FDA Perspective on Addressing the Challenges of Schizophrenia

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Challenges in Addressing Schizophrenia

- Lifelong disease
- Severe functional impairment
  - Social, vocational, independence
- Significant morbidity and mortality
- Very limited understanding of the disease

Who are the Stakeholders with a Role in Addressing Schizophrenia?

- Patients and their families
- Advocacy groups
- Government service funding agencies
  - Health care and many others
- Private health insurers
- NIMH and other research funding groups
- Pharma
- FDA

What is Needed to Better Address Schizophrenia

- Better understanding of schizophrenia
  - Is prodromal schizophrenia ready for prime time?
- Better interventions
  - To address life long nature of schizophrenia
  - Drug treatments
    - Most of questions not addressed
  - Non-drug treatments (social, vocational, educational, etc)
    - Here, as well, have more questions than answers

Efficacy Requirement in Food, Drug, and Cosmetic Act

- USC Title 21, Sec 505(d)
  - A new drug must have "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling…"
  - "substantial evidence means evidence coming from adequate and well-controlled investigations….."
  - CFR 314.126 defines what is meant by "adequate and well-controlled investigations"

Efficacy Requirement in Food, Drug, and Cosmetic Act (continued)

- No requirement for a minimum or clinically meaningful effect size for a new drug
- No requirement that a new drug has to be better than, or even as good as, other drugs in the class
- Evidence for efficacy must come from "adequate and well-controlled investigations"

What does a traditional schizophrenia drug development program look like?

- 4-6 week pbo-controlled trials
- Change from baseline in PANSS
- Active control for assay sensitivity
- Conduct enough studies to get 2 with significant p-values
- Enough safety data to satisfy ICH requirements

Worrisome Trends in Schizophrenia Drug Development Programs

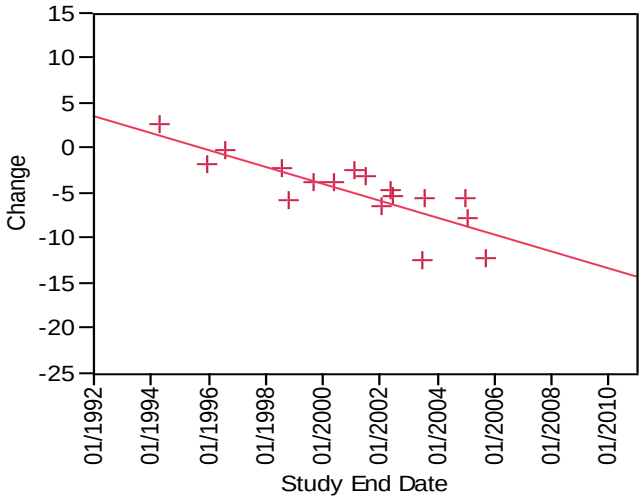
- Increasing placebo response over time
- Decreasing effect size in US trials over time
- Slight decrease in overall trial success rates over time:
  - Before 1999: 85%
  - After 1999: 74%

