Introduction: Rare Diseases, Orphan Drugs

Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology
March 2, 2011
Dallas, Texas

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Director, Office of Clinical Pharmacology
Food and Drug Administration
Silver Spring, Maryland
Update and Highlights: 2010-2011

Guidance for Industry

Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

Released for public comment on 2/17/11

Advisory Committee’s “Strong Encouragement”

By not mandating DNA sample collection, the agency appears to have adopted the consensus view of its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

In 2008, the committee agreed that DNA samples should be collected from all patients in all Phase I-III trials. FDA returned to the committee for further advice in March 2010 because, the agency said, drug developers asserted 100% DNA sample ascertainment was not possible due to differences among how ethics committees, institutional review boards and regulatory health agencies view DNA sample collection and storage processes.

The Pink Sheet Daily on 2/18/11
Other Guidance Updates

**Drug Interaction Studies**
- Transporter mediated DDI
- Decision trees for CYP DDI
  - Inhibition and induction
- Multiple co-factors and DDI
  - Use of PBPK
- Drug-protein DDI
- PGx data to inform DDI
- Non-CYP enzyme DDI

**Renal Impairment Guidance**
- Studies for non-renal routes
- Staging recommendations
  - Clcr (C-G) and MDRD (eGFR)
- Hemodialysis studies
  - Both on and off dialysis
- Renal studies of proteins
- Labeling recommendations
- Address 2010 comments

Under CDER clearance – anticipate June 2011 release

Anticipate to be sent for clearance in June 2011
What Are They?

- **Rare disease** = one affecting fewer than 200,000 people in the US
  - 6000-8000 rare diseases affecting 7% of population
  - 4 out of 5 have a genetic basis
  - 70-75% have a prevalence of < 100,000 people

- **Orphan drug** = one that has been developed to treat a rare disease
  - More than 2200 molecules designated as orphan drugs
  - 30-40% are for rare cancers
  - 362 approved drugs since 1983

http://www.eurodis.org/about-rare-diseases; Tambuyzer, Nat Rev Drug Discovery 2010, 9, 921-929
Orphan Drug Development and Regulatory Challenges

1. Large heterogeneity in disease pathophysiology
2. Poorly understood natural histories and progression
3. Few patients are available conducting clinical trials
4. Uncertain appropriate duration of treatment
5. Lack appropriate endpoints that predict outcomes
6. Large heterogeneity in treatment effects
7. Require compromise, innovation and trade-offs
8. Make difficult decisions in absence of ideal information

Extract most amount of knowledge from least amount of information
National Commitment to Rare Diseases

February 28, 2011

What is Rare Disease Day®?
- Strengthen one voice of patients
- Give hope and information to patients
- Bring stakeholders closer together
- Coordinate policy actions in different countries
- Get equity in access to care and treatment

The development of effective medicines for rare diseases is a primary FDA objective.
Case For Rare Disease and Orphan Drug Development

Trends
- Licensing deals (ex: Pfizer and Protalix)
- Mergers (ex: Sanofi and Genzyme)
- Label extension strategies (ex: EPO for anemia in CRF)
- Government roadmaps (ex: EMA and NIH)
- Dedicated industry units (ex: GSK and Pfizer)

Implementing a national strategy.....apply advances in science and technology, innovation in trial design, and incentives for sharing data....
Categories of Rare Diseases and Orphan Drugs

NME for as yet untreated people with rare disease

-- Example: alglucosidase alfa for Pompe disease (~ 1:40000?)
-- Exogenous source of lysosomal enzyme acid alpha-glucosidase (GAA)
-- Muscle weakness, enlarged hearts, difficulty walking

Drug for common disease → Drug for rare disease (“re-purpose”)

-- Example: sildenafil for pulmonary hypertension (~ 1:50*?)
-- Selective inhibitor of phosphodiesterase type 5 (cardiac biomarkers)
-- SOB, chest pain, tachycardia, ankle/leg swelling

Drug for rare disease → Drug for common disease

-- Example: canakinumab for Muckel-Wells syndrome (~ 1:2000?)
-- Anti-interleukin-1 beta monoclonal antibody (protein biomarkers)
-- Fever, rash, conjunctivitis, swollen joints, hearing loss, renal failure

* Severe pulmonary hypertension after pediatric cardiac surgery as opposed to idiopathic PH
Contrasting Product Development: Disease-Driven vs Drug-Driven

Adapted from J Pharm Bio Sciences 2010 (2), 4:290-299
General Model for Development of Orphan Drugs: Step 1

- Establish linkage between the biological MOA of drug and molecular basis of disease (target ID, get to cures – not only symptom control)

*Inhibition of IL-1 – inflammatory mediator – in synovial fluid of joints can reduce the signs and symptoms of CAPS and RA. IL-1 receptor antagonists can block the effects of over-abundance of IL-1 (causal pathway)*

Adapted from Cohen, Nat Rev Drug Discovery 2010, 9:856-866
General Model for Development of Orphan Drugs: Step 2

- Measure changes in biomarkers that enable proof-of-concept clinical studies of efficacy (supportive evidence and higher efficacy study success rates)

*Competitive inhibition of binding of IL-1 by drug*

Adapted from http://www.kineretx.com
General Model for Development of Orphan Drugs: Step 3

- Innovative trial designs to validate biomarkers-
  outcomes and quantitative methods for analysis of
data (D/R)

PK/PD models and simulation

Ex: correlation between
serum levels of canakinumab
and free and total
interleukin-1 beta as
measured by ELISA in
healthy volunteers at more
than one dose level

Development Strategies Are An Evolving Paradigm

- No consensus exists on what constitutes an ideal drug development program ~ no right way
- FDA seen as many different approaches to drug development as there are approved drugs
- Lessons learned from pediatric and oncology drug development can be applied to rare diseases
- Late-stage clinical development programs can be guided by early-phase clinical pharmacology studies using M/S and CTS
- Biomarkers, D/R and PK/PD study data can be persuasive and provide confirmatory evidence of efficacy
Original NDA/BLA Orphan Drug Approvals: Recent Successes

2006-2010
Total = 34
22 NDAs, 12 BLAs

Source: Dennis Bashaw (FDA)
Further Breakdown of NDA/BLA Approvals For 2006-2010

- 34 approvals represented 27 different indications
  - 6 indications had two approvals

- 26 different companies sponsored 34 approvals
  - No sponsor had more than 3 approvals

Original approvals (38%)
Re-purposed approvals (62%)

