A Regulatory Perspective on Improving Assay Sensitivity in Analgesic Clinical Trials

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The content of this talk does not necessarily reflect the views of the FDA, and is entirely based on my own observations and viewpoints.

Why is Assay Sensitivity Important to FDA?

- Public health mission – get more and better analgesics approved quickly
- Must meet statutory standards for evidence of efficacy
- Must maintain sound scientific standards
- Regulatory responsibility to review from a conservative perspective

Regulatory Concerns and Industry/ Investigator Responsibilities

- Failed trials due to missing data
  - Improve subject retention and adherence
  - Follow up after drop out for real cause
    - "lost to follow up" "investigator decision" are unacceptable
    - Inadequate evaluation of drop outs leads to false positives (e.g., opioid studies with high drop rates mainly due to adverse events and inappropriate imputation strategy for missing data)
    - The we worry about false positives
      - Which results in our imposing requirements such as conservative imputation strategies
    - Which may lead to false negatives

Regulatory Concerns and Industry/ Investigator Responsibilities

- Failed trials because of unacceptable analyses in the protocol, e.g. LOCF imputation
  - This doesn't help if your definition of assay sensitivity is "product approval"
  - Follow our recommendations whenever possible and reasonable
  - Provide strong rationale when you don't
    - Support it with: data, data, data
    - **Not cost!**
    - **Not "unmet need"**
      - This buys "Fast Track" and/or "Priority Review," not a lower standard of evidence!

Regulatory Concerns and Industry/ Investigator Responsibilities

- Failed trials because of missing the correct dose and/or regimen, e.g., titration schedule, dosing interval, fixed or prn, monotherapy or adjunctive
  - Bring back real Phase 2
  - Understand the dose-response and dose-adverse event curves for your drug
  - Use them to design Phase 3 studies
  - Some drugs are just too toxic for the indicated population
    - Not a study design issue, but a definite consideration during product development
  - As stated yesterday, many analgesics have small treatment effect
    - Inadequate Phase 2 evaluation is likely to minimize your ability to demonstrate it

Regulatory Concerns and Industry/ Investigator Responsibilities

- Generalizability
  - Do we need real world populations?
    - What is a "real world population?"
    - Study the population that you have determined is the appropriate one in (yes!) **Phase 2**
    - Study the population that you intend to market your product to – and support that choice with data
      - Not just an efficacy issue as noted yesterday – safety in patients who may be prescribed off label
    - The problem is not having multiple study sites
      - A smaller number of sites supported by experienced qualified investigators
      - Is better than a large number of sites with inexperienced, sloppy investigators

Regulatory Concerns and Industry/ Investigator Responsibilities

- Generalizability
  - It does increase variability
  - But this can be dealt with
    - Analyses should include evaluation of subpopulations
      - Not necessarily to find statistical significance
      - But it helps us assess whether one population is driving the results
    - If the drug effect is actually the same in all patients, but the patients are different, we need to know this
      - Phenotyping
      - Genomics
      - Other biomarkers
      - Again, you need a good **Phase 2** program!

Regulatory Concerns and Industry/ Investigator Responsibilities

- Generalizability
  - Is enrichment OK?
    - Yes, at least for one of your Phase 3 trials
    - Depends on the drug, drug class
    - Depends on whether there has been adequate (yup) **Phase 2**
    - For an old opioid – two enriched trials may be OK
    - For an NME – only one is probably going to be OK
    - Is enrichment OK for all endpoints?
    - Convince us (with data!)

Composite Endpoints

- Will they help improve assay sensitivity?
- Are they acceptable?
  - Depends
    - E.g., opioid reduction
      - How much is clinically relevant?
      - Was there a differential in opioid-related AEs?
    - Best to evaluate and demonstrate in **Phase 2** if you want to incorporate into Phase 3

