CLINICAL ENDPOINT STUDIES IN GENERIC DRUG DEVELOPMENT

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DRUG DEVELOPMENT PATHWAY

• Pharmaceutical Research
  – Pre-Formulation, Process & Medicinal Chemistry, Drug Delivery, Analytical R&D, Clinical Pharmacology
    • Design Engineering, Experimental Testing/Analysis/Evaluation, Target/Lead Optimization, Druggability

• Intellectual Property/ Patents
• Manufacturing Plant
• Stability analysis
• Pre-Clinical Research/ Animal Toxicology
• Clinical Research
PK vs. PD / Clinical Endpoints - What’s the difference?

Evaluation of the *in vivo* performance

Formulation → Solution → Intestinal wall → Blood → Site of action → Effect

PK parameters

Clinical endpoints

- Dose
- Ln Dose
Clinical research is about 33-50% of R&D at a major Pharma company.
Rise of pharmaceutical generics.....and bioequivalence studies!!

“the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”

• Medication cost is a heavy burden for the patient.
• This act provided for three essential elements to the current generic drug approval process.
  – Generic drug approvals - scientific considerations and minimize duplicative testing.
  – Quality criteria for manufacturing.
  – Statistical Calculations
  – therapeutically equivalent drugs.
Therapeutic equivalence: Definition?

Therapeutically equivalent drugs meet the following general criteria:

- They are approved as safe and effective.
- They are pharmaceutical equivalents.
- They are bioequivalent.
- They are adequately labeled with the same conditions of use.
- They are manufactured in compliance with cGMP regulations.

- Pharmaceutical equivalent does not necessarily imply therapeutic equivalence!!

- Differences affecting the bioequivalence:
  - Raw materials
  - Drug (e.g. particle size, polymorphism, etc.)
  - Excipients (e.g. grade)
  - Formulation / composition
  - Q1 and Q2 (effect on in vivo dissolution and absorption)
  - Manufacturing process (e.g. dry vs. wet granulation)
  - Equipment
    - Site of Manufacturing
    - Batch size
But bioequivalence cannot be assumed….

- Clinical studies have to be performed with the Generic Product to support its Efficacy and Safety, thus proving its therapeutic equivalence.
- With data to support similar \textit{in vivo} performance (= Bioequivalence), Efficacy and Safety data can be extrapolated from the Innovator Product to the Generic Product.

### Sensitivity to detect differences

- Pharmacokinetic endpoint
- Pharmacodynamic endpoint
- Clinical endpoint
- In vitro endpoint
Therapeutic equivalence with Clinical or PD endpoints – When are they applicable?

- Systemic action, but no measurable concentrations
- Products for local action
  - Except solutions with the same composition (Q1+Q2)
  - PD design for cutaneous corticosteroids (skin blanching assay)
  - PD design for bronchodilators
    - Bronchoconstriction or Bronchodilation
    - *In vitro* acceptable in very few cases (e.g. BCS Biowaiver, IVIVC, binding studies for cholestyramine, Lanthanum etc)
- Clinical end point studies
- A bioequivalence study with clinical endpoints will use clinical variables from a product-specific clinical indication as per label
Clinical endpoint studies – Challenges

- 21 CFR 320.24 indicates “this approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence.”
- Must meet the established BE limits
- May present more safety concerns
- Long duration
- Very large sample size
- Very expensive
- GCP compliance
- Data management
Clinical endpoint studies – Challenges?

• Unknown inter-subject variability within reference population

• Difficulty in achieving consistency between studies
  – study design
  – study population
  – bioequivalence endpoints

• Some products may require multiple studies

• And further, most of the clinical endpoints may be insensitive to formulation differences.

• All these suggests that Clinical Endpoint studies are at a high risk of failure to demonstrate bioequivalence!!
LANDMARK YEAR: 2005

- Amended Schedule Y
- Clinical Trial Registry launched
- Phase I clinical trial NCE from abroad in Pipeline
- Phase I trial for NCE developed in India: Yes
- Pharmacovigilance launch
- ICH-GCP
- ICMR/Bioethics
- Product patent regime
Data management, Biostatistics, report writing
Central Laboratory Facilities
Multi-centric Clinical Trials
Clinical trial management
Clinical operations management
Clinical trial site management
PK–PD / Bioavailability, Bioequivalence studies

High Volumes  Low value

Value Additions  High Profit
Clinical operations management involves coordinating:

- Feasibility check
- Selection of investigators, patient population
- Timelines, site selection, monitoring
- Managing recruitment goals
- Site instruction
- Monitoring & logistics
- Clinical data review
- Local quality audits

Clinical trial management / Multi-centric clinical trials involve:

- Feasibility check
- Regulatory approvals for the study
- Protocol development
- Selection of investigators & patient population
- Site selection
- Clinical monitoring
- Data management
- Biostatistics
- Medical writing
- Report writing
- Clinical data review
- Managing recruitment goals
- Quality audits (incl. GCP)
- GCP Training
In fact there is no way out, because...