Source: Dennis Bashaw (FDA)
## Orphan Drug Approvals in CDER in 2010

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>AP Month 2010</th>
<th>Division</th>
<th>NDA/BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalfampridine (Anpyra™, Acorda)</td>
<td>Improve walking in Multiple Sclerosis</td>
<td>January</td>
<td>DNP</td>
<td>NDA</td>
</tr>
<tr>
<td>Collagenase (Xiaflex™, Auxilium)</td>
<td>Dupuytren’s contracture</td>
<td>February</td>
<td>DPARP</td>
<td>BLA</td>
</tr>
<tr>
<td>Velaglucerase (VPRIV™, Shire HGT)</td>
<td>Gaucher disease</td>
<td>February</td>
<td>DGP</td>
<td>NDA</td>
</tr>
<tr>
<td>Carglumic acid (Carbaglu®, Orphan Europe)</td>
<td>NAGS deficiency (UCD)</td>
<td>March</td>
<td>DGP</td>
<td>NDA</td>
</tr>
<tr>
<td>Rifaximin (Xifaxan®; Salix Pharms)</td>
<td>Hepatic encephalopathy</td>
<td>March</td>
<td>DGP</td>
<td>NDA</td>
</tr>
<tr>
<td>Alglucosidase alfa (Lumizyme®, Genzyme)</td>
<td>Late-onset Pompe disease</td>
<td>May</td>
<td>DGP</td>
<td>NDA</td>
</tr>
<tr>
<td>Glycopyrrolate (Cuvposa™, Shionogi)</td>
<td>Drooling in children with neurologic disorders (e.g., cerebral palsy)</td>
<td>July</td>
<td>DNP</td>
<td>NDA</td>
</tr>
<tr>
<td>Pegloticase (Krystexxa™, Savient Pharma)</td>
<td>Chronic gout not responsive to conventional therapy</td>
<td>September</td>
<td>DPARP</td>
<td>BLA</td>
</tr>
</tbody>
</table>

Source: John Jenkins (FDA)
Key Features of CDER Orphan Drug Approvals in 2010

- Diverse collection of diseases and patient populations
- Program size varied from 23 to 540 patients
- Broad range of study designs and development processes
- Relied on both novel and well-established endpoint — reliable, meaningful, well-defined and “fit for purpose”
- Wide range of different studies to provide the “totality of evidence” needed for approval
Factors Influencing Success of Orphan Drug Development

- Understand disease pathology (why?)
- Ease of demonstrating proof-of-concept (when?)
- Show linkage between drug and target (where?)
- Delineate drug mechanism of action (how?)
- Clear and identifiable symptoms (who?)

Mechanistic biomarkers as a key scientific foundation
What Has Brought Clinical Pharmacology To This Point?

- Large RCTs and full clinical pharmacology packages are not feasible in developing orphan drugs.
- Mechanistic approaches to drug development lend themselves to quantitative analysis.
- Advances in pharmacometrics – CTS and use of modeling – has made important contributions to pediatric drug approvals.
- Scientifically sound trade-offs between “full” and “light” clinical pharmacology datasets enable oncology drug development.
- Well-designed clinical pharmacology studies and innovative data analysis provide substantial evidence of benefit.
Important Challenge: Identify Safety Signals With Small Populations

- Clinical studies underpowered to detect serious safety issues given the unmet medical need of rare diseases

- Full assurance needed that benefits outweigh the risks

- Approach safety from off-target pharmacological MOA as opposed to whole organ observations
  - Inform adverse event prediction through aggregation of data on molecule – SA relationships, animal toxicology, human pharmacology – from many sources
  - Apply bioinformatics and systems pharmacology to identify potential off-target molecular pathways
  - Collect safety data preapproval, target surveillance postapproval
Goals for Today: Focus on Role of FDA

“...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…”

(CFR314.105)

Regulations provide room for flexibility in the review of treatments for rare diseases and the application of regulatory standards....good scientific judgment

“...and the role that modern clinical pharmacology can play in the application of processes and tools to provide the kind and quantity of data and information applicants need to meet the statutory standards…”
"Why does it take so long to find cures? Consider this: the potential speed of a high speed train is 200 mph, but the average speed of today’s train is 55 mph. It’s not the speed of the train that holds us back, it’s the speed of the track. We need to build faster tracks for faster cures."

*Greg Simon, FasterCures*
Orphan Drug Act: History, Perspective and Challenges for the Future

Tim Coté MD MPH

Director, FDA Office of Orphan Products Development
Presented March 2, 2011
CPAC Meeting, Dallas, TX
Orphan 101: The “Growing-est” Sector of All

- The Orphan Drug Act 101---Promise and Product
- So what is an orphan designation all about anyway?
- Subsets---slicing salami or medically relevant?
- OOPD and Review Divisions--Good neighbors with good fences
Economic Realities: 1982

- Rare diseases = Few potential pill buyers
- 1973-1982: 10 new drugs for rare diseases
- \(\approx 7,000\) rare diseases; 25 million people
- Congressmen/Senators regularly besieged by requests for assistance/research
Abbey Myer:
Grassroots Political Mover

“They are like orphans in that they require special care.” Henry Waxman
The New Deal of the ODA

- Get a drug designated as an “orphan drug”
  - Show (with data) that it’s “promising”
  - For treating <200,000 person in the US

- Do the clinical trials/get marketing approval

- Receive incentives:
  - MARKET EXCLUSIVITY
  - Tax credits
  - Fee exemptions
ODA: A MAJOR SUCCESS

- 362 Approved Drugs
- ≈2,250+ Designated Orphan Drugs
- 2008: 38% of all FDA-approved NMEs were Orphans
The US Orphan Drug Act has been HUGELY Successful

Number of orphan designations and marketing approvals from 1983-2010

* The database is currently being updated to include new marketing approvals for 2010. However, the number of designations for 2010 (192) is accurate.
The Diseased Populations Served have been VERY Small

Distribution of Orphan Designations and Approvals by Size of Patient Population

Source: FDA/OOPD, M. Braun et al
Time from Designation to Market Approval

Life table analysis of Progression from Designation to Market

Proportion of Designations Approved

YEARS
So what is a typical orphan drug?
And all human pathology is targeted by designated orphan drugs*

* 2000-2006 Data

- Oncologic: 36%
- Metabolic: 11%
- Hematologic-immunologic: 7%
- Neurologic: 6%
- Infectious/parasitic: 5%
- Cardiovascular: 4%
- Transplantation: 4%
- Gastrointestinal: 4%
- Respiratory: 3%
- Endocrinologic: 2%
- Dermatologic: 2%
- Ophthalmic: 2%
- Musculoskeletal: 2%
- Injury/poisoning: 1%
- Perinatal: 1%
- Congenital abnormalities: 1%
- Others: 2%
- Congenital abnormalities: 1%
A JOURNEY OF 2,755.8 MILES BEGINS WITH A SINGLE BOUNCE.