Other Suggestions from Thursday

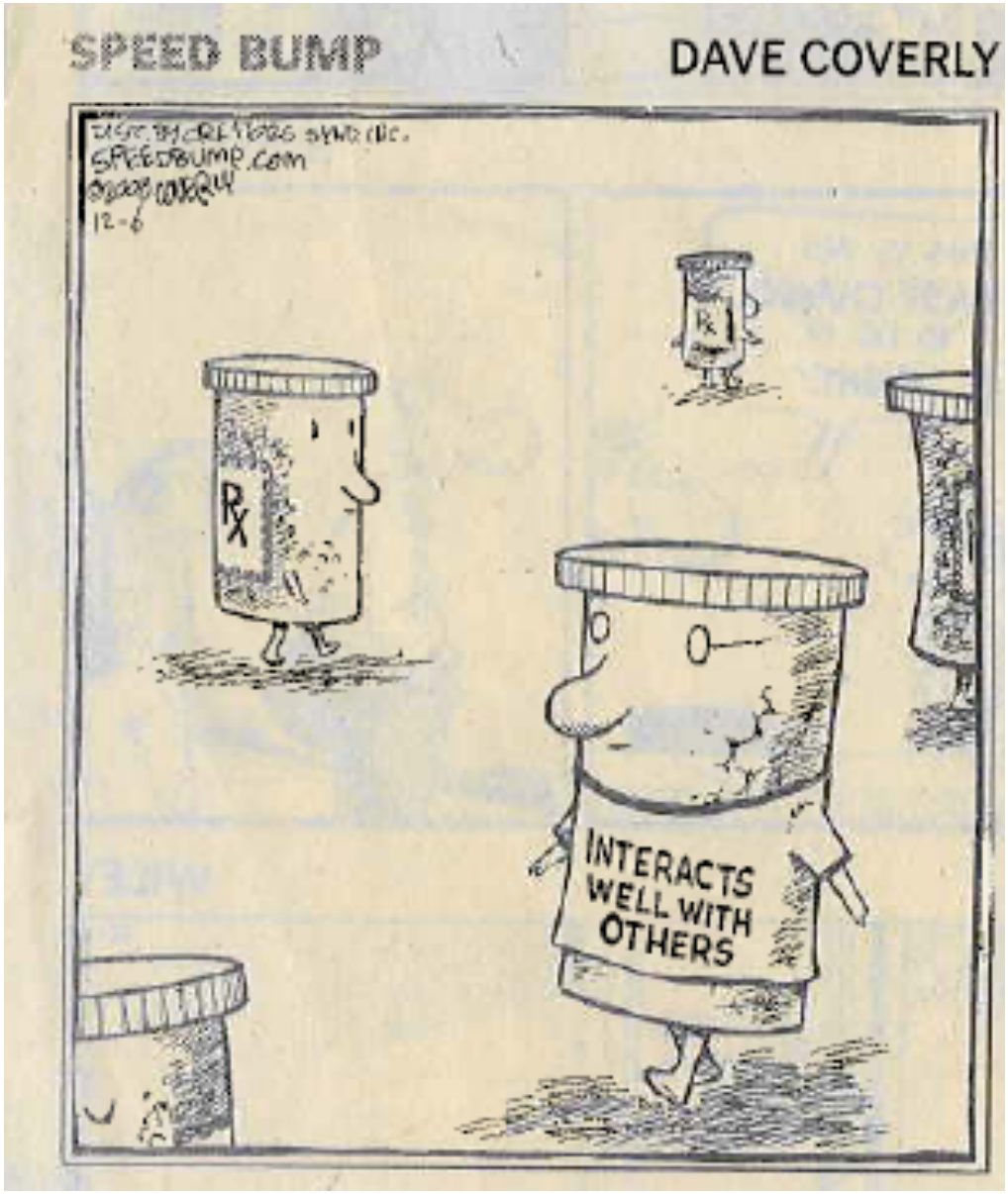
- AUC analyses - Personally, I'd love that
  - But need to figure out how to incorporate "period effects" into the analysis
  - We chose landmark analyses, e.g., average over Week 12, as a surrogate for durability
- Titration – cool!
  - If you've demonstrated the correct dose range in **Phase 2** (not necessary for old drugs)
  - If you carefully capture the dose at the time of adverse event

Other Suggestions from Thursday

- Distinguish between POC studies and confirmatory studies
  - POC: Phase 2, no restrictions, hypothesis generating
  - Confirmatory: regulatory requirement to provide evidentiary basis for approval
- Distinguish between
  - methodological improvements that don't reduce generalizability, e.g. 6/7 returned diaries
  - And limits to the inclusion criteria that will limit the targeted patient population
    - Requires supportive data from Phase 2
    - Must consider safety of the non-targeted population

What Can FDA Do To Help?

- Some ideas suggested by Nat Katz:
  - Sponsor an annual conference on methodological research
    - ?ACTION
  - Find ways to make data available for shared analysis
    - ?ACTION
  - Sponsor a contest for the most interesting methodological research?
    - ?ACTION
    - Not sure what the prize would be – lunch in the White Oak cafeteria? Cute plaque from the FDA?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Thanks!