Regulatory Hurdles for Drug Approvals

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25 min
Conflicts

CPC Clinical Research (University-based Academic Research Center) has received grant support from numerous industry sponsors, perhaps all directly relevant to this presentation.

William Hiatt is a member of the FDA Division of Metabolism and Endocrinology Advisory Committee.

I have no other conflicts and do not receive funds personally from any industry sponsor.
Why Should You Care What Regulators Think?

FDA and EMEA rigorously interpret trial data as a standard for regulatory decisions.

Deliberations based on more information than available in medical literature.

FDA decisions may contradict guideline recommendations or payers (CMS) who may draw different conclusions from the same evidence.
Approve new drugs, expand indications of marketed drugs, withdraw unsafe drugs

Authority derived from US Congress

Control points include approvals, labeling and withdrawals with a standard of safe and effective

Approvals straightforward when:

- Important therapeutic addition with clear efficacy
- Addresses unmet need
- Well defined, minimal risk
- Cost not a consideration
Advisory Committees mandatory for drug approval

- Center for Drug Evaluation and Research (CDER)
  - Cardiovascular & Renal Drugs Advisory Committee
  - Metabolism and Endocrinology Products Advisory Committee
- Advisory to FDA, n=6-8 voting, conflicts reviewed, disclosed
- Composition:
  - Cardiovascular/endocrine & metabolism physicians, trialists, biostatisticians, drug safety expertise
  - Patient and industry rep (non-voting)
- Review process: Includes presentations from sponsor, FDA, and open public forum, pre-defined questions
- Discussions transparent and public
Evaluation of Drug Efficacy

Endpoint issues

- Primary versus secondary
- Composite endpoints
- Surrogate endpoints

Weight of evidence - single study approvals

- Level of statistical significance
- Number of phase 3 trials for approval

Active controlled trials

- Challenges with non-inferiority trials
Primary Endpoint
FDA Perspective

Primary endpoint must test a specific hypothesis
• Sample size calculations usually based on primary
• Secondary endpoints considered informative if primary is positive
• Statistically significant secondary endpoints in the context of a negative primary usually insufficient for drug approval
• Co-primary endpoints can be considered with appropriate alpha spending or hierarchical approach
Aspirin for Primary Prevention

Aspirin evaluated for new indication for primary prevention in 2003

All trials presented in support of indication were negative on primary endpoint

- British Doctors trial: \( 1\) = fatal-nonfatal MI, CVA
- Physicians Health Study: \( 1\) = CV mortality
  - \( 2^{nd} \) = fatal, non-fatal MI \( p < 0.001 \)
- Thrombosis Prevention Trial: \( 1\) = CV death, MI \( p=0.07 \)
- Hypertension Optimal Trial: \( 1\) = CV death, MI, CVA
- Primary Prevention Project: \( 1\) = CV death, MI, CVA
- Women’s Health Study: \( 1\) = CV death, MI, CVA, \( p=NS \)
FDA Denies Approval of Aspirin

Previously approved for secondary prevention
- Strong evidence for benefit to prevent CV events in patients with clinical coronary or cerebral disease

Not approved for primary prevention
- No subgroup responsive, including high risk or diabetics
- Despite negative FDA ruling current guidelines (AHA, ADA, USPSTF) recommend aspirin to prevent MI in men and stroke in women

Subsequent trials in diabetes and meta analysis confirm lack of favorable risk-benefit of aspirin

Composite Endpoints

DREAM trial of rosiglitazone

- Rosiglitazone (relative to placebo) reduced the incidence of new onset diabetes or death by 60% in patients with IGT
  - 95% of outcomes were new diagnoses of diabetes
  - Diabetes RR 0.40 (0.35-0.46)
  - Death RR 0.91 (0.55-1.49)
- Thus the drug reduced the incidence of diabetes by 60% but had an uncertain effect on mortality

Lancet 2006:368:1096-1105
Composite Endpoints

Composite endpoint recommendations:

- Include components of similar importance
  - MI and stroke surrogates for death but hospitalization not
- Similar frequency
  - Hospitalization more frequent than death
- Similar treatment effect
  - Effect size greater for non-fatal than fatal endpoints

JAMA 2010;303:267-8
Surrogates

Approvable surrogates
- Blood pressure
- HbA1c (questionable relationship to CV benefit)
- Weight loss

Potentially approvable surrogates
- LDL cholesterol with statin therapy

Non-approvable surrogates
- Carotid IMT or IVUS as an index of clinical benefit of drugs to treat atherosclerosis
- Ejection fraction in heart failure