LIFE IS AN ADVENTURE. DON'T BLOW IT.
Example: Adagen for ADA

- Population: $1:2 \times 10^5$ to $1:1 \times 10^6$ born with homozygous mutation.
- Causes Severe Combined Immunodeficiency
- Adagen is one of the first orphan drugs (based on $n=12$); enzyme replacement therapy. Designated in 1984.
Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzzi, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Briglia, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Siavn, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alina Ferster, M.D., Andrea Dappenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

ABSTRACT

Background We investigated the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) due to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

Methods We infused autologous CD34+ bone marrow cells transduced with a retroviral vector containing the ADA gene into 10 children with SCID due to ADA deficiency who lacked an HLA-
Naglazyme for MS Type VI (Maroteaux-Lamy syndrome)

- Mucopolysacharridosis, liposomal storage disorder.
- Estimated only 1,100 persons world-wide.
- Enzyme replacement can prevent these changes
Lysosomes—Intracellular Organelles
These membrane-bound structures contain numerous hydrolytic enzymes responsible for degrading a variety of cellular components, including polysaccharides, polypeptides, lipid-linked glycosyl groups, and damaged organelles.

- Complex material is broken down
- Lysosome containing complex material
- Nucleus
- Complex material is excreted or can be reused
Enzyme Replacement Therapies

- Some of the most extraordinarily expensive treatments in the history of mankind (some $\approx 400,000/pt/yr$).
- FDA does not regulate price.
- Radically transformative beneficial to patients lives.
- Exclusivity lasts 7 years; knowledge is eternal.
ExPTPA and Radiogardase for Radiologic Poisonings

- Chelation for highly-specific indications; current zero prevalence.
Example: Eflornithine for African sleeping sickness

- Extremely rare disease in the US and Europe
- Treatment would be highly personalized, based on travel history
So what is the Orphan Designation All about?

- Non-exclusive orphan indication/moiety dyad
- Regulatory incubator of tenuous ideas.
- Target of venture capitalization
- Not a prescribe-able product
- A starting point for communication
Basis for Designation

- **First/Foremost:** What is the disease?
- **Medical Rationale Criteria:** Is there “promise” that your drug will treat it?
- **Prevalence Criteria:** Is the disease rare?
What is the disease/condition?

First question we ask…

Example: appetite suppressant proposed for treating Prader-Willi disease.

Example: Adenoma regressing drug proposed for use in FAP

Sometimes this changes/improves
  – Example: Lymphomas
Medical Rational Criteria

Must demonstrate that there is “promise” that the drug will be effective in treating said disease. “Promise” is liberally interpreted to include—

- Data from clinical trials OR
- Data from case studies/reports OR
- Data from animal models OR (rarely)
- Data from in vitro experiments
- (Note: these are data, not theories)
Prevalence Criteria

- A prevalence CAN be found for each disease.
- This is an epidemiologic question.
- Consider all published estimates. Those on best epidemiologic grounds have preference.
- Extrapolate when necessary.
- MUST be a number, not “<200,000”.
- When a range exists, we take the highest.
- Expert opinions are a last-resort option.
Test of a Medically Relevant Subset

The drug would be expected to treat only the subset of disease and NOT the rest of the disease.
Sub-setting: Truth or Dare

- NO to salami slicing
- YES to “medically relevant subsets”.
- Example: A drug to treat hypertension among left-handed people—NO.
- Example: A drug to treat renal cell carcinoma among those refractory to 1st line treatment---NO.
- Example: A drug (monoclonal Ab) against a surface antigen found in only a rare subset of breast cancer cases---YES.
- Example: A drug to be used only for stage IIb-IV melanoma---YES.
- Example---Pediatric Crohn’s Disease---YES
Rare Disease Grant Opportunities

FDA OPD Grant Program (R01) - clinical development of products, including drugs, biologics, medical devices, or medical foods, for use in rare diseases.

OOPD is interested in the potential of Pharmacometric analyses to support rare disease clinical trial designs and/or to evaluate clinical trial data.

Pharmacometric studies associated with a current clinical trial would be eligible for this request for applications (RFA).

We encourage collaboration with pharmacometricians to incorporate pharmacometric analyses.

For more information visit the OPD Grant Program website:
http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/default.htm
The current annual budget for grant funding is approximately $14 million.

– Clinical trials may be awarded (in total costs (direct and indirect)):

- Up to $200,000 (Phase 1) per year for up to 3 years

or

- Up to $400,000 (Phase 2 and 3) per year for up to 4 years.
Overview Timeline FY 2012/2013
Grant Program

- Receipt dates:
  - Next Full Application receipt date (FY2013) - February 1, 2012

- IND/IDE must be in effect at time of the grant application submission (IND must be active and include the protocol for which funding is requested)

- Earliest start date for award - November 2012

- All FY 2013 funding completed by September 2013
### Roles: OOPD v Review Divisions

<table>
<thead>
<tr>
<th>OOPD</th>
<th>Review Divisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Promise”</td>
<td>Safety and Efficacy</td>
</tr>
<tr>
<td>Bragging rights</td>
<td>Marketing rights</td>
</tr>
<tr>
<td>Cheerleaders/advocates</td>
<td>Monks/dispassionate</td>
</tr>
<tr>
<td>Guests @ pre-IND/EOP2 mtgs,etc</td>
<td>Own pre-IND/EOP2, etc mtgs</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Prev Irrelevant</td>
</tr>
<tr>
<td>Share shortage issues</td>
<td>Share shortage issues</td>
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</tbody>
</table>
Questions?
A Paradox in Orphan Drug Development

Trevor Mundel, M.D., Ph.D
Global Head of Development
Novartis Pharma AG

This document represents proposals for discussion by Management. Strategies/Concepts/Projects described herein may need significant modifications before implementation, and no project should be considered final until it has been fully approved by the appropriate Novartis review process. Novartis will only implement programs that are fully consistent with all applicable laws and regulations as well as Novartis companies’ policies. Before local implementation, you must ensure compliance with all applicable laws and regulations, including local industry codes, as well as local Novartis companies’ policies.
The Paradox to explain

At Novartis we do not have a specific rare or orphan disease indication strategy

and yet

We spend more time and resources on Orphan/ rare disease indications than others in the industry
Our Approach: Focusing on Greatest Patient Need and Scientific Promise

- Diseases of high morbidity/mortality without good treatments
- Mechanism is well understood. Human genetic insights available

- Diseases of high morbidity/mortality without good treatments
- Mechanism is well understood. Human genetic insights available
**ACZ885: Anti-IL-1β antibody**

**Proof of Concept in Homogeneous Population followed by Mechanistic Expansion**

**CAPS¹**

<0.020 Million

**Gout**

20 Million

**Atherosclerosis**

130 Million

---

**NALP3 (Cryopyrin) Inflammasome**

- Activation of Caspase-1
  - Caspase-1
  - IL-1β Precursor
  - Activated IL-1β

**Monosodium urate crystals**

**Cholesterol crystals**

**Normal vessel**

---

¹: Cryopyrin-associated periodic syndrome

*Source for patient numbers: global prevalence estimate from Patient Base*

SJIA patients are aged <16 years and show distinctive extra-articular disease features

Osteoporosis in juvenile idiopathic arthritis

- Arthritis (usually polyarticular)
- Spiking fever (39°C or higher)
- Peak age of onset 18 months–2 years
- Distinctive erythematous skin rash
- Distinctive joint disease
- Growth retardation

