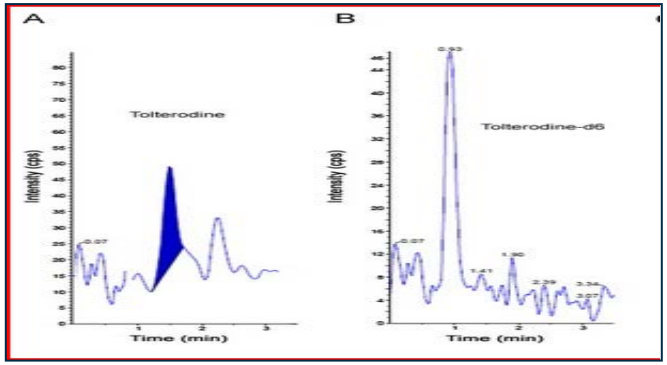
Analytical aspects

- Adequate analytical method details [normally LC/MS/MS]
- Calibration Standards (at least 6 x) and QC standards (at least 3 levels, in replicates)

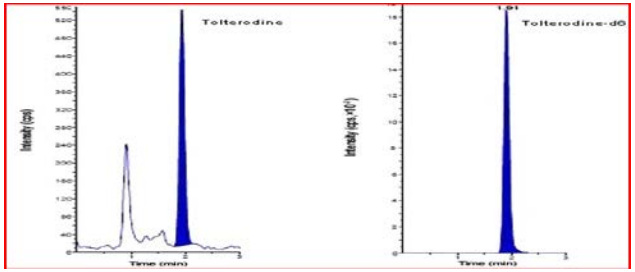
Pre-study validation [common issues]

- Specificity:
  - Free from endogenous matrix components, metabolites and concomitant medications
  - Free from matrix effect in 6 separate plasma lots, and haemolysed and lipemic lots

- Sensitivity (LLOQ): NMT 5% Cmax



Peaks in blank plasma



Peaks in analyte and IS at LLOQ level

Journal of Pharmaceutical Analysis (2013), volume 3: issue 6, 489-499.

Analytical aspects

- Long term stability of analyte in matrix
  - Stored under the same storage condition as subject samples?
  - Cover maximum duration between first sample collection and last sample analysis?
  - Long term stability samples (prepared in multiple replicates at LOQ and HQC) at T-0 and T-last should be analysed against freshly prepared standards
    - Stability samples prepared as one bulk solution and sampled multiple times are **not acceptable**

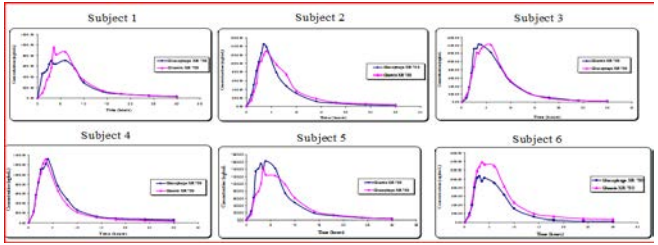
See guideline EMEA/CHP/192217/2009, Rev Corr. 2 for all other parameters required to validate the bioassay method

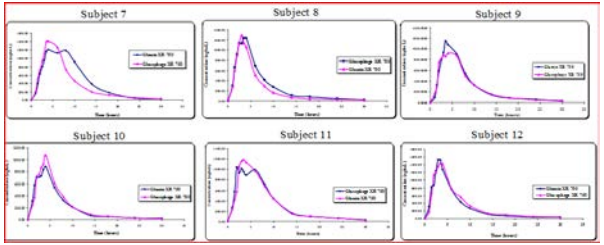
Analytical aspects

Subject Sample Analysis

- Calibration curves and QC standards used during analytical run acceptable?
- Incurred sample analysis
- Sample chromatograms
  - Any anomalies? Peak interferences? No retention times drift?

