

Rare Disease Challenges: A Pharmacist's Perspective



- Rare diseases are chronic, progressive, debilitating, disabling, severe and often life-threatening.
- Information is scarce and research is insufficient.
- People affected face challenges such as diagnosis delay, misdiagnosis, psychological burden and lack of practical support.
- Many rare disease patients are denied their right to the highest attainable standard of health and continue to advocate their need to overcome common obstacles.

The Mission of The Office of Orphan Products Development

To assist and encourage the identification, development, and availability of safe and effective products for people with rare diseases/disorders.

Cerebrontendinous Xanthomatosis

- Genetic disorder affecting <200 U.S. patients
- Misdiagnosis is common for rare disorders
- Once diagnosed, then what? Does a tx exist?
- There is, but it's off-label. Some insurers reimburse, others don't
- Drug goes off the market, now what?
- OPD searches world locates supplies in Germany

- Arranges protocol for pts. to import drug from English exporter under the FDA Personal Importation Policy. Out of pocket payment.
- Fine for 1 yr., then German firm says they are DC'ing in 2 years.
- OPD works with NORD, Adrenoleukodystrophy Foundation, and CDER Drug Shortages to identify a firm interested in bringing a product back to the market that will only be used in 200-300 pts. And it needs to be done within 2 yrs.
- Found a firm with experience in such things AND who was interested.
- Now decide HOW?: NDA or ANDA

- ANDA route chosen as fastest. Now had to develop matching product to one that no longer exists.
- Generic Drugs expedites and facilitates due to medical necessity. Works directly with firm on validations and comparability.
- ANDA approved 2 months BEFORE supplies cease but for previously marketed indication.
- Problem with some insurers remain but drug is available.

Hereditary Orotic Aciduria (uridine monophosphate synthetase deficiency)

- Mother trying to obtain uridine for her 13 yo daughter
- < 20 living patients in the world
- Genetic deficiency of the enzyme resulting in orotic acid accumulation. The onset of sx usually occurs in first few months of life with subsequent clinical manifestations of megaloblastic anemia, orotic crystalluria, nephropathy, failure to thrive, retardation, cardiac malformations, bilateral strabismus, inability to sit unaided, and gross crystalluria, cardiac malformations, strabismus, and recurrent infections leading to *death normally prior to age 5*.

- She has epileptiform activity (irregular brain activity), as often as every 10 seconds, is insulin resistant, and has severe rises in ammonia levels sometimes leading to dehydration and a catabolic state.
- Dx in Amsterdam after visiting >30 U.S. docs.
- Tx was oral uridine only available from chemical suppliers. NOT pharmaceutical grade.
- FDA stopped shipments to hospital pharmacy when they found out it was for a patient.
- Supplier was not willing to provide m & c info to FDA to support use under IND: so NO drug.

- After call on Jan. 24, searched <http://clinicaltrials.gov/> to see if anyone was studying uridine in the U.S.
- There was one firm investigating another indication.
- Called firm asked if they could provide drug if IND was permitted by FDA: yes
- OPD contacted patient's medical geneticist to see if they would sponsor single-pt IND. Worked with review division at FDA.
- Patient rec'd uridine tx March 1 and continues today.

Drug X

- Citizen's Petition filed to withdraw Drug X
- Abbott discontinues production in late 2005.
- Calls to OPD began Jan. 2006 about patient's need in adults with subgroups of narcolepsy and ADD nonresponsive to standard therapy.
- Unique tx for adults on X >10 years: very little tolerance and low cardiovascular S.E.

- Internet search for available sources U.S. and abroad revealed none; No studies in ClinTrials.gov
- Call Abbott to see if supplies remained which these few pts might be treated with under an IND.
- Searched Drug Master File FDA database for supplier
- Only 1 Active DMF holder in the world in Switzerland
- Called to see if they would supply if a manuf. could be found in the U.S.: yes
- For import, I would need to get the ok from DEA since X was a controlled drug. They would ok if a single manuf. or pharmacy could be used.

- First pharmacy in NY wanted \$25/cap to cpd
- Identified a Pharmacy in Minnesota. Owned and operated by pharmacists. They were willing to assist though they had not manuf. drugs under IND regs before.
- DEA and Import licenses and a small amt of bulk X were purchased.
- Numerous discussions on the types of analyses that FDA chemists would require for batches.
- Agreement of 1 MD to serve as repository for manuf. docs. for all future INDs

- Developed protocol for treating physicians to EASILY apply for X under a single-pt. IND.
- First pt received Drug X in November 2009.
- Nearly 10 other physicians have since begun the IND process for their pts.
- If many pts. are identified, may approach drug company to gauge interest in taking over.