Woo P (2006) Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome

Acute Gout
Phase II

Systemic JIA
Phase II

NALP3 (Cryopyrin)
Inflammasome

Activation of Caspase-1

Caspase-1

IL-1β Precursor

Activated IL-1β

COPD
Phase II

Osteoarthritis
Phase II

Refractory Gout
Phase III (On track for Q4 2010 submission)

CV Risk reduction
Phase II

SJIA
Phase III

CAPS
Marketed

1 Chronic Obstructive Pulmonary Disease

2 Systemic juvenile idiopathic arthritis

3 Cryopyrin associated periodic syndrome
The mTOR Pathway Is Activated in Tuberous Sclerosis – targeted by Everolimus

Growth factors including IGF-1, VEGF, ErbB

Oxygen, energy, and nutrients

PTEN

Estrogen receptor

TSC2/TSC1

Ras/Raf pathway kinases

mTOR

S6K1

Protein production

Cell growth and proliferation

Nutrient uptake and metabolism

Angiogenesis

S6

4E-BP1
eIF-4E
Tuberous Sclerosis: A rare Autosomal Dominant Genetic Disease

Skin lesions including facial angiofibromas in >90% of patients

SEGA Volume Response and Resolution of Hydrocephalus

Baseline

3 months of everolimus

AIN457 (secukinumab) Potential to be first-in-class in immune mediated diseases

IL–17A, a key product of Th17 cells, plays an important role in the pathogenesis of immune diseases such as psoriasis, and rheumatoid arthritis. AIN457 is a fully human monoclonal antibody that neutralizes IL–17A activity.
AIN457 – proof in psoriasis

Baseline

After 2 weeks of treatment

After 4 weeks of treatment
AIN457 – Parallel indication expansion

Psoriatic Arthritis Phase II
Psoriasis (Moderate to severe) Phase II
Ankylosing spondylitis Phase II
Rheumatoid arthritis Phase II
Multiple Sclerosis In PoC trial¹
Crohn’s Disease In PoC trial¹

Note: Non-infectious uveitis in patients with Behcet’s disease did not meet its primary endpoint and the data did not support submission of AIN457 for this indication. Other uveitis studies are continuing.

¹ Proof of Concept not yet established
Three indications being pursued based on AFQ056’s inhibition of hyperglutamnergic transmission

AFQ056 MoA

Fragile X Syndrome
• Phase II

Huntington’s Disease
• in PoC trial

Parkinson’s Disease
L-dopa-induced dyskinesia
• Phase II

1 Proof of Concept not yet established
2 Mode of Action
Driving patient outcomes through focused solutions & interventions

- Potential for AFQ056 to be first targeted Fragile X Syndrome therapy

- Difficult diagnostic - quantitatively measuring small differences in a DNA modification to predict response. No existing test

- Biomarker Development Group (BMD) and MDx have developed a novel platform and validated test that is ready for clinical trials and FDA submission

- Opportunity for long term clinical-diagnostic approach spanning prenatal, neonatal, pediatric, adolescent and adults

Issues & Conclusion

- **Ethics**
  - Continuation of prescription for responders if few and no extension

- **Geography**
  - Sparse patient population spread across vast geographies/countries, with varying constraints

- **Incentive**
  - Regulatory & market incentive must be significant to overcome barriers to innovation
A Clinical Pharmacology Decision Tree for Orphan Drugs

CAPT E. Dennis Bashaw, Pharm.D.
Dir. Division of Clinical Pharmacology-3
Office of Clinical Pharmacology
US Food and Drug Administration
Disclaimer: The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the US Food and Drug Administration.
The Orphan Drug Act  
Jan. 4th, 1983

- While the ODA does NOT comment on the issue of informational needs or reviewing standards, it does provide incentives for the developer, including:
  - 7-year market exclusivity provision granted for FDA-designated orphan drug indications
  - a 50% tax credit for expenditures incurred during the clinical testing phase
  - Grants available to pursue development
  - Fee Waivers
Informational Considerations

• New Molecular Entity vs. Repurposed Drug
• Population Size Affected
  - <200,000-10,000  Juvenile Rheumatoid Arthritis  (150,000)
  - <10,000-1,000  Pompe Disease  (7,300)
  - <1,000  N-acetylglutamate Synthase Deficiency  (<200?)
• Ability to use healthy subject data
  - Toxicity
• Special Populations
1983-2006 & Clinical Pharmacology

- In 1983 the state of the art of Clinical Pharmacology was very rudimentary
  - Pharmacokinetics was only required for an NDA filed after July 4th 1977.
  - In 1987, the Division of Biopharmaceutics had a total of 5 IBM PC-XTs
  - Handwritten draft reviews were the norm.
Original Orphan Approvals (1983-1987)*

- 27 Orphan Approvals
  - 4 BLAs
  - 23 NDAs

- First Orphan Drug Approved
  - (7/20/83) Hemin for acute intermittent porphyria

- Approval Clock did not allow for Priority or Standard Review timelines.

Computing 2011

• In 2011, while paper NDA submissions are still submitted, more and more data comes to the FDA in an electronic format for review.

• The FDA has continued to upgrade its computer resources including the Computational Science Center whose mission is

  - To support CDER in continually improving the optimal drug evaluation and review process for the entire drug lifecycle while addressing the dynamic nature of the healthcare system

CDER Computational Science Center

Better Data, Better Tools, Better Decisions
Recent Approvals (2006-2010)*

- 36 Approvals
  - 13 BLAs
  - 23 NDAs
- The 36 approvals represent 30 separate indications, 6 indications had 2 approvals
- These represent 29 different companies, both Novartis and Genzyme had 3 approvals each in this period.

*1/1/2006-12/31/2010
Therapeutic Areas Over Time

1/1/1983-1/1/1988*

1/1/2006-1/1/2011

*Categories as of 2011
## Informational Content of Orphan/Rare NDAs/BLAs 2006-2010

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Radio-labeled</th>
<th>Single Dose</th>
<th>Multiple Dose</th>
<th>DDI</th>
<th>QT</th>
<th>Renal</th>
<th>Hepatic</th>
<th>PopPK</th>
<th>Other*</th>
<th>Total</th>
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</thead>
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<td><strong>NDA (P)</strong></td>
<td>18</td>
<td>9</td>
<td>40</td>
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*includes, analytical reports, literature articles, animal data, protein binding, In vitro CYP450 studies, etc.
Decision Tree As A Strawman Proposal

- Presented to stimulate discussion-Not as a lockstep roadmap
- To challenge assumptions
- To propose a pathway for rational drug development that makes use of existing paradigms.
Developmental Paradigms

**Pediatric**
- Using data from adult subjects to define metabolism, dose response, drug interactions and allowing us to focus on the pediatric aspects.

