FDA Advisory Committees: Message to Pharmaceutical Industry and Academia

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Disclaimer

- This is a bait and switch talk
- I don’t really have general messages to the pharmaceutical industry and academia
- My comments concern participation as an FDA Advisory Committee panel member or as a presenter to an FDA Advisory Committee
Introduction

• FDA Advisory Committees are outside experts without major conflicts of interest
  – MDs with expertise in specialty under study
  – Statisticians & epidemiologists
  – Other experts as needed
  – Patient/Consumer Representative
  – Industry representative (non-voting)
Introduction

• FDA asks specific questions like:
  – Do you have significant safety concerns with respect to liver toxicity with Product X?
  – Has the sponsor demonstrated efficacy of product X with respect to CHD?

• Committee discusses issues, votes on questions & recommendations to FDA

• FDA makes ultimate decision on approval
Introduction

• Typical order of meetings
  – Sponsor presents
  – Committee asks “clarifying” questions
  – FDA presents
  – Committee asks “clarifying” questions
  – Public Hearing portion
  – Advisory Committee discussion/deliberation
  – Advisory Committee votes & explains vote
Interpretations, not Datasets

• Before meeting, you get briefing documents—FDA’s and sponsor’s interpretations of data, not datasets
  – Good: not as much work
  – Bad: you can’t do your own analyses

• Given that you get only 2 interpretations, want to quickly find where they disagree
  – I read FDA briefing document first
  – If FDA has no issues, easy decision
They Don’t Give You The Easy Ones

• Very rarely, decisions are easy
  – Sometimes the FDA is required to have FDA Advisory Committee meetings, even if they agree with sponsor (e.g., when there is a new molecular entity)

• Usually the FDA and Sponsor disagree about some things

• You usually don’t get the easy ones
  – If they were easy, they wouldn’t need you!
Analogous to Criminal Trial

- Advisory Committees have commonalities with criminal trials
  - Sponsor is like prosecutor: must prove case beyond reasonable doubt
  - FDA is like defense: makes sponsor prove their case
  - Advisory Committee like jury
    - Sometimes 1 or 2 members are very influential
    - Difference from jury: experts, not peers
Analogous to Criminal Trial

– Each side has its own experts
– Each side presents case separately
  • Evidence can seem overwhelming after one side, but then change when other side presents
– Discovery process: each side sees other side’s evidence before trial
– Good strategic decision to present your side’s weaknesses before other side does
  • Never want to give impression of hiding something
Analogous to Criminal Trial

- One important difference from criminal trial: jury (Advisory Committee) sees evidence in advance
  - Voluminous materials sent out weeks in advance (though “jury” doesn’t always read them)

- Still, sometimes things come up and you have to think fast

- Example: LOTS trial of Pompe disease
LOTS Trial and Minimization

- 10/21/2008 Endocrinologic and Metabolic Drugs Advisory Committee meeting on Pompe disease
  - Very rare, debilitating neuromuscular disease
    - Infant onset, juvenile onset, adult onset
  - Infant onset is most deadly, adult onset is still bad
  - Patients often progress to wheelchair dependence, ventilator, and death
LOTS Trial and Minimization

- Genzyme conducted Late Onset Treatment Study (LOTS)
- 90 patients with late onset Pompe disease
- Primary outcome: 6 minute walk test
- 2:1 allocation to drug/placebo using minimization
  - Try to balance on site, BL 6 minute walk (≤300m, >300m), and forced vital capacity (≤55% pred., >55% pred.)
LOTS Trial and Minimization

- The FDA is skeptical about minimization, so they require companies to use a re-randomization test
  - Compute observed test statistic $T_{obs}$
  - Fix data, regenerate treatment labels using allocation algorithm, compute $T$, and repeat thousands of times
  - Compute p-value by seeing where $T_{obs}$ is in this *re-randomization distribution*
LOTS Trial and Minimization

• Proponents of minimization argue that you can do a re-randomization test, but it is unnecessary because you get about same answer as t-test

• The statistician argued that re-randomization test doesn’t work in LOTS
Problem with Application of Rerandomization Test in Analysis of 6MWT

- Distribution of 6MWT ANCOVA test statistics

ANCOVA $p = 0.035$  
Re-randomization $p = 0.06$
LOTS Trial and Minimization

• Big problem: mean of re-randomization distribution is NOT 0 because of 2:1 allocation
  – It is 0 for standard randomization methods
• Nonzero mean causes loss of efficiency of re-randomization test: no longer close to t-test even for very large sample sizes
• Problem is that minimization severely limits amount of randomization
LOTS Trial and Minimization

• For more details on LOTS trial, see Van der Ploeg et al (2010) *NEJM* **362**, 1396-1406

Experts and Presentation

• Most important job for expert is to communicate effectively to statisticians and non-statisticians
  – Try to explain, not to impress
  – Give analogies
    • A p-value of .03 is like rolling a pair of sixes
    • Interaction:
      – 2 kids in the back seat
      – Will better team still win in soccer if it rains
Experts and Presentation

• Use graphs whenever possible
• Graphs are very helpful for illustrating statistical concepts
• E.g., for regression to the mean:
Baseline eGFR<60

(kidney measure)

Needed eGFR<60 at time 0 to qualify for kidney substudy
Month 1 eGFR<60

Month
eGFR (ml/min/1.73 sq m)
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
40 60 80 100 120

n=41 38 30 32 27 30 30 27 23 20 19 17 14 12 7 1
Experts and Presentation

• What to avoid in graphs:
  – Overcrowding with labels
  – Needless 3-dimensionality
  – Gratuitous use of colors
    • Think carefully about choice of colors (use placid blue for your drug, alarming red for placebo)
  – Scaling games
Freedom From Efficacy Failure Through 24 months
Study XXX—Kaplan-Meier Analysis

Prevention of rejection of heart in heart transplant

3.0 mg vs Control: HR = 0.53, \( P < 0.0001 \)
1.5 mg vs Control: HR = 0.73, \( P = 0.021 \)
3.0 mg vs 1.5 mg: HR = 0.729, \( P = 0.0395 \)
Survival* Through 24 months
Study XXX—Kaplan-Meier Analysis

95% CIs and number of patients at risk shown at 3, 6, 12, and 24 months.
*Freedom from graft loss/death/lost to follow-up through 24 months.
Experts and Presentation

• Sometimes the experts are very well known (e.g., L.J. Wei, Richard Peto, Donald Rubin, etc.)