- Therapeutic equivalence stud approach has become the fall-back method for various products (Derma, Ophthalmic, Pulmonary, oncology etc)

Few approaches to ensure appropriate results in clinical end point studies are

- **Right CT design**
- **Right indication** that is **most sensitive**
- **Placebo arm**, wherever possible.
  (The placebo arm ensures that the study and its conduct are sufficiently sensitive to differences between treatments)
- Scientific & statistical understanding (**exposure–response relationship**)
- Keep the **data close & the statistician closer** !! 😊
Therapeutic equivalence with Clinical endpoints – How important is a Statistician?

By Signe Wilkinson, Philadelphia Daily News, Cartoonists & Writers Syndicate
Also always brainstorm before the big decision....

- It's very important that all the data, statistical info & proposed study design should be discussed openly with FDA. Else.......
• The mantra should be:
  – *Begin with the end in mind* .... *(Stephen R. Covey, The Seven Habits of Highly Effectively People)*

• What would you like to be able to say about your drug:
  – How is it effective? What does it alleviate? How soon can you expect results?
  – How is it safe? Is it safer than other drugs that do similar things? Can you place an upper bound on the rate of side effects, or serious side effects?
Therapeutic equivalence with Clinical endpoints – How to decide the right CT design?

• Immediately, for purposes of drawing conclusions from collected data, we run into the need for statistical reasoning!!

• Thus, rightly the definition of statistics is: *a summary measure calculated from data.*
The importance of coming up with the right CT design is to avoid the......
Dichotomous endpoint; the treatment either succeeds or fails.

Test product is declared bioequivalent to the RLD, if the success proportion for each treatment being calculated, and found the 90% confidence interval for the difference in success is within ±20%.

The two treatments could be called equivalent if the observed difference and its 95% CI are completely inside the interval of clinical equivalence.
Superiority: Does the 95% CI contain zero?

-1%  0%  +1%

Equivalence: Does the 95% CI lie between -1% and +1%?

-1%  0%  +1%

To left of -1% is clinically meaningful

Between -1% and +1% is not clinically meaningful

To right of -1% is clinically meaningful
Non-Inferiority Trial Example

Window of Non-Inferiority Margin

Superior

5.1 5.5 6.0 6.5 6.9

Inferior

Hypothetical Control Treatment Event Rate

• If the experimental treatment event rate is $< 5.1$, then the experimental treatment would be *superior* to the active control.

• If the experimental treatment event rate falls between the 5.1 and 6.9 range, then the experimental treatment is *non-inferior* to the active control.

• If the experimental treatment event rate is $> 6.9$, then the experimental treatment is *inferior* to the active control.
In an equivalence trial, if the experimental treatment event rate falls between 5.1 and 6.9, the study would establish equivalence between the experimental therapy and the active control.

If the experimental treatment event rate falls outside the 5.1 to 6.9 range, the study would fail to establish equivalence between the experimental treatment and the active control.
Equivalence Trials

• The aim is to show that both generic (treatment T) and RLD (treatment R) have equal efficacy. But this is impossible to show with statistical tests.*

• Hence, we have to resort to a practical definition of “equally good”, which may be -
  
  – Based on the data available, a value $\Delta E^+$ has to be agreed upon such that the two treatments can be considered not to differ (too much) when their true $\Delta$ lies in an interval of clinical equivalence $[-\Delta E, \Delta E]$
  
  – And then the two treatments could be called equivalent if the observed difference and its 95% CI are completely inside the interval of clinical equivalence


$\Delta E = $ defined as the value for which “the patient will not detect any change in effect when replacing one drug by the other.”
In terms of null and alternative hypotheses, proving equivalence boils down to rejecting the \( H_0: \Delta > \Delta E \) or \( \Delta < -\Delta E \) in favor of the alternative hypothesis, \( HA: -\Delta E \leq \Delta \leq \Delta E \), with an appropriate statistical test.

For an equivalence trial, a significant result \( (p < 0.05) \) means that the two treatments are equivalent, according the definition of equivalence as defined clinically.

In case \( p \geq 0.05 \), corresponding to a 95% CI that crosses one or both boundary values of the interval of clinical equivalence, the two treatments cannot be called equivalent.
Non-inferiority Trials

• Non-inferiority trials are sometimes (wrongly) referred to as equivalence trials.

