Clinical Trials for Rare Diseases in CDER

CDER Antibacterial Task Force/CTTI Think Tank

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Objective

To describe the regulatory basis for approval of rare disease drugs and biologics in CDER

Drug Development Challenges

- Populations are small, often exceptionally so
- Natural history often incompletely understood
- Robust endpoints, measures, biomarkers lacking
- Large pediatric representation → special trial design and ethical challenges
- Often extraordinary disease burden on patients and families → logistical trial challenges

What are the regulatory standards for rare disease drug approval?

- Statutory requirements for demonstrating effectiveness and safety are the same for rare and common diseases

- Thus, studies must demonstrate substantial evidence of clinical benefit (21CFR 314.50)

- **The statutory requirements *do* allow flexibility in how that demonstration is accomplished**

Substantial Evidence of Effectiveness

- Typically two adequate and well-controlled studies for independent substantiation of results

- However, other pathways are described in Guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products"
  - for example, a single study with multiple event measures, pharmacologic/pathophysiologic endpoints, statistically persuasive findings

NDA Regulations: 21 CFR 314.105

Approval of an Application

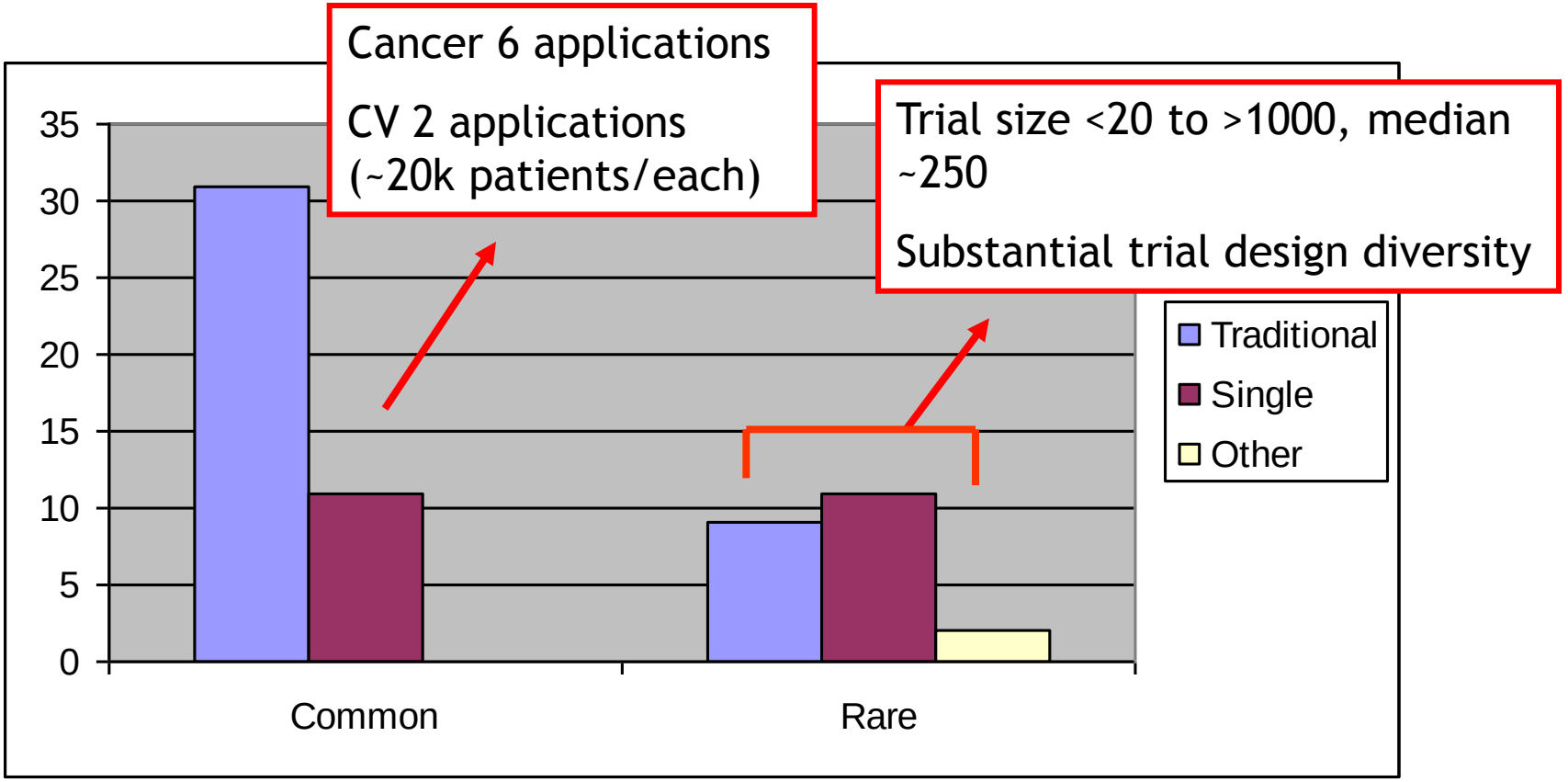
While the statutory standards apply to all drugs…the wide range of uses demand flexibility in applying the standards

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 is this working for rare diseases?

