Bioequivalence – Clinical Endpoint Studies

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BE and Clinical Endpoint Studies

Plan

- Clinical Pharmacology background
- Pharmacokinetic (PK) vs. Therapeutic Equivalence (TE) studies
- Dose scale approach for TE studies
- Simulation studies to show utility (or not) of Dose Scale approach
- Examples of different locally acting products
- Inhaler products
- Conclusion
**BE and Clinical Endpoint Studies**

Clinical Pharmacology background

- Definition of Pharmacokinetics (PK)
  - “What a body does to a drug…”

- Definition of Pharmacodynamics (PD)
  - “What a drug does to a body…”
Active moiety that appears systemically before or at the same time as it reaches the different sites of activity.

No need for an efficacy/safety study to prove BE in addition to the regular PK one.
**Locally acting compounds**

“GI Tract” \[\rightarrow\] DOSE \[\rightarrow\] “Local concentrations”

\[\downarrow\] Ka

PK \[\leftrightarrow\] PD

PK AND Therapeutic Equivalence (TE) studies Needed

Conc. \[\uparrow\] Effect

Time (h) \[\uparrow\] Conc. (biophase)
**BE and Clinical Endpoint Studies**

**PK and TE Studies**

- **PK Study**
  - *Demonstrates that a Test formulation has equivalent systemic exposure to a reference one.*
  - *Need to pass on PK metrics, most often Cmax and AUC0-t.*

- **TE study**
  - Demonstrates that a test formulation has equivalent efficacy to a reference one.
  - Need to pass on PD (Biomarker reflecting efficacy) or Clinical Endpoint (what is ultimately seen in terms of efficacy).
BE and Clinical Endpoint Studies
PK and TE Studies

• PK Study
  – Exposure increases proportionally with dose (most often).
  – Exposure is nil for a placebo (for endogenous products, exposure can be baseline adjusted).
  – 90% CIs around Exposure Ratios can be used for equivalence.

• TE study
  – Effect does not increase proportionally with dose.
  – Placebo effect can be very large.
  – 90% CIs around Response ratios should not be used for equivalence.
• **TE study**
  - Effect does not increase proportionally with dose.
  - Placebo effect can be very large.
  - 90% CIs around Response ratios should not be used for equivalence.

**Legend:**
- **Reference product**
- **Test product**

Fitted curves for the Test or Reference products using an Emax model.
DOSE SCALE APPROACH
(when there are multiple Commercialized doses)

The “Dose-Scale” approach allows the creation of a T/R ratio on the Dose Scale based on the Emax curve that is derived for the reference product.

But,
• Necessitates a robust Emax curve for the ref product.
• T/R ratio needs to be assessed at a lower dose in the “steep” part of the curve, meaning a dose-response must be observed.
• The lower dose needs to be associated with efficacy vs. placebo.
DOSE SCALE APPROACH (when there are multiple Commercialized doses)

Is it a Good Methodology?

1000 5-way (Placebo, Low Test, Low Ref, High Test, high Ref) crossover studies including 100 patients each were simulated for each of the following scenarios:
1) No dose response present with EC50< lowest marketed dose
2) Dose response present with EC50~ lowest marketed dose
3) Dose response present with EC50~ Intermediate marketed dose
DOSE SCALE APPROACH (when there are multiple Commercialized doses)

Simulations methodology:

- 1000 5-way (Placebo, Low Test, Low Ref, High Test, high Ref) crossover studies including 100 patients each were simulated for each scenarios.
- NONMEM® and Wings for NONMEM® were used to simulate and analyze all the different studies.
- A priori analysis suggested that 100 per group would be adequate for 80% power
- The intra-individual variability (e.g., residual variability) of the PD marker was set at 34%.
- The ED50 was set at values 100x lower than the lowest marketed dose (no dose response), at the lowest marketed dose (dose response), and at the intermediate marketed dose (twice the lowest marketed dose).
**BE and Clinical Endpoint Studies**  
**PK and TE Studies**

DOSE SCALE APPROACH  
(when there are multiple Commercialized doses)

Is it a Good Methodology?

