Susan McCune, M.D.
Director, Office of Pediatric Therapeutics
Office of the Commissioner, FDA

QUALITY AND INNOVATION IN DRUG DEVELOPMENT

Pediatric Trial Design and Modeling: Moving into the Next Decade
September 8, 2017
Slides courtesy of Dr. Janet Woodcock, CDER/FDA

Problems with Current Clinical Trial Methods

- Very costly and time-consuming
- At the end of a development program, after expenditure of huge amounts of dollars and effort, many questions about drug use remain unanswered
- Limits what can be asked premarket
- Postmarket many questions remain unanswered
- Most practices of health care not evidence-based

Thinking about Demonstrating Benefit in a Development Program

- What is the quality and robustness of the evidence of an effect (including totality of evidence)?
- Given that it exists, how meaningful will this effect be in the overall context of the disease? How much will it matter to patients?
- If it matters, what would be the impact of failing to provide this benefit, if real?
- This reasoning has to be weighed against the potential harms of the intervention

Very Rare Diseases: Examples of FDA Approvals

- Lumizyme for Pompe Disease: survival data from an international registry of infantile-onset disease
- Carbaglu: Plasma level ammonia reductions in a case series
- Cholbam for bile acid synthesis disorders: data on growth, survival and reduction in abnormal cholestatic markers in a case series
- Glucarpidase for MTX toxicity: data on approx. 20 patients from NIH treatment protocol

What Did These Have in Common?

- Highly plausible mechanistic hypothesis
- Natural history data on untreated patients
- Highly plausible biomarkers; most could be measured in a standard manner
- Serious unmet medical need
- Relatively large treatment effect

Development Programs for Ultra-Rare Diseases

- Performing standard clinical trials may be very difficult
- N-of-1 studies looking at disease trajectory (e.g., slopes of various declines pre and post Rx) may be feasible. Start observational part early
- Data from natural history may be helpful if treatment results in a convincing departure and disease not too heterogeneous
- Oncology: "basket" trials with biomarker defined targets across histologic diagnoses; NCI "MATCH" trial
- More generally: grouping rare subsets together by functional status or other method (ivacaftor)
- Emergencies: NIAID Ebola trial with Bayesian method

Hopefully the Future: Platform Trials/Master Protocols

- Continuous, ongoing trials rather than start and stop
- Goal: continuous improvement in disease outcomes
- Usually run by consortia with experienced trialists as PI's
- Capacity to evaluate multiple interventions, biomarkers, patient subgroups over time
- Comparative effectiveness usually baked in

FDA is Evaluating Use of RWE

- We have approved drugs for rare diseases based on data from registry-like case series
- We have used registry data as external controls
- We are exploring how randomization would work in registry or healthcare settings
- We are collaborating with groups working to improve the validity of key data elements collected in the process of health care
- We have spoken to many groups that are assembling oncology care data in various ways and hope to provide valid platforms for investigations

Summary

- Clinical trials are a prohibitively expensive element of drug development, limiting the amount of information that can be generated
- Trial designs, no matter how novel, will only be as good as the knowledge that underlies them
- Great variability in the types of products being developed and the indications being sought are driving new types of development programs and clinical trials


FDA
U.S. FOOD & DRUG
ADMINISTRATION