Regulatory Flexibility and Lessons Learned: Drugs for Rare Diseases

John K. Jenkins, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research/FDA

NORD Summit Meeting
Arlington, VA
October 18, 2016

Disclosures

- No Conflicts of Interest
- Nothing to Report
- Opinions expressed are personal and do not reflect those of the FDA

Statutory Requirements for new drug approval:

- Substantial evidence of effectiveness for treatment of the proposed indication
- Benefits for proposed population outweigh risks
- Manufacturing that ensures product identity, strength, quality (purity)
- Evidence-based drug labeling that adequately guides providers and patients to use the drug safely and effectively

Substantial Evidence of Effectiveness

- Demonstration of **substantial evidence** of effectiveness requires studies designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change… placebo effect, or biased observation"

- Usual approval standard is two **adequate and well-controlled** studies

21CFR 314.50 and 21CFR 314.126

A Problem?

Can drug development programs for rare diseases meet the same approval standards as programs for diseases with millions of potential trial participants?

Solution: Flexibility Is Part of FDA Regulations

- Regulations allow for flexibility and judgment in applying the standards
- FDA has a solid record of appropriately applying regulatory flexibility

Flexibility

"While the statutory standards apply to all drugs… the many kinds of drugs… and wide range of uses for those drugs demand **flexibility** in applying the standards.

Thus FDA is **required** to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."

How Much Evidence Is Enough?

FDA may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence

Flexibility in FDA regulations does ***not*** mean marketing approval prior to demonstration of substantial evidence of effectiveness

Application of Flexible Clinical Development Programs

CDER NME approvals 1/1/2008 – 9/25/2015

Flexible Development Programs	Rare Approvals	Non-Rare Approvals
Use of ≥ 1 flexible development approaches*	81% N=73	36% N=64
Traditional development program**	19% N=17	64% N=113

*Flexible Development approaches are defined as approval supported by other than 2 AWC Studies and/or use of a novel end point

**Traditional Development defined as ≥2 AWC studies using endpoints with prior precedents

Programs to Expedite Drug Development

- **Fast Track Designation**
  - FDAMA 1997/FDASIA 2012
- **Breakthrough Therapy Designation**
  - FD&C Act/FDASIA 2012
- **Priority Review**
  - PDUFA 1992
- **Accelerated Approval**
  - 21CFR314 subpart H, 601 subpart E/FDASIA 2012

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

Expedited Clinical Development Programs

CDER NME approvals 2008-2016*

Expedited Programs	Number Rare (n = 109)	Number Non-Rare (n = 193)
Priority Review	75%	30%
Fast Track	54%	22%
Accelerated Approval	26%	2%
Breakthrough Therapy**	18%	4%
Used any Expedited Program	86%	35%

*as of September 7, 2016, **BT initiated 2012

Highlights of Recent Novel New Drug Approvals October 2015 – 03 October 2016

- 17 Approvals for Rare Disease Indications
  - 10 for were for oncology indications
- 7 BLAs and 10 NDAs
- 8 Designated as Breakthrough Therapy
- 2 Received a Rare Pediatric Disease Priority Review Voucher

Highlights of Recent Novel New Drug Approvals October 2015 – 03 October 2016 (cont.)

- 6 Received Accelerated Approval
  - 4 for oncology Indications
- 1 Employed a novel End Point
- 12 Approved with fewer than 2 Adequate and Well Controlled Trials

Understanding FDA Pathways to Drug Approval

There are TWO Approval Pathways in the US

Traditional (regular or "full") **Approval**

and

Accelerated Approval

the statutory standards are the same for both

demonstration of substantial evidence based on adequate and well-controlled clinical study(ies)

- **Accelerated approval** is **not** about faster review - it is a **regulatory pathway** to speed availability of drugs for serious unmet need by using an appropriate, *more readily measured, surrogate or intermediate clinical endpoint* when a lengthy trial would be needed to measure direct clinical benefit of a drug

Accelerated Approval

- The candidate drug must provide a meaningful advantage over available therapies to treat a serious condition, generally irreversible morbidity or mortality
- Relies on a more readily measured **surrogate** or intermediate clinical **endpoint**
- A post-approval confirmatory study to further define **clinical benefit** is generally required

Clinical vs. Surrogate Endpoints

- **Clinical** endpoint: characteristic or variable that *directly* measures a therapeutic effect - how a patient feels, functions, or survives

- **Surrogate** endpoint for accelerated approval: marker *thought reasonably likely to predict* clinical benefit; not itself a measure of benefit

Lessons learned from eteplirsen and other recent rare disease programs

- A poorly planned and executed development program for a rare disease misuses valuable patient resources and serves to delay obtaining the knowledge required to understand the benefits and risks of a drug to support regulatory review and approval
  - FDA provides valuable advice and guidance to sponsors, we cannot require sponsors to follow our advice
  - Path taken by Sarepta **NOT** a good model for other development programs

- Assays for biomarkers should be well validated before use to avoid obtaining misleading information and wasting clinical specimens
  - Particularly true when invasive procedure required to collect tissue in children
- Rigorous blinding and control procedures should be in place to minimize bias in assay interpretation
  - Protocol should specify blinding procedures, adjudication methods, independence of readers, etc.

- In many cases, randomized controlled clinical trials represent the fastest way to determine if a drug is effective
  - Randomize as early as possible in development to avoid potentially misleading and uninterpretable findings from open-label trials
  - Employ methods to limit time on placebo (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)
  - Report early trial results accurately, *post hoc* analyses of failed trials are generally hypothesis generating for next trial, not evidence to support approval

- Knowledge of natural history of disease critical to intelligent design of clinical trials
  - Conduct natural history trials before clinical trials begin
- If a natural history external control group is proposed, it should be identified prospectively to ensure comparability to treatment group
  - Natural history external control group created *post hoc* is very difficult to interpret, unless effect of test drug is very large, due to known and unknown confounding

- Use of accelerated approval pathway should be prospectively planned, **NOT** as a "rescue" for a failed program
  - Sponsor and FDA should agree on the surrogate and drug effect considered "reasonably likely" to predict clinical benefit **before** unblinding data
  - "Any" effect of a drug on a biomarker is not a basis for AA
  - Ideally, the confirmatory trial to further define clinical benefit should be started before AA is granted to ensure the trial will be completed in a timely manner

- FDA welcomes the engagement of patients and caregivers in helping to design development programs that will result in drugs that provide meaningful clinical benefit to those with disease
- Approval decisions must be based on data from adequate and well-controlled clinical trials, which may include PROs and other patient-derived measures
- Experience of patients enrolled in trials can be very helpful; discordant results between trial data and patient anecdotes are very hard to reconcile

- FDA reviewers are committed to facilitating development of effective and safe drugs for rare diseases
- Upholding statutory standards for approval in face of hopes and desires of patients, families, sponsors, and investors is a very difficult job
- Personal attacks on FDA reviewers creates an atmosphere of distrust and isolation rather than collaboration
- Recruitment and retention of qualified review staff is very challenging in such an environment

Thank you very much for your attention!

John Jenkins, MD
Director Office of New Drugs
CDER/FDA