**Oncologic**
- Using a combination of small numbers of patients with appropriate use of animal and other collateral data along with pharmacometric tools to assess dose/concentration response features.
Developmental Paradigms (cont’d)

Re-purposing

- As used in this discussion is the development of an already approved drug for use in an orphan indication.

- The use of knowledge of related disease/drug mechanisms to identify potential drug candidates at any stage of development.

- Generally allows the fastest route for a drug as the initial mass-balance, animal safety, drug interaction, and special population work is already done.

- Development program is targeted to the orphan populations needs in terms of dose and any potential intrinsic factors that may affect drug disposition.
Rare Disease Repurposing Database (RDRD)-*BETA Version*

- The Office of Orphan Products Development (OOPD) has established a new resource for drug developers—a database of products that:
  - have received orphan status designation (i.e. they’ve been found “promising” for treating a rare disease)
  - are already market-approved for the treatment of some *other* diseases.

- While the data included in the RDRD is a re-configuration/cross-indexing of already FDA-released information, it offers a new tool for finding special opportunities to develop niche therapies that are already well-advanced through development.
  - These drugs have already been subjected to pre-clinical (e.g., pharmacokinetic and toxicologic) testing and are already deemed to be pharmacologically active, effective and safe in some clinical context.
Clinical Pharmacology
Decision Tree for Orphan Drugs

Drug for Orphan Indication

New Molecular Entity

Studies in Healthy Subjects
Follow Modified Oncology Model

Oncology Model

Patients Only

Re-Purposed 505(b)(2) or NDA Supplement
Follow Pediatric Strategy
Pediatric Drug Development Model (Re-Purposing)

- Drug already approved for use in an Adult population
  - Basic Pharmacokinetic Properties and Clinical Pharmacology studies already conducted and can be “borrowed” to support use in pediatric patients.
- For an Orphan Disease
  - Dose response (efficacy) relationship needs to be established
  - Safety in targeted population
  - Biomarker Development and Qualification
    - Clarify Pharmacodynamics
Re-Purposing Example-Sildenafil

- Sildenafil is a potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), and was initially studied for use in hypertension and angina pectoris.
- It was approved in March 1998 for the “treatment of erectile dysfunction”

<table>
<thead>
<tr>
<th>Clinical Pharmacology Studies</th>
<th># Subjects</th>
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<tr>
<td>Pharmacokinetics</td>
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<td>Pharmacodynamic DDI</td>
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<tr>
<td><strong>Total Clinical Pharmacology Population</strong></td>
<td><strong>676</strong></td>
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</table>
Re-Purposing Example-Sildenafil

• Idiopathic pulmonary arterial hypertension (PAH) is a rare disease with an incidence of about 2-3 per million per year and a prevalence of about 15 per million.
• In June 2005 sildenafil was approved under an orphan drug designation for treatment of PAH to improve exercise ability under the brand name Revatio.
• The Clinical Pharmacology section of the sNDA consisted of 15 post-marketing study reports (DDIs in non-PAH subjects), 3 new studies in PAH, and 1 DDI study (bosentan).
• A total of 230 patients with PAH were studied in the Clinical Pharmacology portion of the sNDA.
Clinical Pharmacology
Decision Tree for Orphan Drugs

Drug for Orphan Indication

- New Molecular Entity
  - Studies in Healthy Subjects
    - Follow Modified Oncology Model
  - Patients Only
    - Oncology Model
- Re-Purposed 505(b)(2) or NDA Supplement
  - Follow Modified Pediatric Strategy
New Molecular Entity-Patients Only

- Oncologic Drug Development Model
  - Basic Clinical Pharmacology
    - Pre-Clinical
    - Mass Balance
    - **Use of Animal Models**
    - Biomarker Development
  - Characterize Pharmacokinetics in Patients With Population Based Tools
    - Special Populations Within Orphan Population
  - Prioritize Drug-Drug Interaction Studies Based on Mechanism
DRUG EXAMPLE-Carbaglu

• Carbgumic acid is a structural analogue of N-acetyl-glutamate
• \(N\)-acetylglutamate synthase (NAGS) deficiency is the rarest disorder of the urea cycle, with only a handful of cases worldwide—a true prevalence is unknown.
• Without that enzyme, \(N\)-acetylglutamate does not form and activate the first enzyme of the urea cycle. The consequence is a buildup of ammonia, which can eventually cross the blood–brain barrier and cause neurologic problems, cerebral edema, coma, and death.

<table>
<thead>
<tr>
<th>Clinical Pharmacology Studies</th>
<th># Subjects</th>
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<tr>
<td>Pharmacokinetics/Pharmacodynamics</td>
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</table>
Carbaglu-Orphan
Development Paradox

While Clinical Pharmacology studies could have been done in healthy subjects, the nature of NAGS deficiency is such that the validity of extrapolating healthy subject data to the target patient population is unknowable.

Ironically, given the small number of subjects in the entire population the number of subjects studied is actually a higher percentage of the total disease population. Thus, our understanding of the drug:disease is quite high.
Clinical Pharmacology
Decision Tree for Orphan Drugs

- Drug for Orphan Indication
  - New Molecular Entity
    - Studies in Healthy Subjects
      - Follow Modified Oncology Model
    - Patients Only
  - Re-Purposed 505(b)(2) or NDA Supplement
    - Follow Modified Pediatric Strategy
New Molecular Entity-Healthy Subjects

• Modified Oncologic Drug Development Model
  – Basic Clinical Pharmacology
    • Pre-Clinical
    • Mass Balance
    • Biomarker Development
  – Basic Pharmacokinetic Development (SAD, MAD, etc.)
    Can Be Done in *Healthy* Subjects
    • Special Populations
    • Drug-Drug Interaction Studies
  – Characterize Pharmacokinetics in Patients With Population Based Tools
Drug Example- Argatroban

Argatroban is a small molecule direct thrombin inhibitor, it was approved in 2000 for the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). The prevalence of HIT is unknown.

<table>
<thead>
<tr>
<th>Clinical Pharmacology Studies</th>
<th># Subjects</th>
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<tbody>
<tr>
<td>Pharmacokinetics</td>
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<td>Pharmacodynamics</td>
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<td>DDI Studies</td>
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<td>Cardiac Studies (angina/cardiac catheterization)</td>
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<tr>
<td><strong>Total Clinical Pharmacology Population</strong></td>
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</tbody>
</table>
Quo Vadis?

- The ODA has had a major influence on the development of therapies for orphan and rare diseases, much more remains to be done.