<table>
<thead>
<tr>
<th></th>
<th>True Ratio T/R</th>
<th>% studies passing</th>
<th>% failing</th>
<th>Power %</th>
<th>Alpha error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent</td>
<td>95%</td>
<td>14%</td>
<td>86%</td>
<td>&lt;20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>13%</td>
<td>87%</td>
<td>&lt;20%</td>
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<tr>
<td>Non-equivalent</td>
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<td>87%</td>
<td></td>
<td>&gt;5%</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>14%</td>
<td>86%</td>
<td></td>
<td>&gt;5%</td>
</tr>
</tbody>
</table>

**No Dose Response, EC50 << lowest dose**
DOSE SCALE APPROACH
(when there are multiple commercialized doses)

**BE and Clinical Endpoint Studies**
PK and TE Studies

**Is it a Good Methodology?**

### Dose Response, EC50 ~ lowest dose

<table>
<thead>
<tr>
<th></th>
<th>True Ratio T/R</th>
<th>% studies passing</th>
<th>% failing</th>
<th>Power %</th>
<th>Alpha error %</th>
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</thead>
<tbody>
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<td>Equivalent</td>
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</tr>
<tr>
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<td>75%</td>
<td>25%</td>
<td>75%</td>
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<tr>
<td>Non-equivalent</td>
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<td>18%</td>
<td>82%</td>
<td></td>
<td>18%!!</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>3%</td>
<td>97%</td>
<td></td>
<td>&lt;5%</td>
</tr>
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</table>
DOSE SCALE APPROACH (when there are multiple Commercialized doses)

**BE and Clinical Endpoint Studies**

**PK and TE Studies**

**Is it a Good Methodology?**

### Dose Response, EC50 ~ Intermediate dose

<table>
<thead>
<tr>
<th></th>
<th>True Ratio T/R</th>
<th>% studies passing</th>
<th>% failing</th>
<th>Power %</th>
<th>Alpha error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent</td>
<td>95%</td>
<td>90%</td>
<td>10%</td>
<td>&gt;80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>80%</td>
<td>20%</td>
<td>&gt;80%</td>
<td></td>
</tr>
<tr>
<td>Non-equivalent</td>
<td>70%</td>
<td>13.5%</td>
<td>86.5%</td>
<td>&gt;5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>1%</td>
<td>99%</td>
<td></td>
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</table>
DOSE SCALE APPROACH
(when there are multiple Commercialized doses)

Simulations show:

• TE studies have >80% power to prove equivalence when there is a dose response and the EC$_{50}$ is AT LEAST equal to the lowest dose. The higher the EC50, the better the power becomes.

• TE studies have no power at all when there is no dose response. The study becomes useless to conduct as it never passes equivalence criteria.

• TE studies will have an alpha error much higher than 5% when there is a dose response. The alpha error was seen to be as large as 50% when the true T/R ratio approximated 80%.

Is it a Good Methodology?
**What to do when only one dose is commercialized and/or there is NO dose-response?**

- **TE study**
  - Treatments have to be superior to Placebo.
  - T has to show equivalence to R.

Without Dose-response and dose-scale analysis, two products can have equivalent efficacy while having a large difference in terms of their relative bioavailability at the site of activity.
Exemples of Locally acting products

- **Nasal corticosteroids** for Allergic Rhinitis, ex. Flonase®
- **Opthalmic products** for Glaucoma, ex. Azopt®, for infection, ex. Tobradex®, for dry Eye, ex. Restasis®
- **Corticosteroids** for dermatitis, eczema, psoriasis, ex. Diprolene®, Halog®
- **Intestinally active drugs**, such as Asacol HD® for UC
- **Inhalers for Asthma and/or COPD**, ex.: Advair®

Exemples of non-locally acting products

- Insulin given via inhalation (not commercialized)
- Nasal Desmopressin, ex. DDAVP® for diabetes insipidous
- Transdermal patches for systemic action, ex. Fentanyl Duragesic®
BE and Clinical Endpoint Studies
”Locally” acting Corticosteroids

FDA / OGD Guidance published since 1995

- Corticosteroids produce vasoconstriction microvasculature of skin ("Blanching effect")
- Vasoconstriction relates to amount in the skin of the active moiety
  - Using the Vasoconstrictor assay, the PD here replaces the PK (similarly to the Albuterol previous example)
  - Observations: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4 and 6 hours (dose durations)
  - ED50 identified in pilot study with reference only
  - Data fitted: \( E = E_0 + \frac{E_{\text{max}} \times D}{ED50 + D} \)
  - 90% CI for ratio of AUEC\(_{\text{test}}\) / AUEC\(_{\text{ref}}\)