Rare Disease Challenges

- Misdiagnoses
- No therapies; no clinical trials – too rare.
- Import foreign drug via Personal Importation Policy and FDA discretion.
- Off-label uses – but out-of-pocket payment
- Possible insurer coverage as exception with MD help: Justify the cost of the therapy vs. cost of NOT receiving the therapy.
- Ask firms to provide as a Public Health need for INDs
- Drugs DC'd are sometimes being used by the rare dis community.

- Contact CDER Drug Shortage get a Determination of Medical Necessity for that use
- Many rare disorders are being tx by MDs in the U.S. through use of compounding pharmacies.
- Difficult to interest firms in developing therapies in small pops. in which not much profit may be gained.
- IND regulations revised August 2009 to permit greater access to single and small numbers of pts and to permit firms to charge.

Rare Disease Therapy Access

- Internet searches – trade and generic names
- <http://clinicaltrials.gov/> for active study for the disease
- If not your disease perhaps firm can support tx under IND/open-use if FDA ok's
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm>
- If no U.S. source, consider importation
*<http://www.fda.gov/ForIndustry/ImportProgram/ucm173751.htm>:
*www.johnbelleroyden.co.uk
- Check with Patient Advocacy Groups: *Dis. specific; NORD, Genetic Alliance
- Off-Label Uses in U.S., file appeals to insurers with M.D. justification of tx
- Push drug firm through Pt Advocacy Grp to conduct trial – indicate there's a market out there if indication is IN the LABEL.
- Office of Special Health Issues
<http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficofExternalAffairs/OficofSpecialHealthIssues/default.htm>

The U.S. Orphan Drug Act Signed in 1983

- Established the public policy that the Federal Government could/would assist in the development of treatment for rare diseases
- Created the FDA Office of Orphan Products Development



What is an Orphan Drug? U.S. Definition

An orphan drug is defined as a drug intended to treat a condition affecting <200,000 persons in the US, or which will not be profitable within 7 years following approval by the US FDA.

Orphan Diseases

- 'Rare' defined as prevalence of <200,000 in the US at time of designation request
- Includes over 6,000 rare diseases
- Collectively affects approximately 25 million Americans
- Frequently serious/life threatening

How does OOPD serve its Mission?

- Conducts scientific and regulatory review of orphan drug and humanitarian use device designation requests
- Serves as liaison for medical product companies, FDA review divisions, patient advocacy groups, and other government agencies.
- Awards and administers grants to defray orphan product clinical study costs

The FDA Office of Orphan Products Development

Works closely with:

- FDA regulatory programs
- Other PHS agencies, e.g., NIH & CDC
- Academic researchers
- Patient organizations
- Industry



U.S. Orphan-Drug Act Incentives

- 7-year marketing exclusivity to the first sponsor obtaining FDA approval of a designated drug
- Tax credit equal to 50% of clinical investigation expenses
- Exemption/Waiver of application (filing) fees (PDUFA)
- Assistance in drug development process
- Orphan Products Grant funding

How are these incentives helpful?

Tax Credits for Orphan Designated Products

- A 50% tax credit for clinical research and testing expenses

How does this help the company?

- The credit can be applied to Federal taxes incurred in prior year or for up to 20 years against future taxes

Marketing Application Fee for Orphan Designated Products

- In the Orphan Drug Act, Congress exempted designated orphan products from the user fee requirement

How does this help the company?

- In FY 2008, saved the user fee of \$1,178,000 per NDA, which would otherwise be paid to FDA whether their product is approved or not (FY 2009 \$1,247,200)

Marketing Exclusivity

- Company receives 7 years of marketing exclusivity upon FDA approval of a specific orphan drug for a specific indication.

How does this help the company?

- FDA cannot approve the same drug for the same indication during the exclusivity period

Successes Since 1983

- Designation requests submitted: 2668
- Approximately 1900 products have received orphan-drug designation.
- 330 orphan-designated products have received FDA approval for marketing.
- Approved orphan-designated products are available to treat patient populations totaling 25 million in the U.S.