CRAC June 2005
Active Comparator Non-Inferiority Trials

Ethical imperative

- Loss of equipoise for placebo-controlled trial when established therapy convincingly bests placebo
- Strategy is to demonstrate new therapy retains the benefit of established therapy

Understanding of established therapy benefit

- Established treatment has benefit that is substantial in magnitude
- Treatment effect size and CI’s precise, well defined
- Constancy assumption is valid (event rates and response to established treatment retained over time and relevant to the setting in which the NI trial is being conducted)
Non-Inferiority Trials
Definition of the margin

Definition of non-inferiority margin

- Pre-specified and FDA approved
- Retain at least 50% of benefit of standard Rx defined by upper boundary 95% CI
  - If the upper bound 95% CI of the difference between two treatments lies entirely below the pre-specified margin then the results support that the new treatment retains the benefit of the established treatment
- Approvability issues often based on sponsor versus FDA definition of the margin
Upper 95% confidence limit of the relative risk between new and established drug can be no worse than 1.XX to demonstrate non-inferiority.
Non-Inferiority Trials
Assay Sensitivity

Assumption that the active control will have similar activity in a new study as was demonstrated historically when shown superior to placebo

- Without a placebo it is impossible to ‘prove’ efficacy
- The assumption is that the active control is active
- Related to the constancy assumption

Poor trial conduct may bias to showing non-inferiority, for example:

- Poorly defined and potentially biased endpoints
- Poor treatment compliance or loss to follow up
### Warfarin vs Placebo for AF
**Estimation of the non-inferiority margin**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Warfarin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>OL, PP</td>
<td>2.18%</td>
<td>5.28%</td>
</tr>
<tr>
<td>BAATAF</td>
<td>OL, PP</td>
<td>0.62%</td>
<td>2.99%</td>
</tr>
<tr>
<td>CAFA</td>
<td>DB, PP</td>
<td>2.95%</td>
<td>4.56%</td>
</tr>
<tr>
<td>SPAF I</td>
<td>OL, PP</td>
<td>3.08%</td>
<td>8.20%</td>
</tr>
<tr>
<td>SPINAF</td>
<td>DB, PP</td>
<td>1.84%</td>
<td>4.97%</td>
</tr>
<tr>
<td>EAF T</td>
<td>OL, SP</td>
<td>4.14%</td>
<td>13.3%</td>
</tr>
</tbody>
</table>

#### Events/patient years

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>95% Confidence Interval</th>
<th>Non-inferiority Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled analysis (n=6)</td>
<td></td>
<td>2.38%</td>
<td>2.90</td>
</tr>
<tr>
<td>Fixed-effect MA (n=6)</td>
<td></td>
<td>1.91%</td>
<td>2.66</td>
</tr>
<tr>
<td>Random-effect MA (n=6)</td>
<td></td>
<td>1.84%</td>
<td>1.52</td>
</tr>
</tbody>
</table>

#### ARD RR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>95% Confidence Interval</th>
<th>Non-inferiority Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo-warfarin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled analysis (n=5)</td>
<td></td>
<td>6.48%</td>
<td>1.86</td>
</tr>
<tr>
<td>Fixed-effect MA (n=5)</td>
<td></td>
<td>4.94%</td>
<td>1.71</td>
</tr>
<tr>
<td>Random-effect MA (n=5)</td>
<td></td>
<td>4.97%</td>
<td>1.52</td>
</tr>
</tbody>
</table>

**NI margin = 1.22**

JACC 2005;46:1986-95
Dabigatran

Dabigatran is a direct thrombin inhibitor tested in AF RE-LY (random eval long-term anticoag therapy)
• Primary endpoint = stroke or systemic emboli
• Primary analysis = noninferiority with margin < 1.46
• Retains half the 95% CI estimated effect of warfarin over control
  • P adjusted for multiple comparisons to 0.025
• Blinded study drug, open label warfarin
• 18,000 patients followed median 2 years

<table>
<thead>
<tr>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>0.91 (0.74-1.11)</td>
</tr>
<tr>
<td>P-noninferiority</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Outcome – 150 mg dose approved as noninferior to warfarin

Recent FDA Safety Topics

How to assess CV drug safety in trials that utilize non-mortal, surrogate or symptomatic endpoints

- Well defined for event-driven trials
- Limited for symptomatic trials or trials using surrogate endpoints
- Importance of pre-specifying key safety endpoints and adjudication
How Does a Trial Evaluate Safety?