- While the FDA has increased its capacity for improved data analysis since 1984, much more can be done with improved tools.
Oncologic and Pediatric Models for Orphan Drug Development

• The use of these models is not new, they have been used successfully since the earliest work in these populations.
• The purpose of the strawman proposal presented here at the Advisory Committee is to encourage a broader recognition of it in the community and to invite discussion as to how and where the informational needs can be modified without compromising patient safety.
Acknowledgements

• OCP Rare Disease Working Group
  – Larry Lesko
  – Shiew Mei Huang
  – Joga Gobburu
  – Issam Zineh
  – Dennis Bashaw
  – Gilbert Burckart
  – Rosane Charlab Orbach
  – Angela Men
  – Lei Zhang
  – Christine Le
Clinical Pharmacology
Tools for Developing Drugs for Rare Diseases

Christine Garnett, Pharm.D.
Division of Pharmacometrics
Office of Clinical Pharmacology
Impact of Quantitative Pharmacology—Selected Examples

**Argatroban**
- Exposure-response (ER) modeling primary basis for dosing approval in pediatrics

**Tetrabenazine**
- ER supportive evidence of effectiveness
- Basis for dosing in poor metabolizers

**Levofloxacin**
- PK matching primary basis for dosing approval in pediatrics

**Sildenafil**
- PBPK modeling alleviated need for additional DDI study
Quantitative Tools During Drug Development

**Decisions**
- Target ID
- ADME, Biomarkers, POC, Dose, Efficacy, Safety, Approval, Labeling
- Safety, New Indication

**Process**
- Pre-IND
- EOP2A EOP2
- NDA/BLA

**Tools**
- Mechanistic
- Quantitative Models
- Innovative Designs
- Empirical
Quantitative Tools

INNOVATIVE ANALYSES
• Quantitative drug-disease-trial models
• Exposure-response models

INNOVATIVE TRIAL DESIGNS
• Clinical trial simulations
• Enrichment, adaptive, dose-response

KNOWLEDGE MANAGEMENT
• Leverage prior data
Innovative Analyses

- Exposure-response to support B/R and dose selection
- Disease-drug-trial models to gain insights into biomarkers and endpoints
- Prioritize drug interactions studies based on in vitro and in silico predictions (PBPK)
- PopPK approaches for intrinsic/extrinsic factors

**DEVELOPMENT IMPACT**
- Streamline Clin-Pharm package
- More efficient trials based on mechanistic reasoning

**REGULATORY PATHWAY**
- Guidance documents
- Critical Path modeling consortia
Everolimus for Patients with SEGA

- **Re-purposed Drug**
  - Approved for RCC and prophylaxis of organ rejection

- **Regulatory Pathway**
  - Accelerated approval based on single-arm clinical trial in 28 patients
  - No new clinical pharmacology trials
  - Dosing based on therapeutic drug monitoring

- **Tool Used for Regulatory Decision**
  - Exposure response analysis supported anti-tumor activity in single arm trial and target therapeutic range.

*Subependymal giant-cell astrocytoma (SEGA)*
Evidence of Anti-Tumor Activity in Single-Arm Trial

% Reduction in Tumor Volume

Ave. Cminss (ng/ml)

Therapeutic Range

Clinical Response
Innovative Trial Design

- Enrichment
- Design
  - Crossover designs
  - Dose-response
  - Adaptive dosing and sample size
- Clinical Trial Simulation
  - Explore competing trial designs to maximize power & informativeness
  - Dose selection

**DEVELOPMENT IMPACT**
- Increase success rate of clinical trials
- Fewer numbers subjects in trials

**REGULATORY PATHWAY**
- EOP2a Meetings
NuDrug for Rare Disease

- NuDrug is new formulation of reference product
- Clinical Development
  - Pilot dose-ranging PKPD trial in 9 patients
  - Single phase-3 trial in ~30 patients using crossover design with adaptive dosing and sample size; primary endpoint is biochemical biomarker
- Tool Used for Regulatory Decision
  - Clinical trial simulation used to assess dose-selection and sample size
Clinical Trial Simulation to Evaluate Competing Dosing Regimens

- Evaluate proposed NuDrug dose and dose adjustment
  - 50% Total Daily Dose (TDD) of Reference + 20% dose increase for patients (proposed by sponsor)
  - 50% TDD + 50% dose increase
  - 50% TDD + No increase
Over 45% Patients Reached PD Target with 50% Dose Increase
>95% of Simulated Trials Met Endpoint with 50% Dose Increase

% Trials (N=200)
Knowledge Management

- Develop databases of data (e.g., VXDS, clinical trials) to support future decisions

- Evaluate biomarker-outcome relationships across programs

- Provide disease-drug-trial models as a tool for drug developers

**DEVELOPMENT IMPACT**
- Leverage prior quantitative information to select doses and design future trials

**REGULATORY PATHWAY**
- Critical Path modeling consortia
- Biomarker Qualification
Pediatric Pulmonary Arterial Hypertension

- No approved treatment for pediatrics

- No suitable measures for assessing effectiveness (6-minute walk distance) for possible approval of drugs for PAH in pediatric population

- The WHO Group I (idiopathic/familial PAH etiology) is considered to represent similar populations in children and adults
\( \Delta PVRI \) is Significant Predictor of \( \Delta 6MWD \) in 13 Adult Trials
ΔPVRI-Δ6MWD Relationship Can Guide Pediatric Drug Development

**Adults:** Establish relationship between ΔPVRI and Δ6MWD to specify target for pediatrics.

**Pediatrics:** Placebo controlled, dose ranging studies performed to achieve different degrees of hemodynamic benefit.

*Derive dosing based on the desired benefit in exercise capacity*

FDA CRDAC Meeting, July 29, 2010
"…for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in pediatric PAH population?"
- Yes 7, No 6 and Abstain 0

Suggestions for next steps
- Evaluate other endpoints, e.g., oxygen consumption, time to clinical worsening, right atrial pressure
- Further validation, e.g., using available data to predict study result
Good Drug Development Practices for Rare Diseases

- Understand mechanism of action, when possible
- Include biomarker of drug response for B/R
- Use innovative trial designs supported by clinical trial simulation
  - Develop disease-drug-trial models using prior data to guide future trial designs
- Use powerful methods of analyses for small clinical trials
Acknowledgements

- **SEGA Case**
  - Nitin Mehrotra
  - Elimika Pfuma
  - Amir Shahlaee

- **NuDrug Case**
  - Jane Bai
  - Carla Epps

- **PAH Case**
  - Satjit Brar
  - Pravin Jadhav

- **OCP Rare Disease Working Group**
  - Larry Lesko
  - Shiew Mei Huang
  - Joga Gobburu
  - Issam Zineh
  - Dennis Bashaw
  - Gilbert Burckart
  - Rosane Charlab Orbach
  - Angela Men
  - Lei Zhang
  - Christine Le
Perspectives on Academic-Industry-Government Collaboration on Orphan Drug Development

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
Center for Drug Evaluation and Research
Food and Drug Administration
March 2, 2011; Dallas, TX

James Cloyd, PharmD
Lawrence C. Weaver Endowed Chair-Orphan Drug Development
Thesis

Academic institutions can play a significant role in orphan drug development, but are presently limited by resources, regulatory issues, and funding.
Conventional Paradigm for Drug Discovery & Development