PK data and statistical analysis





Significant inconsistencies observed in individual graphs could be an issue

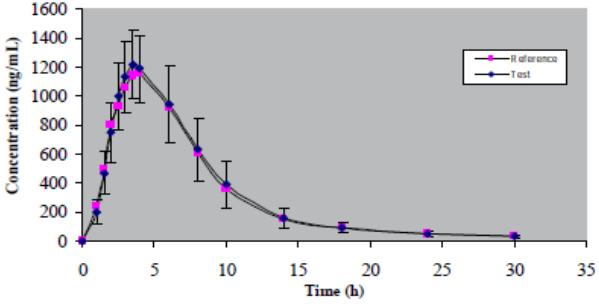


Figure 2: Plasma concentration-time versus of metformin HCl after oral administration of two different formulations containing 750 mg of metfromin HCl. Data are shown as`mean ± SD for 12 subjects.

Parameter	Test Formulation	Reference Formulation
$AUC_{0\text{-}30\,h}$ (ng x h/mL) Geometric mean Range	9425.41 6230.64 – 13717.76	9248.57 6859.31 – 12387.35
$AUC_{0\text{-}\infty}$ (ng x h/mL) Geometric mean Range	9810.29 6568.96 – 13887.61	9664.95 7114.34 – 12623.70
C_{max} (ng/mL) Geometric mean Range	1251.27 884.95 – 1623.95	1181.23 702.42 – 1448.87
T_{max} (h) mean ± SD	3.58 0.36	3.96 1.12
$t_{1/2}$ (h) Geometric mean Range	7.67 3.86 – 11.47	7.96 5.40 – 19.97

Parameter	$AUC_{0\text{-}30\,h}$	$AUC_{0\text{-}\infty}$	C_{max}
T/R point estimate 90% CI	101.88	101.50	105.93
Lower Limit	94.78	93.77	97.00
Upper Limit	109.54	109.87	115.98

Table 2: Statistical evaluation of comparison of 12 subjects $AUC_{0\text{-}30\,h}$, $AUC_{0\text{-}\infty}$, and C_{max} of two formulations.

Journal of Bioequivalence and Bioavailability, 2011, issue 3, volume 1, 016-019

Statistical analysis (Exclusion of PK data)

*CPMP/EWP/QWP/1401/98 Rev. 1/Corr **-Guideline on the investigation of bioequivalence*

Reason for exclusion of PK data must be pre-specified in the study protocol.

- Only accepted for clinical reasons, not statistical analysis reason, unless:
  - Baseline concentration >5% of C_{max} (carry-over effect)
  - Subject AUC for reference product is <5% of geometric mean AUC of reference product (possible subject non-compliance).
- PK data from subjects with AUC_{0-t} <80% of AUC_{0-inf} → included in statistical analysis
- PK data from drop-out subjects→ not included in statistical analysis

Statistical Analysis (Outliers consideration)

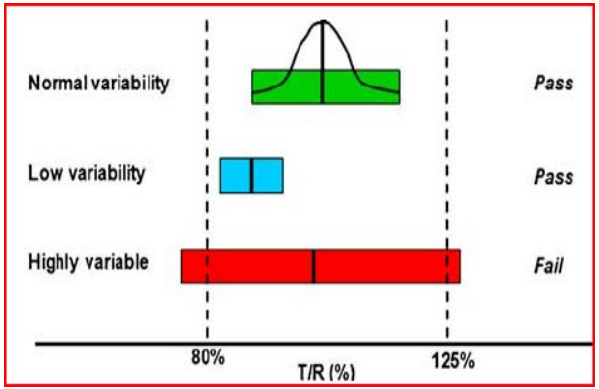
[Guidance 15 Biopharmaceutics , Section 15.7 {FDA guidance for Industry: statistical approaches to establishing bioequivalence}]

Outliers: *Subject data for one or more BA measures that are discordant with corresponding data for that subject and/or for the rest of the subjects in a study*