• Unlike an equivalence trial, a standard **non-inferiority test** is performed nowadays at **p< 0.025 level (one-sided)**

• Further, for the reporting of the results, in non-inferiority trials, it is customary to **use the (two-sided) 95% CI** rather than **p-values**.

• The aim of non-inferiority trial is to prove that the experimental treatment is not (much) worse, i.e., non-inferior, to the control treatment, whereby the conclusion “non-inferior” depends on the chosen value for **ΔNI#**.

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# Non-inferiority margin= chosen by combining the clinical and statistical reasoning, resulting in a ΔNI that is clinically acceptable and ensures the superiority of T over placebo
Non-inferiority Trials

- Demonstrating non-inferiority necessitates rejecting the null hypothesis (H0: Δ > ΔNI) in favor of the alternative hypothesis (HA: Δ < ΔNI) with an adapted classical statistical test (as for an equivalence test).
- In a non-inferiority trial, only an upper bound ΔNI is defined, and when the 95% CI for Δ lies left to ΔNI, treatment T will be called non-inferior to treatment R.
- The interval of non-inferiority is unbounded on the left side and is, therefore, also referred to as the region of non-inferiority.
- In case p ≥ 0.025, i.e., when the right boundary of the one-sided 97.5% CI (two-sided 95% CI) exceeds ΔNI, we have failed to show that the experimental treatment is non-inferior.
- If placebo arm is suggested, then both treatment T and treatment R must be statistically superior to placebo (p<0.05) in order to assure that the study is sensitive enough to show a difference between products.
Prior to undertaking the trial, the degree of inferiority (or difference) that is clinically relevant must first be established.

A trial is then designed and to reject the hypothesis that a difference of that size or larger exists\(^1\).

Establishing a margin - the smallest unacceptable degree of clinical inferiority (and of superiority in an equivalence trial) of the new treatment must be prospectively defined.

An estimate of the efficacy of the active control group is then made based upon event rates prior trials.

Based upon the projected efficacy of the active control, the trial is then appropriately powered to determine if the two drugs lie within this margin.

Patient population, concomitant therapies and endpoints are important both for estimating active-control effect size and for ensuring a fair comparison between study drug and active control.

1. Jay P. Siegel, American Heart Journal April 2000:S166-S170
High Quality Randomized Trials

• Tamper-proof randomization
• Blinding of participants, study staff, lab staff, outcome ascertainment and adjudication
• Adherence to study intervention
• Complete follow-up
• Adequate power
Blinding

• Maintains balanced groups during follow-up
• Eliminates
  -- co-intervention
  -- biased outcome ascertainment
  -- biased measurement of outcome
• Difficult even for drugs
  – identical placebo difficult to prepare
  – drug may smell, taste, feel different
  – drug may cause side effects
  – test results may unblind
  – participants may test drug
• Be courageous, if you can’t blind
• Do the best you can
  - minimize differential cointervention
  - blind those measuring outcome
  - use “hard” outcomes
• Measure degree of unblinding
• Assess impact in discussion of dossier
Outcomes in Clinical Trials

- Efficacy Outcomes
  - Primary
  - Secondary
  - Surrogate
  - Composite
- Adverse Effects
  - rare
  - common
- Measure all outcomes
- Pick one primary outcome
  - estimate sample size
  - FDA requirement
- Make all the rest secondary
The biggest dilemma for any clinical researcher is to decide whether.....
Issues with equivalence, or non-inferiority trials

• People may be carrying out equivalence trials without realising it.

• Analysis with respect to a pre-stated margin of non-inferiority (smallest clinically interesting difference)

• ITT analysis may increase risk of type 1 error

• Choice of outcomes important

Piaggio et al., 2006, JAMA,295,1152-1160
Reporting equivalence trials

• Need to reference established efficacy of “standard” treatment
• Hypotheses should be framed in terms of non-inferiority
• “Margins of equivalence” should be reported
Implications for ANDA Sponsors

• Long Approval Times
  – Internal discussion and meetings
  – Challenges by RLD sponsors
    • Correspondence
    • Citizen Petitions
  – Ask ANDA sponsors for more information to resolve issues (multiple review cycles)

• More Product Development information in ANDA may help OGD be more efficient
"Over the last fifty years, How to Lie with Statistics has sold more copies than any other statistical text" - J. M. Steele
Books any successful statistician would love to write are.....

How to LIE

How to LIE with Statistics

How to LIE without Statistics
Local Clinical Research – Global Regulatory Reach
THANK YOU

Our inspiration:

The Lupin flower nourishes the soil in which it grows, benefiting the environment in the process.