**PRE-CLINICAL RESEARCH**
- Academe
- Industry

**Disease Biology**
- Targets
- Drug Design
- Screening
- Optimization

**CLINICAL STUDIES**
- Industry

**PHASE 1**
- Synthesis
- Formulation
- Academic Researchers

**PHASE 2**
- Animal Testing

**PHASE 3**
- SHORT-TERM
- LONG-TERM

**IND**

**NDA REVIEW**

**NDA ACTION**
New Paradigm for Orphan Drug Discovery & Development

PRE-CLINICAL RESEARCH

- Disease Biology
- Targets
- Drug Design
- Computer-based Optimization
- Hi-throughput Screening

Industry

Academe

CLINICAL STUDIES

Synthesis
Formulation

Animal Testing

PHASE 1

PHASE 2

PHASE 3

SHORT-TERM

LONG-TERM

IND

NDA

ACTION

NDA REVIEW
Case Studies Exemplifying Opportunities and Challenges of Orphan Drug Development at Academic Institutions
Mission

Improve the care of individuals suffering from rare pediatric neurological disorders through research on new therapies, education of health professionals and health profession students, and rare diseases/orphan drugs advocacy.
CODR Model for Research

**Sources:**
- Biomedical Industry
- Government
- University Laboratories
- Generic Drugs* (repurposing)

**Translational Research**

**Pre-clinical Development**

**Phase I-II Clinical Development**

**Late Stage:**
- Phase III and Registration

**Partnerships with the Pharmaceutical Industry and Government**
CODR Research

Capabilities

- Pharmacometrics, Selected Animal Studies, Clinical Pharmacology and Phase I-IV Trials
- Bioanalytical Laboratory
- Drug Design, Synthesis, and Formulation
- Orphan Drug Regulatory Support
- Plus Resources of Medicine, Pharmacy, Vet Med, Public Health, and Biomedical Engineering
Case Studies in Academic-Industry-Government Collaboration on Orphan Drug Development

• Intravenous Topiramate for Neonatal Seizures
  ▪ Commercial partner-CyDex Pharmaceuticals
• N-acetylcysteine as Adjunctive Therapy for Adrenoleukodystrophy
Use of Topiramate for Neonates Seizures

- Seizures that occur in first 28 days of life
- Annual incidence: 4,000-7,200 live births
- Therapy: phenobarbital, phenytoin
  - Open-labeled trials without placebo: 40-45% response rate
  - Tx results in significant acute and long-term AEs
- Topiramate
  - Approved as antiseizure drug for patients ≥ 2 yrs
- Development Plan: 2008-?
  - Adult patients and volunteers (N = 32) completed
  - Amended IND to study younger patients: 2011
  - Studies in older children and pilot PK study in newborns: 2113
  - Completion of Phase III trial by 2017+)
  - Data and expertise shared with CyDex
Issues in Developing IV Topiramate

• Funding tends to be short term (1-3 yrs) with long lead times
  - FDA Orphan Grants, Epilepsy Research Foundation, NIH TRND

• Maintenance of research team (project time table = 10 yrs)

• Early and timely guidance from FDA

• Design of clinical trials-IRB approval of placebo-controlled designs

• Reliance on commercial sponsor to market product
Use of N-acetylcysteine for Late-stage Adrenoleukodystrophy (ALD): A True Orphan

- Rare genetic disorder affecting boys: prevalence 1:20,000 births
- If disease progresses to late stage, death in 3-5 yrs
- In early 2000s, UMN begins hematopoietic stem cell transplantation
- Initial results disappointing

Orchard et al, University of Minnesota, 2009

N = 8 for both groups

Percent survival

P<0.003

Months

Orchard et al, University of Minnesota, 2009
Issues in Developing NAC for ALD

1. IV formulation: Acetadote®, an orphan product (exclusivity expires 2011)
2. Who funds the clinical trials, especially long-term outcome studies?
3. Is there a mechanism to change the product label when there is no commercial sponsor?
4. Does #3 matter, if research is published in peer-reviewed journals?
5. Is there a pathway to commercialization and product support? If not, so what?
Challenges in Getting Academic Groups Involved in Orphan Drug Development

Academic Researchers and Centers
7. Often not interested in commercialization
6. Do not operate GMP and GLP facilities including animal toxicology
5. Unable to secure NIH funding for drug development
   • Particularly for re-purposing of available drugs
4. Unaware of federal programs that support orphan drug development
3. Unable to sustain development programs during funding gaps
2. Difficulty in finding industry partners interested in commercializing orphan drug

And the top reason why academicians reluctant to participate in drug development
1. Fear and loathing of regulatory requirements related to drug development and unfamiliarity with FDA procedures
Academic-Industry-Government Collaborations: Opportunities

Academic Centers

• Possess most, but not all, the personnel and facilities for drug discovery and development
• Are increasingly involved in designing and performing Phase I-IV studies
• Are expanding capabilities in drug discovery and pre-clinical development
• Are accustomed to competing for federal research funding
• Commonly serve as centers for care of those with rare disorders
• Frequently participate in clinical research consortia
Harnessing the Potential for Academic Centers in Discovery and Development of Orphan Drugs

• Expand efforts to make academicians aware of opportunities and funding for orphan drug development
• Create mechanisms to ensure program continuity
• Enhance and expand government efforts to assist academicians in developing drugs for rare and neglected disorders
e.g. assistance with INDs, GMP and GLP issues, guidance in adhering to regulations, collaboration as well as oversite
• Integrate drug discovery and development into rare disease research
  • e.g. NIH-funded Rare Disease Clinical Research Network
Perspective

• Academic centers can and should play a greater (complementary) role in the development of orphan drugs

• Early signs of growing involvement are encouraging
  • Greater awareness of rare and neglected disorders by society, government, and the pharmaceutical industry
  • Targeted funding by NIH, FDA, venture philanthropists, and patient advocacy organizations for pre-clinical and clinical development
    (NIH TRND, FDA Orphan Grants, Michael J. Fox Fdn)
  • Increasing involvement of academic groups

“Prediction is very difficult, especially of the future.”
(Niels Bohr)
## FDA Designation of Orphan Products

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FDA Next Steps

Anne Pariser, M.D.
Office of New Drugs, Rare Diseases Program
Center for Drug Evaluation and Research
Food and Drug Administration
Rare Diseases

• Rare diseases
  – One of the most rapidly expanding areas of research and clinical development
  – Remarkable progress in molecular biology, pharma/biotech science and novel target identification in recent years
  • ~7000 rare diseases – ~85% genetic
    – Increasing by ~100 new diseases/year
    – Common diseases being divided into medically plausible subsets
      » E.g., alk+ subset of NSCLC
RD Clinical Development Challenges