- Adverse and serious adverse event reporting (AE/SAE)
- Evaluated at each study visit by spontaneous patient reporting
- Medical dictionaries code AE/SAE’s to common terms that lack specificity
  - Cardiac ischemic events reported as “angina”, “acute coronary syndrome”, “heart attack”, “myocardial infarction”, “chest pain”
  - Most common events may be non-informative “headache”, “fatigue” and mask less common but more critical safety signals
Targeted Safety Evaluation

- If drug mechanism has specific, targeted risk then trial will employ specific AE/SAE adjudication
- Independent, blinded Clinical Events Committee (CEC)
- CEC reports adjudicated events to independent and often unblinded Data Safety Monitoring Board (DSMB)
- DSMB reports to independent Steering Committee regarding trial conduct
- Examples, major and minor bleeding with new antithrombotic drugs (clopidogrel, prasugrel, dabigatran)
FDA Guidance Evaluating CV Risk
Diabetes Drugs

- Establish independent CV endpoints committee
- Adjudicate all CV events from all phase 2 and 3 trials
- Meta-analysis and prospective analysis plan
- Upper boundary of 2-sided 95% CI of risk < 1.8
- Risk ratio < 1.3. If 1.3-1.8 then additional safety study (phase 4) required
- New development programs may be subject to greater scrutiny

CDER Guidance Dec 2008
Exclusion of Risk Approach
Cilostazol as a Symptomatic Rx for PAD

Brass and Hiatt, Clin Pharmacol Ther 2006;79:165-72
Liraglutide

Glucagon-like peptide-1 indicated as an adjunct to diet and exercise to improve glycemic control in type 2 DM.

5 phase 3 trials in 4655 subjects, 2412 for 24 weeks.
Liraglutide Safety

Safety evaluated in all phase 2 & 3 RCT's included 6638 patients, 2926 patient years (1880 on Liraglutide)

114 events acquired as possible MACE with RR of:

- Lira v placebo 0.80 (0.23-2.83)
- Lira v active 0.68 (0.28-1.66)
- Lira v all 0.72 (0.32-1.61)

Endocrine Metabolism Advisory Committee voted 8 to 5 that the data ruled out excess CV risk

CDER April 2009
CV Risk of Weight Loss Drugs

FDA approved weight loss drugs
- Phentermine (sympathomimetic)
- Orlistat (inhibits fat absorption)
- Sibutramine (sympathomimetic/antidepressant)

FDA 2010 weight loss drug reviews
- Phentermine/topiramate (denied)
- Lorcaserine (denied)
- Naltrexone SR/Bupropion SR (split vote)
Why Approve a Weight Loss Drug?

Weight loss per se is purely cosmetic

But…FDA obesity drug guidance 2007 links a reduction in fat mass to clinical benefit:

- Reduced morbidity and mortality
- “through quantifiable improvements in biomarkers, such as blood pressure, lipids and HbA1c”
- Therefore weight loss alone not sufficient

FDA Weight Management Guidance 2007
SCOUT
Sibutramine Cardiovascular Outcomes Trial

Enrolled patients at increased CV risk
- Diabetes with additional CV risk factor (n=2385)
- H/O cardiovascular disease (n=1552)
- Diabetes + CV disease (n=5807)
- Duration 3.4 years, but only 58% completed on Rx
- Primary endpoint = MI, CVA, vascular death, resuscitated cardiac arrest

# Cardiovascular Risk by Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.16</td>
<td>1.03-1.31</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.01</td>
<td>0.74-1.38</td>
</tr>
<tr>
<td>CV disease</td>
<td>1.28</td>
<td>0.92-1.78</td>
</tr>
<tr>
<td>DM &amp; CV disease</td>
<td>1.18</td>
<td>1.02-1.37</td>
</tr>
</tbody>
</table>

P for interaction 0.56
Sponsor argued to change product label to exclude CV disease
But risk generalizable to entire study population
No other subgroups or strategy identified to mitigate risk
Sibutramine Outcome

FDA voting question: minor label change, major label change (limited use, black box) or remove from market

16 voting members, 8 to remove, 8 to retain on market (2 with minor label change!!)

One month later FDA reports sponsor ‘voluntarily’ agreed to withdraw drug from market (could there have been any other outcome?)
Subsequent Obesity Drug Approvals
Cardiovascular Outcome Trial Requirement

Naltrexone/Bupropion (Contrave)
• Not approved in 2010 or 2012 due to increased BP
• Pre-approval CVOT required
• Run trial to interim to exclude risk ratio 2.0 and then drug can be approved
• Continue CVOT to exclude risk ratio 1.4

Lorcaserin
• Approved June 2012 with post approval CVOT commitment
• No pre-approval cardiac risk, but post approval must address valvulopathy and pulmonary hypertension risk