Confirm & Learn?

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University of Maryland
Recent
Early Signs of Focus on Key Questions

Past
Focus on Methodology

Future
Need to choose between Methodology vs. Key Questions

Evolution of Evidence of Effectiveness
Evolution of Evidence of Effectiveness

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Efficacy Requirement

Kefauver-Harris Drug Amendments (1962) passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them.
Motivation to Focus on Methodology

• “In the Soule, Wasserman, and Burstein study of the effect of the OPE Chymoral (marketed by Armour) on symptoms associated with episiotomy, the investigators made 240 comparisons between the study and control group on factors such as edema (swelling), erythema (skin redness), bruising, and the subject's pain while resting, sitting, and walking. These were studied at different time periods after delivery. Of the 240 tests, statistically significant results were reached showing effectiveness of Chymoral for reduction of pain "on sitting on day four in subjects with labors over eight hours"; for reduction of pain "on sitting, on post-partum days two and three, in the 20 subjects less than 21 years old"

2 AWC Trials (Substantial Evidence)

• With regard to quantity, it has been FDA's position that Congress generally intended to require at least **two adequate and well-controlled studies**, each convincing on its own, to establish effectiveness.

• *Warner-Lambert Co. V. Heckler, 787 F. 2d 147 (3d Cir. 1986)*). FDA’s position is based on the language in the statute and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence.
Replication of Evidence

• The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results.

• The inherent variability in biological systems may produce a positive trial result by chance alone.

• Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet).
Replication of Evidence

• The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.
Totality of Evidence

• Evidence of effectiveness ought to be sought by establishing a body of evidence via multiple sources. A positive p-value by itself does not establish effectiveness.

• Internal consistency to demonstrate that the primary finding is consistent across different trials, sub-groups, endpoints is typically what drives approval. This is critical for generalizability of findings.
Once randomized, always analyzed!
Almighty P
Primary Goals of Registration Trials

- Establish substantial evidence of efficacy
- Support safety
- Derive rational dosing based on benefit/risk
- Marketing claims
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## Carvedilol

<table>
<thead>
<tr>
<th>Study</th>
<th>Selected Patient Eligibility Criteria</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>220</td>
<td>LVEF ≤ 0.35 NYHA class II–IV</td>
<td>Change in exercise distance from baseline. Both 6-min corridor walk distance 150–450 m and 9-min treadmill test.</td>
</tr>
<tr>
<td></td>
<td>CHF 6-min corridor walk distance 150–450 m</td>
<td></td>
</tr>
<tr>
<td>221</td>
<td>LVEF ≤ 0.35 NYHA class II–IV</td>
<td>Change in exercise distance from baseline. Both 6-min corridor walk distance 150–450 m and 9-min treadmill test.</td>
</tr>
<tr>
<td></td>
<td>CHF 6-min corridor walk distance 150–450 m</td>
<td></td>
</tr>
<tr>
<td>239</td>
<td>LVEF ≤ 0.35 NYHA class II–IV</td>
<td>Change in exercise distance from baseline and Minnesota quality of life score.</td>
</tr>
<tr>
<td></td>
<td>CHF 6-min corridor walk distance &lt; 150 m</td>
<td></td>
</tr>
<tr>
<td>240</td>
<td>LVEF ≤ 0.35 NYHA class II–IV</td>
<td>Clinical progression of heart failure, defined as death due to CHF, or hospitalization for CHF, or worsening CHF requiring increasing background medications by 50% for at least 30 days.</td>
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<tr>
<td></td>
<td>CHF 6-min corridor walk distance &gt; 450–550 m</td>
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<tr>
<td>Australia New</td>
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<td>Zealand Study</td>
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<tr>
<td>223</td>
<td>Early phase History of dyspnea at rest or fatigue at rest with EF &lt; 0.45 NYHA class IV was excluded</td>
<td>Maximal exercise tolerance on treadmill plus two hemodynamic measurements (LVEF and the LV internal dimensions).</td>
</tr>
<tr>
<td></td>
<td>Later phase Same as above.</td>
<td>All cause death and all cause hospitalization. (This was only clarified later in the study.)</td>
</tr>
</tbody>
</table>

May 1996, Feb 1997
Bridging Efficacy & Safety to Other Populations
Zometa
FDA News – Certican

Nov 2005

Routine Discussion of ClinPharm Topics
Bring your presentation to life. Capture your audience’s attention.
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FDA Uses Computer Simulations to Guide Future Trial Design
Your Text Goes here. Download this awesome diagram. Bring your presentation to life. Capture your audience’s attention. All images are 100% editable in PowerPoint. Pitch your ideas convincingly.

Dosing proposed was tested for kidney transplant trial successfully

FDA Advisory Committee Meeting
Posaconazole for Invasive Fungal Infections (200 mg TID)

Decisions

Indication
Treatment of HepC + Peg Interferon + Ribavirin (PR)

Efficacy
SPRINT II in untreated +ve
RESPOND II in treated +ve
(Nulls excluded)

1
Approve Prior Null Responders?
More trials needed before approval?
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Root Causes

- Lack of Organizational Power
- Risk Averse & Prescriptive Behavior
- Lack of Expertise
- Uncertain FDA Expectations
Learn & Apply Paradigm

- Disease
- Drug
- Trial
- Go, No-go
- Dose Selection
- Endpoint
- Approval
- Label
- Therapeutics

Knowledge is an important asset
Confirmation – Not important?

To confirm is important, but that cannot be the sole goal of drug development. Confirmation does not apply to safety, dose, biomarker-endpoint relationships...
An approximate answer to the right question is worth a good deal more than an exact answer to the approximate problem.
Widespread use of 'statistical significance' (generally interpreted as '$p < 0.05$') as a license for making a claim of a scientific finding (or implied truth) leads to considerable distortion of the scientific process."
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