• Rare disorder with few patients available for study
  – Chronic, progressive, serious, life-limiting and life-threatening with unmet medical need
  – Natural history incompletely understood
    • Rate of progression variable
  – Specific endpoints, outcome measures, tools, instruments and biomarkers usually lacking
    • From regulatory standpoint, no precedent no “validated” or qualified endpoints, biomarkers or surrogates
  – Datasets (efficacy and safety) will almost always be small
    • Often limited by what is feasible
  – Often, pediatric population
  – Target tissue delivery (e.g., CNS)
Orphan Drug Act History

• ODA
  – Highly successful
    • >360 approvals, >2200 designations
    • 90% of Orphans in CDER
      – Remaining 10% in CBER
        » Mainly blood-derived products (e.g., coagulation factors)
  – In past few years
    • ~1/3 of all NME approvals are Orphan products
    • 2/3 of therapeutic biological product approvals
CDER Orphan History 2006-2010

- CDER’s marketing applications for NMEs and new biologics 2006-2010*
- Orphans are 30% of all new applications
  - 13 biologics, 22 drugs approved
  - 29 different indications
    - 10 different therapeutic areas, ~1/3 oncology
  - 28 different companies (~1/3 each S, M, L)
  - Disease prevalence ranges ~50-180,000 patients (median 43k, mean 58k)

*source: CDER/Office of New Drugs Rare Diseases Program database project, Pariser et al
CDER Orphan History (2)*

- 75% of Orphan marketing applications are approved (vs. 70% for non-rare)
- 20% of rare disease approvals are for first-in-disease indications
  - Compared to 3% for non-rare
  - 75% of first-in-disease therapies from small companies

*source: CDER/OND RDP database project, Pariser et al
Regulatory Pathways to Approval

- Two possible pathways to approval for serious/life-threatening disorders
  - Regular approval
    - Aka standard approval, full approval
  - Accelerated approval
    - Based on a surrogate endpoint “reasonably likely to predict clinical benefit”
    - For new drug products to treat serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments
Evidentiary Standard for Approval

• To be approved, all drugs (Orphan and non-Orphan) must:
  – Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  – Clinical benefit:
    • The impact of treatment on how patient feels, functions or survives
      – Improvement or delay in progression
  – Evidence of effectiveness [PHS act 505(d)]
    • “Evidence consisting of adequate and well–controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports”
Accelerated Approval

• Accelerated approval (§314.510, Subpart H)
  – “FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit”
  – Requires postmarketing verification study to verify and describe its clinical benefit.
    • Postmarketing study must also be adequate and well-controlled
    • Should be conducted “with due diligence”.
Surrogate vs. Biomarker

- Biomarker ≠ Surrogate
- Biomarkers have many potential roles
  - Exploratory/preliminary/PD activity
  - Patient or dose selection
  - Safety markers, etc.
Flexibility

• Regulations leave room for flexibility:
  – “FDA is required to exercise its scientific judgment to determine the kind and quality of data and information an applicant is required to provide for a particular drug to meet the statutory standards.” (§314.105)
CDER History 2006-2010 (3)

• Level of evidence – most programs unique and non-traditional
  – E.g., Single trial + other evidence supporting application
    • E.g., historical control, evidence in a related population, non-traditional study designs, PD endpoints
“Non-Traditional”

CSL Behring's Corifact Clears FDA On 14-Patient Trial

FDA is reaffirming its willingness to clear drugs for orphan conditions on very unusual data sets with its approval of CSL Behring's Corifact for prevention of bleeding in people with congenital Factor XIII deficiency.
What are our Plans for the Future?

• Addressing the scientific challenges
  – Institute of Medicine (IOM) October 2010
    “Rare Diseases and Orphan Products: Accelerating Research and Development”
  – Central message: Implementation of an integrated national strategy to promote rare disease research and product development
    – Collaboration
    – Timely application of advances in science
    – Appropriate use and development of trial design and analytic methods
    – Creative strategies for sharing resources
Traditional Drug Development Overview

- Basic Research/Discovery
  - Translational
  - Translational Gap
  - Pre-IND
  - IND

- Clinical
  - Ph 1
  - Ph 2
  - Ph 3

- Post-marketing
  - NDA/BLA Review
  - NDA/BLA
  - FDA Interaction

- Drug Developers

- Timeframes:
  - Undefined
  - ~5-10 years
  - ~5-10 years
  - Ongoing
A new paradigm?

Drug Development Overview

- Basic Research/Discovery
  - Natural history studies
  - Target identification
  - Modeling/pharmacometrics
  - Biomarkers
  - Repurposing

- Translational
  - Scientific Fdn
  - Clinical Pharmacology

- Pre-IND
- Post-marketing Clinical

- NDA/BLA Review

- FDA Interactions

Phases:
- Ph 1
- Ph 2
- Ph 3
- Ph 4

Timeframes:
- undefined
- ~5-10 years
- ~5-10 years
- ongoing
Opportunities for Collaboration

• Milestone meetings:
  – Pre-IND, EOP1, EOP2A, EOP2, pre-NDA/BLA
    • EOP2A meeting – to facilitate interaction btw FDA and sponsors for
      – “clinical trial design employing clinical trial simulation and quantitative modeling or prior knowledge…”
      – designing trials for better dose response estimation and dose selection…
      – related issues”
    • EOP2A especially critical for rare disease applications
Goal

• Comprehensive clinical development based on a strong scientific foundation

From here…. To there
Areas of Focus

• Clinical Pharmacology critical piece in rare disease product development
  – Understand the disease
  – Early candidate and target identification
  – Decision tree
    • Best practices by situation
  – Building drug’s entire “story”
    • PK/PD, dose identification, biomarkers at all phases of development
    • Support evidentiary standards for approval
Next Steps

• Map out clinical development programs as early as possible
  – Essential first step is scientific foundation support (e.g., natural history study)
    • Can be started even before a candidate drug is identified
  – Early and frequent communication with FDA is essential
• Make the most of early phase development
• All the evidence will be considered in rare disease applications
• Collect/develop/explore best practices to move more products into development
  – Quantitative model-based (pharmacometric) approach
  – Other tools, study designs, endpoints
FDA’s New Initiatives

• Rare Disease Review Group
  – Legislative mandate
    • Open public hearing June 2010
    • Report due March 2011, Guidance Sept 2011
• Comprehensive database analysis in progress
  – Successes, barriers, advice generation expected
  – Inform paradigms for rare disease drug development
• New Rare Diseases Program in CDER
  – Established Feb 2010
    • Support and accelerate rare disease drug development
• Numerous collaborations
  – NIH, NIH TRND, NORD
  – Workshops, scientific development
  – Repurposing database – OOPD, OCP, NIH TRND
  – Internal and External rare disease-specific training courses
    • Next investigator training course October 2011
Rare Disease Day USA

Alone we are Rare. Together we are Strong.

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  – Website
    http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm221248.htm
References

1. Formal meetings between the FDA and sponsors or applicants

2. End-of-Phase 2A Meetings

3. Providing clinical evidence of effectiveness for human drug and biological products