- Regulatory review of novel therapeutics - comparison of three regulatory agencies NEJM 366:24 June 2012, Downing et al
- Substantial trial design diversity in applications for rare disease drugs DIA Global Forum 2012;4:24-31, Pariser AR & Bauer LJ
- Quantum of effectiveness evidence in FDA's approval of orphan drugs: cataloguing FDA's fexibility in regulating therapies for persons with rare disorders Drug Information Journal. 2012;46(2):238-263, Sasinowski FJ

Level of Evidence for Approvals 2010-2012 NMEs and New Biologics



Slide courtesy of A. Pariser

CDER new molecular entities & new biologic approvals for rare diseases 2011-2012

Disease Precedent ?	
Yes	**No**
2012 (as of September 18, 2012) Gaucher disease Multiple myeloma Chronic myelogenous leukemia	 Methotrexate toxicity Cystic fibrosis *G551D* mutation
2011 Organ rejection, kidney transplant Hodgkins lymphoma Hereditary angioedema Acute lymphoblastic leukemia Transfusional iron overload Lennox-Gastaut	 Advanced melanoma Melanoma *BRAF* mutation Medullary thyroid cancer Anaplastic systemic large cell lymphoma Alk+ non-small cell lung cancer Myelofibrosis

Compare with 39 NME/NBs for common indications: 3 had no disease precedent

slide data courtesy of A. Pariser

Drugs for rare diseases: approval basis examples

- glucarpidase

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125327Orig1s000TOC.cfm

- ivacaftor

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203188s000TOC.cfm

- rilonacept

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125249s000TOC.cfm

The presented information is derived from FDA reviews posted on Drugs@FDA; consult these links for complete information about basis for approval

Glucarpidase is a carboxypeptidase enzyme indicated for the treatment of toxic plasma methotrexate concentrations (>1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function

Glucarpidase

- Single-arm, open-label, historically-controlled trial in patients with delayed methotrexate clearance secondary to renal impairment

- Pharmacodynamic endpoint in 22 patients who met pre-specified inclusion criteria: proportion who had rapid and sustained clinically important MTX reduction (to ≤1 µmol/L)

Strong scientific rationale for glucarpidase historical control

- Extensive clinical MTX use since 1948: effects, mechanism of action, toxicity, excretion and metabolism well understood, including dose specific mean methotrexate excretion curves

- Well established that 1 µmol/L plasma concentration at 48 hours → severe toxicity not treatable with leucovorin or hemodialysis rescue

Glucarpidase results

From P Dinndorf MD clinical review BLA 123327

- All patients showed large pharmacodynamic effect: ≥ 97% reduction within 15 minutes
- All patients had > 95% reduction in MTX concentration maintained for up to 8 days
- Efficacy endpoint success dependent on pre-treatment MTX concentration

Ivacaftor is a cystic fibrosis transmembrane conductance regulator potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene

Ivacaftor

- Strong natural history/pathophysiology
  - CF registry and care network since 1960
  - CFTR consortia since 2005 focused on trafficking, structure, and function
  - Ivacaftor developed to target specific mutated cell surface chloride ion channel - first drug to treat the underlying defect in the CFTR ion channel protein
- Two phase 3 randomized, double blind, placebo controlled trials in 213 patients
- Primary efficacy endpoint: change from baseline in % predicted FEV1 at week 24

Ivacaftor results

From C Rosebraugh MD Office Director review NDA 203188

- 10 to 12% absolute change primary endpoint apparent by Day 15 and maintained through trial end ($p < 0.0001$)
  - Equates to mean absolute change of 10.4% in ivacaftor group vs. -0.2% placebo (~annual decline in CF is 1-4%)
- Secondary clinical endpoints showed benefit, for example:
  - Week 48 pulmonary exacerbation-free rate 78% vs. 51% placebo
  - Mean change weight was 3.1 kg ivacaftor vs. 0.4 kg placebo week 48
- Mean change sweat chloride mmol/L -48.7 vs. -0.6
  - did *not* correlate with FEV1 improvement

Rilonacept is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older

Rilonacept

- 47 patients in 1 trial with 2 parts
  - Part A: 6 week randomized, double-blind, placebo-controlled
  - Part B: after 9 weeks all receiving rilonacept, patients again randomized to continue or switch to placebo

- Primary efficacy endpoint: change in disease symptom composite score 0-10 (daily record of fever/chills, rash, eye redness/pain, fatigue, joint pain)

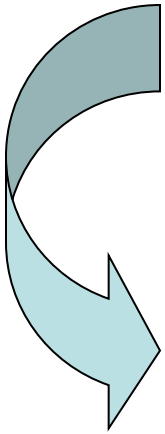
Rilonacept results

K Burkhart, MD Clinical Review BLA 125249

- Trial Part A: Change in disease activity with rilonacept -2.6 compared to -0.3 for placebo ($p<0.0001$)
- Part B: No change in patients remaining on rilonacept compared to increase from 0.2 to 1.2 for placebo ($p=0.0002$)
- Effect seen within a few days after a single injection
- Consistent results for multiple pre-specified secondary endpoints and serum acute phase reactant levels

Basic Laboratory and Clinical Science

Regulatory Science



Understand natural history and pathophysiology

+

Apply knowledge about mechanism of action/expected effect

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Develop meaningful endpoints and trial design

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Robust, efficient, innovative INDs

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Destination: approved drugs

"FDA is fully committed to applying the requisite flexibility in the development and review of products for rare diseases, while fulfilling its important responsibility to assure that the products are safe and effective for these highly vulnerable populations...This is possible **when the best science is flexibly applied and when therapies are truly effective**."

Dr. Jesse Goodman, FDA Chief Scientist and Deputy Commissioner for Science and Public Health, testifying June 23, 2010 U.S. Senate on "FDA's Efforts on Rare and Neglected Diseases"

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