- Deletion of these outliers (if detected) is not encouraged
  - Assuming there is no protocol violation, the “within-subject” outlier with respect to Test vs Reference could be of concern
    - E.g. Cmax of test product in period 2 is 10 times lower than Cmax of reference in period 1 in the same subject.
- Two sets of calculations for mean PK parameters and 90% CI results, with and without outliers results, should be provided for evaluation

Conclusion of bioequivalence studies

- Study design appropriate and study conduct satisfactory
- No critical deficiencies or abnormalities (methods or statistical analysis)
- Bioequivalence established?
  - 90% CI of mean T/R: **80.00-125.00%** [C_{max}, AUC_{0-t} and AUC_{0-inf}]
- *Narrow therapeutic index drug:*
  - 90% CI of mean T/R: **90.00% -111.11%** for AUC, and C_{max} (if clinically important)
- *Highly variable drug:*
  - C_{max} (but not AUC) can be **widened** as per ICH guideline.



Example 1 (Analytical Issue)

- **Retention time drift in subject chromatograms**
  - Run time extended in subsequent runs, and retention time of analyte doubled
  - Not discussed in the protocol

- **Significant peak interference with analyte peak in subject samples**
  - Unexplained
  - Samples should have been reanalysed, but were not

Outcome: Serious concerns about proper conduct of the study
The bioequivalence study was not accepted to support this application

Example 2 (Clinical and Statistical Issues)

Test Product A: Enteric Coated Tablet (food effect study)

- Individual subject plasma concentration graphs varied significantly
  - Several subjects have zero results, or plasma levels appear at a late time point
  - Test Product is significantly larger than Reference Product

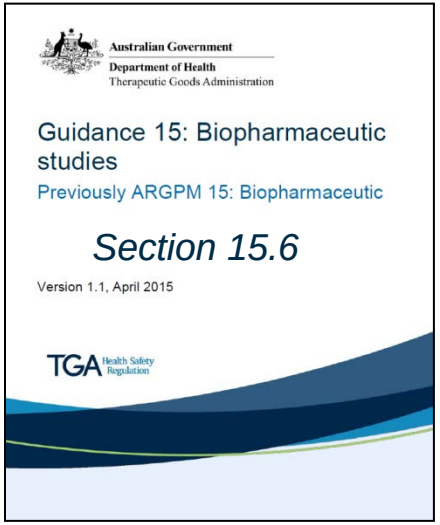
- Expired reference product (by 1 year) was administered to subjects
  - No CoA was provided to confirm that the out-of-date reference product was still within the specification limits

Outcome: A combination of concerns resulting in this submission being withdrawn

Example 3 (Overseas Reference Product)

The reference product must be:

- A conventional, immediate-release oral dosage form or an enteric-coated tablet or capsule.
- Registered in, and obtained from, a country with a regulatory system comparable to Australia.
- Marketed in the country of origin by the same innovator company (or through licensing arrangement) as the product in Australia.



Evidence demonstrating the overseas and Australian reference products are identical

Note: Sustained release tablets and capsules may be considered on a case-by-case basis.

Example 3 (Overseas Reference Product)

Product B: Extended Release Tablet

- UK Reference Product and AUS Reference product contain different marking
- UK and AUS Reference Product are manufactured at different countries →higher possibility of different manufacturing process
- One excipient result is different (~10%) between UK and AUS Reference Product. The results for AUS reference product is also different to the registered value

Outcome: UK Reference Product was **not identical** to AUS Reference Product. Bioequivalence study using the UK reference product was not accepted.