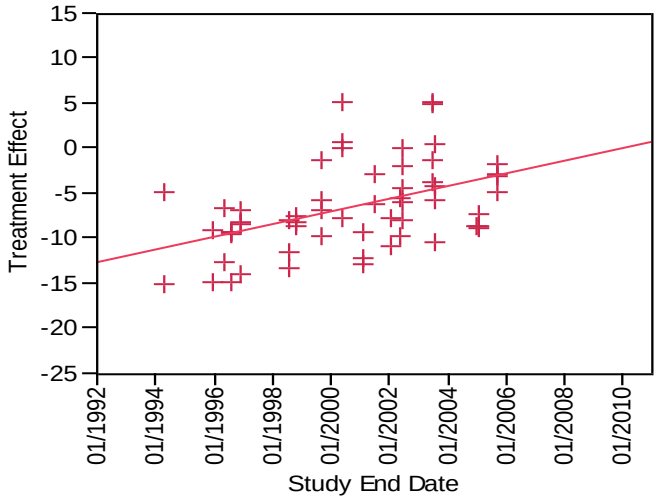
Time Plot in Schizophrenia

Placebo Response

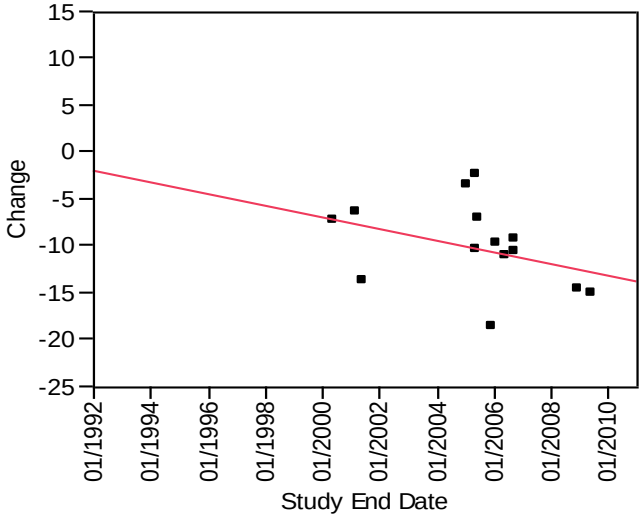
Treatment Effect

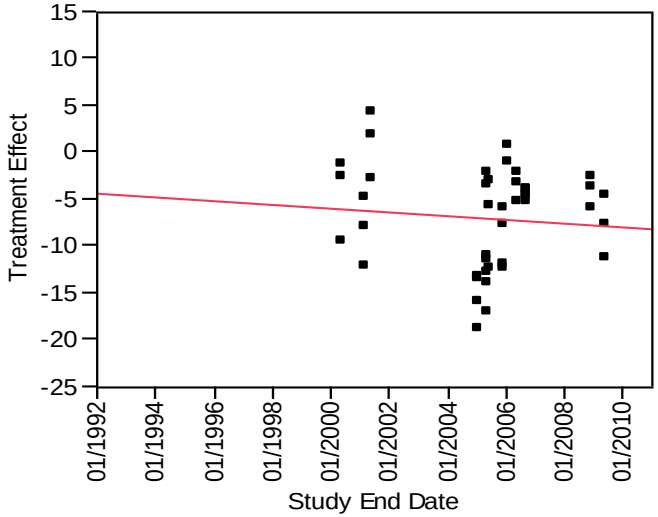
US





Non US





What About Longer-Term Data?

- Maintenance studies not pre-approval requirement in US
  - Oct, 2005 PDAC meeting
  - Generally done post-approval
- Maintenance trial design
  - Randomized withdrawal
  - Short stabilization (3 months), then observation for relapse
  - Assess time to relapse
  - Always positive
- Minimally informative
- Longer-term RCTs not feasible

What Changes are being Suggested for Registration Trials?

- More efficient short-term trials
  - Emphasize effect size, not p-value
  - Use moderator analyses to inform subsequent trials in development program
  - Questions:
    - Is there an actual demonstration of this being an efficient approach?
    - Would a company delay a program to do sequential trials?
- "Update" regulatory environment to embrace observational studies
  - Safety: business as usual; have relied on these for many years
  - Efficacy:
    - Fails on adequate and well-controlled trial legal requirement
    - May serve as confirmatory evidence
      - e.g., clozapine for suicidal behavior

Initiatives to Explore Accumulated Clinical Trials Data to Improve Future Trials

- FDA Efforts
  - Exploration of MDD and schizophrenia trials
    - Summary data
    - Patient level data
  - Establishing data standards for clinical trials
    - Current effort with schizophrenia
    - One potential benefit: facilitation of future explorations
- NEWMEDS/Jonathon Rabinowitz

Who is Responsible for Providing Answers to All the Questions We Would Like Answered in Regard to Drug Treatments in Schizophrenia?

- What is Pharma's (FDA's) responsibility?
  - FD&C Act sets a minimum standard
  - Some large companies have already decided that trying to meet even this minimum standard is not a good bet
- Other stakeholders share in this responsibility
  - Government, health insurers, private funding groups
  - Note: no requirement that other stakeholders adhere to FDA's regulatory standard in making funding decisions