Recent FDA Approvals of Designated Products

- NeoProfen (ibuprofen lysine) – Patent Ductus Arteriosus
- Soliris (eculizumab) – Paroxysmal Nocturnal Hemoglobinuria
- Cyanokit (hydroxocobalamin) – Cyanide Poisoning
- Elaprase (idursulfase) – Mucopolysaccharidosis II
- Revlimid (lenalidomide) – Multiple Myeloma
- Kuvan (saproterin) – Hyperphenylalanemia
- Norditropin (somatropin) – Noonan Syndrome
- Myozyme (alpha-glucosidase) – Glycogen Storage Disease II

Humanitarian Use Devices (HUD)

How are Devices Designated?

- A HUD is a medical device intended to treat or diagnose a disease or condition that affects or is manifested in < 4,000 individuals in the US /year
- A HUD then undergoes further FDA review to determine if it qualifies for a Humanitarian Device Exemption (HDE). FDA approval of a HDE authorizes marketing of the HUD.

Why Humanitarian Device Exemptions?

- Premarket approval applications for new medical devices must show that products are safe and **effective**.
- For very rare diseases, FDA will approve such devices if manufacturers demonstrate the safety and **probable benefit** to patients.
- This exemption from the effectiveness standard is the HDE provision.

What is a HUD? An HDE?

- HUD = Device treating a disease affecting <4,000 in the US per year (incidence)
- 192 HUD requests received – 123 granted (64%)
- 43 HDE Humanitarian Device Exemption Marketing Approval via CDRH with probable benefit outweighing the risks
 - Not for profit (unless pediatric device)
 - Device to be used with facility IRB approval
 - No comparable device marketed

Contacts

- 1. Request for HUD Designation
 - Office of Orphan Products Development (contact: Debra Lewis 301-827-0059)
- 2. HDE application
 - CDRH/ODE (contact: Stephen Rhodes)

*For more device information, go to <http://www.fda.gov/cdrh/ode/guidance/1381.pdf>

HDE Approvals

- **Enterra Therapy System** for the treatment of chronic, drug refractory symptoms, secondary to gastroparesis
- **Medtronic Activa Dystonia Therapy Kit for Deep brain stimulation (DBS) therapy** for chronic, intractable (drug refractory) dystonia
- **NeuRx DPS RA/4 Respiratory Stimulation System** electrically stimulates the muscles and nerves that run through the diaphragm which allows some spinal cord injury patients to breathe for at least four hours a day without a mechanical ventilator.

Orphan Products Grants Program

Orphan Products Grants Program

- The goal is to encourage clinical development of products, including drugs, biologics, medical devices, or medical foods, for use in rare diseases.
- Supports academic & industry sponsored research.
- Domestic or foreign, public or private, for-profit or nonprofit entities.
- The disease affecting <200,000 persons in the U.S., but orphan designation is not a grant requirement.

Orphan Products Grants Program

- A practical program: advancing marketing approvals and relevant publications that impact care for rare diseases
- Approximately 80 applications per year
- Competitive grant program – ~30% success
 - Fund 15-20 new grants per year
- Request for Application (RFA) available at <http://www.fda.gov/orphan>
- Application, review, and scoring much like NIH grant application
- Electronic submissions: Grants.gov Date: 2/4/09

OPD Grants Program: Budget

- The current annual budget for grant funding is approximately \$14 million.
- Clinical trials may be awarded in total costs:
 - Up to \$200,000 (Phase 1)/year for up to 3 yrs
or
 - Up to \$400,000 (Phase 2 or 3)/year up to 4 yrs

Overview Timeline FY 2010 Grant Program

- Application receipt date - February 4, 2010
- Earliest start date for award - November 1, 2010
- FY 2010 funding completed by September 2011

Grants Statistics

- To date, since 1983, FDA has provided >\$232 million for >460 grants for studies on rare diseases.
- Current annual budget ≈ \$14 million
- 43 FDA approved products were at least partially funded through the OOPD Grants Program.

Grant Examples

- Hydroxocobalamin/Thiosulfate as a Cyanide Antidote
- Phase 1 Alum-formulated recombinant ricin vaccine

Is the Orphan Drug Act a Success?

- More than 320 drugs and biological products for rare diseases have been brought to the U.S. market since the Act began (1983)
- In contrast, less than 10 such products came to market in the decade prior to 1983
- Products Approved through Grants Program = 43
- More than 25,000,000 patients treated
- Lots more to be done

OOPD Website

- <http://www.fda.gov/orphan>

Your Link to:

- FDA Office of Orphan Products Development
- Guidelines for designation application
- List of designated and approved orphan products
- Grant application information
- List of ongoing orphan grant studies
- Contact information for OOPD staff
- Main Telephone # is (301) 827-3666
- My direct line: 301-827-0978; or james.bona@fda.hhs.gov