Example 4 (Biowaver of additional strength)

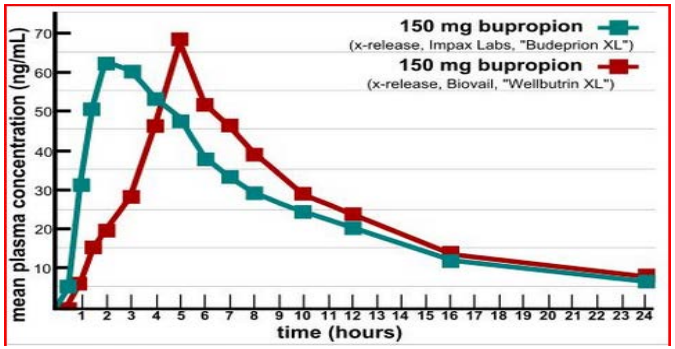
{See Appendix 15 ARGMP and relevant EMA guidelines for the criteria}

"Wellburin XL" bupropion extended release tablet 150 mg and 300 mg (GSK) (FDA approved)

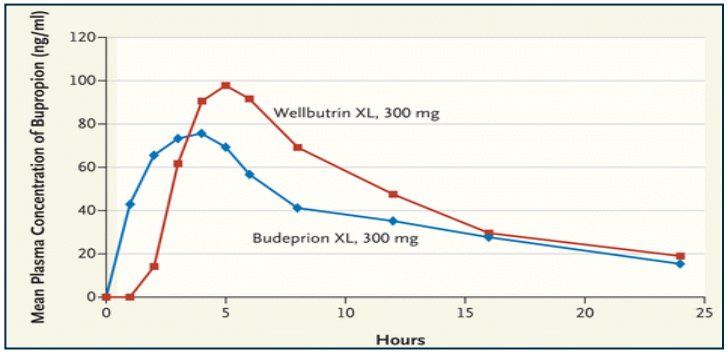
- Antidepressant. Has a narrow therapeutic index
- Maintenance dose: 300 mg once daily. Maximum daily dose: 400 mg/day
- Increase risk of seizure at dose > 450 mg
- XL formulation is designed to reduce this risk (observed with IR tablet)
- No food effect
- Has a complicated pharmacokinetic profile

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021515

Bupropion XL tablet 150 mg and 300 mg (Generic vs GSK)



https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm153270.htm



https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm153270.htm

150 mg: bioequivalent (registration granted in 2006)

- Cmax fasted: 89% (**90% CI: 80.3 - 98.2%);** AUC fasted: 98% (**90% CI: 91.9-104.4%)**

300 mg: Registered in 2006 with a biowaiver (due to potential risk of seizure)

- Bioequivalence study conducted in 2012 by FDA due to complaints
- Cmax fasted: 75% (**90% CI: 65-87%**); AUC fasted: 86% (**90% CI: 77-96%)**

  → **Not bioequivalent → withdrawn from market**

Bupropion XL tablet 150 mg and 300 mg (Generic vs GSK)

How would the TGA approach this?

Our Initial Position (in accordance with EMA guideline for modified release product {CPMP/EWP/280/96}):

- For an extended release dosage form, with no food effect identified in the innovator product:
  - Single dose bioequivalence studies (fasted) is required for each strength
  - Food Effect Study and Steady State Study are required on higher strength (300 mg), possible biowaiver of lower strength (150 mg)

Bupropion XL tablet 150 mg and 300 mg (Generic vs GSK)

- **Is the clinical justification <u>"risk of seizure at 300 mg"</u> sufficient to consider the reverse approach?**
  - Could be accepted for evaluation
  - But will consider other aspects:
    - How many AEs were observed due to the generic 150 mg tablet?
    - It has narrow therapeutic index and complex pharmacokinetic
    - C_{max} of 150 mg is on the borderline of acceptance limit (90%CI: **80.3%- 98.2%**)

- **Steady state bioequivalence study on higher strength (300 mg) in patients more appropriate?**

Conclusion

- Critical deficiencies in any of clinical, analytical or statistical aspects → will result in bioequivalence study NOT being accepted, even if 90% CI for C_{max} and AUC are within the criteria
- We actively identify clinical sites of concern and take this into consideration during the evaluation process
- We encourage the use of the Australian reference product whenever possible
- Justification of biowaiver for an additional strength (see EMA guideline and ARGPM)
  - if it is against the normal approach, a pre-submission meeting with the TGA is recommended to discuss any alternatives

Thank you

Questions?

Australian Government

Department of Health

Therapeutic Goods Administration