• If you are on AC, the FDA wants YOUR opinion; don’t be swept away if expert is famous

• No-no: “We have some world renowned experts here—let’s ask them”
Example: Artesunate for Malaria

• 4/29/2010 FDA Anti-Infective Drugs Advisory Committee meeting:

• In remote locations, malaria sometimes kills people before they can reach the hospital

• Artesunate suppositories intended to reduce parasites & keep person alive until they reach a hospital
Example: Artesunate for Malaria

- Trial 13 compared artesunate suppository to placebo suppository
  - Children under 6 got 100mg dose
  - Adults & children over 6 got 400mg
- Analysis plan called for separate analyses in the two age subgroups
- Results suggested benefit for young children, harm for older children
- Is this real?
Figure 4. Kaplan-Meier Survival Curves for Time to Death, All Randomized Patients

**Young Children**

- **Proportion Surviving**
  - RX: PLA (red dashed line)
  - RX: ART (blue line)

**Older Children & Adults**

- **Proportion Surviving**
  - RX: PLA (red dashed line)
  - RX: ART (blue line)

**L.R.: p**
- Young Children: 0.0679
- Older Children & Adults: 0.1403

**Time to Death (DAYS)**
- 1 3 5 7 9 11 13 15 17
<table>
<thead>
<tr>
<th>Younger Children Bangladesh/Chittagong</th>
<th>Older Children/Adults Bangladesh/Chittagong</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART 14/1022 (1.4%)</td>
<td>ART 31/2009 (1.5%)</td>
</tr>
<tr>
<td>PLA 31/988 (3.1%)</td>
<td>PLA 14/2009 (0.7%)</td>
</tr>
<tr>
<td>RR=0.43 (0.2,0.8) p=.007</td>
<td>RR=2.2 (1.1,4.2) p=.01</td>
</tr>
</tbody>
</table>

**Modified ITT Population**
Example: Artesunate for Malaria

- Richard Peto argued conflicting results are due to play of chance
- As with many other AC meetings, I had not made up my mind in advance
- It is okay to have doubts
  - The FDA values your thinking
    - Talk! Don’t be afraid your questions are dumb
  - People with no doubts may be less convincing
Example: Artesunate for Malaria

• Expert was Richard Peto:
  – Famous & brilliant
  – Excellent at explaining things to statisticians and non-statisticians

• I began thinking:
  – I can’t disagree with Peto!
  – He’s probably right—he usually is
    • Cholesterol lowering and suicide/victim of homicide
Example: Artesunate for Malaria

- In the end, you have to go with your gut
- You are there to give an independent opinion
- If you are not convinced, it doesn’t matter how famous the expert is
- We decided that differences between younger and older children were probably not the play of chance
Not JUST A Statistician

• Statisticians also need to use non-statistical judgment as well, e.g. :

• 12/14-15/2006 Anti-Infective Drugs AC and Drug Safety and Risk Management AC – Ketek for 3 different conditions:
  • Community acquired pneumonia (CAP)
  • Acute exacerbations of chronic bronchitis (AECB)
  • Acute bacterial sinusitis (ABS)
Not JUST A Statistician

• Rare, but troubling side effect-diplopia
  – Concern about driving

• I thought it should be approve for more serious condition (CAP) because less likely to drive
  – Patients with CAP are less likely to feel well enough to drive
Respect the Public Hearing: You Might Learn Something

• Advisory Committee members sometimes ignore public speakers
  – They talk, read e-mails, etc.

• This is bad on several levels
  – Disrespectful to people who may already be afraid of public speaking
  – It gives an impression that you don’t care about patients suffering from the disease
  – You might learn something useful
    • Better understanding of disease and patients
Respect the Public Hearing: You Might Learn Something

• I have been on several ACs involving weight loss drugs
• Some have had troubling side effects, especially in large doses
• One public speaker talked about how desperate extremely obese people are:
  – Likely to take more than prescribed dose
• Had a big effect on my deliberations
May Not Want to Participate if You Have the Disease

- I have kidney disease (IGA nephropathy)

- On 10/16/2007 I was a consultant on the Cardiovascular and Renal Drugs AC meeting
  - Phosphate binders for treatment of hyperphosphatemia in patients with chronic kidney disease (CKD)

- Sponsor presented slide with these bullet points:
May Not Want to Participate if You Have the Disease

- 11.3 million Americans have CKD, and excessively high mortality risk due to cardiovascular disease
- Most patients with CKD die before reaching dialysis
- Risk of death is extreme in end stage kidney failure
- 30 year old person with CKD Stage 5 on dialysis has risk of death equivalent to 90 year old
Summary

- FDA AC participation is a great way to help the FDA and a great learning experience
  - Exciting learning experience as a spectator too
- Talk! The FDA wants to hear your reasoning
  - Try to explain, not to impress
- Use both statistical reasoning and common sense
- Don’t ignore the public speakers
- Avoid ACs for diseases you have!