BE and Clinical Endpoint Studies
Inhaler products for asthma and/or COPD

BE program composed of 4 components

- Device
- In Vitro Performance
- Therapeutic Equivalence
- Systemic Equivalence
- Local Equivalence

```
"GI Tract"  →  DOSE  →  "Local concentrations"
  ↓    ↓
   PK    PD
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• **Pharmacodynamic (PD) or endpoint measure**
  – Has to be relevant to the disease and the mechanism of action of the drug
  – Ideally it is the marker directly used in the clinic to assess efficacy
  – Has to be affected quickly by the drug & show reversibility
## BE and Clinical Endpoint Studies

Inhaler products for asthma and/or COPD

<table>
<thead>
<tr>
<th>Examples of drug products</th>
<th>PD</th>
<th>Dx and MOA relevance</th>
<th>Used in the clinic</th>
<th>Affected quickly</th>
<th>Reversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled B-agonists</td>
<td>FEV1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>FEV1</td>
<td></td>
<td></td>
<td>~</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>ENO</td>
<td>~</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Sputum eosinophils</td>
<td>~</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
**Design of the trial**

- Need for Baseline assessment?
- Need for placebo?
- Need for dose response for Reference?
- Need for dose response for test?
- How do we determine that the pivotal dose is in the right portion of the Emax curve?

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**BE and Clinical Endpoint Studies**

*Inhaler products for asthma and/or COPD*

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**Legend:**
- Reference product
- Test product

Fitted curves for the Test or Reference products using an Emax model
How to analyze the data?

- If the effect and dose relationship is characterized by an Emax curve then the data is fitted to the following Emax equation:

  \[ \text{Effect} = E_0 + \frac{\text{Emax} \times (\text{Dose} \times \text{Frel})}{(\text{Dose}_{50} + \text{Dose} \times \text{Frel})} \]

  - Where \( E_0 \) is either the baseline effect or the effect of the placebo + baseline
  - \( \text{Emax} \) is the maximum theoretical effect of the drug
  - \( \text{Frel} \) is the relative bioavailability of the Test to the reference product
  - \( \text{Dose}_{50} \) is the dose associated with 50% of the \( \text{Emax} \)

- \( \text{Emax} \), \( \text{Dose}_{50} \) and \( \text{Frel} \) are to be fitted with the above equation, which mean that a minimum of 3 doses are necessary (e.g., Test low, Ref low, Ref high).

  - If more than 2 doses are fitted, then the curvature of the Emax curve may also be fitted if necessary (e.g., “Hill” coefficient)
How to analyze the data?

- Effect = $E_0 + \frac{E_{\text{max}} \times (Dose \times Frel)}{Dose_{50} + Dose \times Frel}$

Parameters can be obtained from an individual basis or using the naïve pooled data approach

- **Individual approach**
  - Preferred if crossover design (Consistent with BE approaches)
  - $E_{\text{max}}$ model fitted on individual data

- **Pooled or mean approach**
  - Historically method of choice when computers were slow and individual approach was too time-intensive
  - Can lead to biased estimates of the mean (Sheiner LB 1984)
    - Assumes wrongly that a crossover design is parallel in nature or that every subject is the same and that all periods are balanced

Confidence intervals are obtained using the Bootstrap approach

- Typically a minimum of 1000 bootstrap is needed
FEV1 and/or FeNO:

Not great for ICS because of their inability at discriminating between doses (no dose response)
In the 1990’s, some products were approved with larger CIs (67-150) and with equivalence of a biomarker effect (e.g., FEV1) without the need for a dose response.

By the late 90’s, requirements were to use the dose scale approach (dose-response) and 80-125 CIs.

2003, drop of the requirement for Dose-Response for nasal corticosteroid products:

“Clinical studies are at times incapable of showing a dose-response relationship and may not be consistently reproducible. However, a showing of dose-response is not necessary for BE studies with a clinical endpoint, as these studies are intended only to confirm the lack of important clinical differences between T and R suspension formulation nasal aerosol and nasal spray products”.

Ref.: Li B, Lee, SL, Chowdhury B, Caramenico HT, Conner DP. AAPS J 2013

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Recently, drop of the requirement for TE studies for some locally acting products (e.g., mesalamine) with addition of further PK metrics in the PK study.

2013, Individual BE guidance specifies dose scale analysis for Albuterol inhalers.

2013, drop of the requirement for dose response for generic formulation of Advair® and recommendation for use of FEV1 data only.
But:

*The Lung is one of the most perfused organ because of the $O_2 / CO_2$ exchanges*

One can argue that as soon as the active ingredient, in solution, reaches the "lung/site of activity" it reaches the systemic circulation.
Two different approaches should be scientifically sound from a clinical pharmacology perspective, in order to bring a Subsequent Entry ICS product on the market:

**Conventional / Phase III**

**Phase I**
- PK
  - Proves Systemic safety and efficacy is equivalent

**Phase III**
- Pivotal comparability efficacy trial(s)
  - Proves Therapeutic Equivalence

**PK-PD / Phase I**
- PK
  - Proves Therapeutic Equivalence
- PK with/without charcoal
  - Similar to EU guideline
BE and Clinical Endpoint Studies

Conclusion

• Pharmacokinetic (PK) vs. Therapeutic Equivalence (TE) studies.
• Utility or lack of Utility of the Dose Scale approach.
• Recommendations in this field evolve all the time.