OPPORTUNITIES IN STATISTICAL DESIGN, ANALYSIS AND MODELING

Susan S. Ellenberg, Ph.D.
University of Pennsylvania School of Medicine

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FULL DISCLOSURE

- I headed the Office of Biostatistics and Epidemiology in FDA's Center for Biologics Evaluation and Research (CBER) 1993-2004
- After joining FDA, despite substantial prior experience in designing and analyzing clinical trials, I found there were many issues related to regulated trials that I had not fully understood
- Since joining U Penn I have done some consulting with pharmaceutical companies, and have learned more

PRELIMINARY CONSIDERATIONS I

- FDA staff take their responsibilities extremely seriously—they do not want to make mistakes in marketing approval decisions
- They are well versed in the potential biases and distortions of traditional design and analytical approaches
- They are concerned about the potential biases and distortions that may be lurking in newer and/or less familiar methods
- This inevitably leads to great caution in accepting new methodological approaches

PRELIMINARY CONSIDERATIONS II

- Statisticians who want to focus on statistical research will not seek FDA reviewer positions
- Many important statistical problems arise out of FDA reviews and assessments
- Full access to such problems typically limited to
  - FDA statisticians
  - Industry statisticians
  - Academic statisticians serving on FDA advisory committees or doing substantial industry consulting
- Need for more statisticians focusing on research to have in-depth appreciation of statistical issues in regulatory arena

PRELIMINARY CONSIDERATIONS III

- It is unrealistic to imagine that improved quantitative approaches can eliminate need for
  - Adequate size populations for safety assessment
  - Adequate duration of follow-up for documenting sustained efficacy and longer-term safety
  - Adequate long-term data to validate use of surrogate endpoints
- Tension between efficiency in getting products to market, and adequacy of safety assessments, is fundamental characteristic of regulatory decision-making

STATISTICAL INNOVATION: NEEDS

- Bayesian methods
  - Bayesian methods are not new, but only relatively recently have become widely practicable due to modern computing power
  - These methods offer approaches to understanding data that complement traditional methods and may be preferable in some contexts
  - Bayesian methods have been adopted for medical device review but their use in evaluating new drugs has been more limited
  - FDA reviewers need to become comfortable with these methods so that they can use them effectively without concern for being misled

STATISTICAL INNOVATION: NEEDS

- Using genomic information
  - Design of clinical trials of targeted therapies
  - Analytical approaches to identify potential influence of genomic characteristics on response to therapy
  - Design and analysis of studies to simultaneously evaluate targeted therapy and assays to permit use of such therapies
  - More efficient strategies to develop and evaluate combination regimens aimed at molecular targets

STATISTICAL INNOVATION: NEEDS

- Post-marketing safety surveillance
  - Critical area for regulatory decision-making
  - Frontier area for development of quantitative methodology
  - Few statisticians (although some very good ones) focusing on methods in this area
  - Need involvement of FDA scientists in both the pre-market and post-market review units
  - Many sub-areas of importance
    - Monitoring spontaneous reports
    - Conducting and evaluating meta-analyses of completed trials
    - Designing and analyzing post-market observational studies and clinical trials to yield reliable data

STATISTICAL INNOVATION: NEEDS

- Assessing multiple related outcomes
  - Regulatory approach to new products: identify a single primary endpoint, to avoid concerns about multiple opportunities for a "win" and consequent inflation of false positive error
  - Problem: often there are multiple aspects of benefit which are likely highly correlated
  - Arbitrary to select just one
  - Statistical methods to account for multiple comparisons are not calibrated to the extent of correlation among the outcome variables and hence tend to be overly conservative
  - "Global" approaches that combine multiple outcomes into a multidimensional variable are not always satisfactory

STATISTICAL INNOVATION: NEEDS

- Adaptive designs
  - Much adaptation already built in to traditional clinical trials but many new approaches have been proposed in last decade
  - Purpose: greater efficiency
  - Legitimate concerns
    - Complicating process without increasing efficiency
    - Getting to the wrong answer faster
    - Introducing biases
    - Getting more efficient answers about efficacy but reducing information about safety
  - Critical need to evaluate such approaches so that true increased efficiencies can be achieved without unacceptable tradeoffs

STATISTICAL INNOVATION: NEEDS

- Comparative effectiveness research
  - Value of reliable comparisons of widely used treatments is unquestioned
  - Complexities of interpreting results of active control studies well appreciated within FDA and industry, less so outside
  - Although primary purpose of CER is not regulatory, results will likely end up at FDA in supplemental applications and label changes
  - Optimal design of CER studies merits study

STATISTICAL INNOVATION: NEEDS

- Other areas for which innovative quantitative approaches are needed
  - Developing regulatory pathways for "biosimilars"
  - Phase 1 trial design
  - Strategies for developing pediatric indications for drugs already studied in adults
  - Strategies for developing therapies for rare diseases and conditions
  - Identifying optimal dose levels during phase 2/3
  - Identifying safety signals during "translational phase"

COLLABORATION IS ESSENTIAL

- FDA statisticians are very capable but
  - have little discretionary time for methodological research
  - most have a primary interest in their applied work
- Approaches developed by research statisticians may not account for regulatory constraints or certain pitfalls that are well known to statisticians at FDA and in industry
- To make progress, need two components
  - More FDA statisticians getting comfortable with newly developed approaches to design/analysis
  - More research statisticians becoming knowledgeable about regulatory environment

IDEAL SITUATION

- FDA internship program that would bring to the agency statisticians with at least 5 years post-graduate experience and an interest in methodological research for 1-3 years
- Statisticians would contribute to review work but would spend half their time on research
- Research projects would be collaborative with FDA statisticians and others interested in the development of new methodology
- FDA experience would inform their post-internship work

CHALLENGES AND OBSTACLES

- Internship program would be challenging to establish
  - Participants would have to abide by strict FDA conflict-of-interest rules for review staff
  - Culture of confidentiality with regard to proprietary information might be difficult to maintain for many who return to academia or other research positions after a short time
  - Regular shifts in reviewer assignments could be disruptive to review process
  - For this to be most effective, time frame would be longer than typical academic visiting position