Pfizer

Orphan and Genetic Diseases Research Unit

Mission

The mission of the Pfizer Orphan and Genetic Diseases Unit (OGD) is to invest Pfizer's capital to make safe and effective medicines for those patients afflicted with orphan and genetic diseases.

We are an enthusiastic team of professionals dedicated to developing biopharmaceutical therapeutics with the technical expertise and financial backing of one of the largest pharmaceutical companies in the world.

We are building a portfolio of biopharmaceutical assets across targets, clinical diseases, and developmental stages.

Orphan Drug Act of 1983

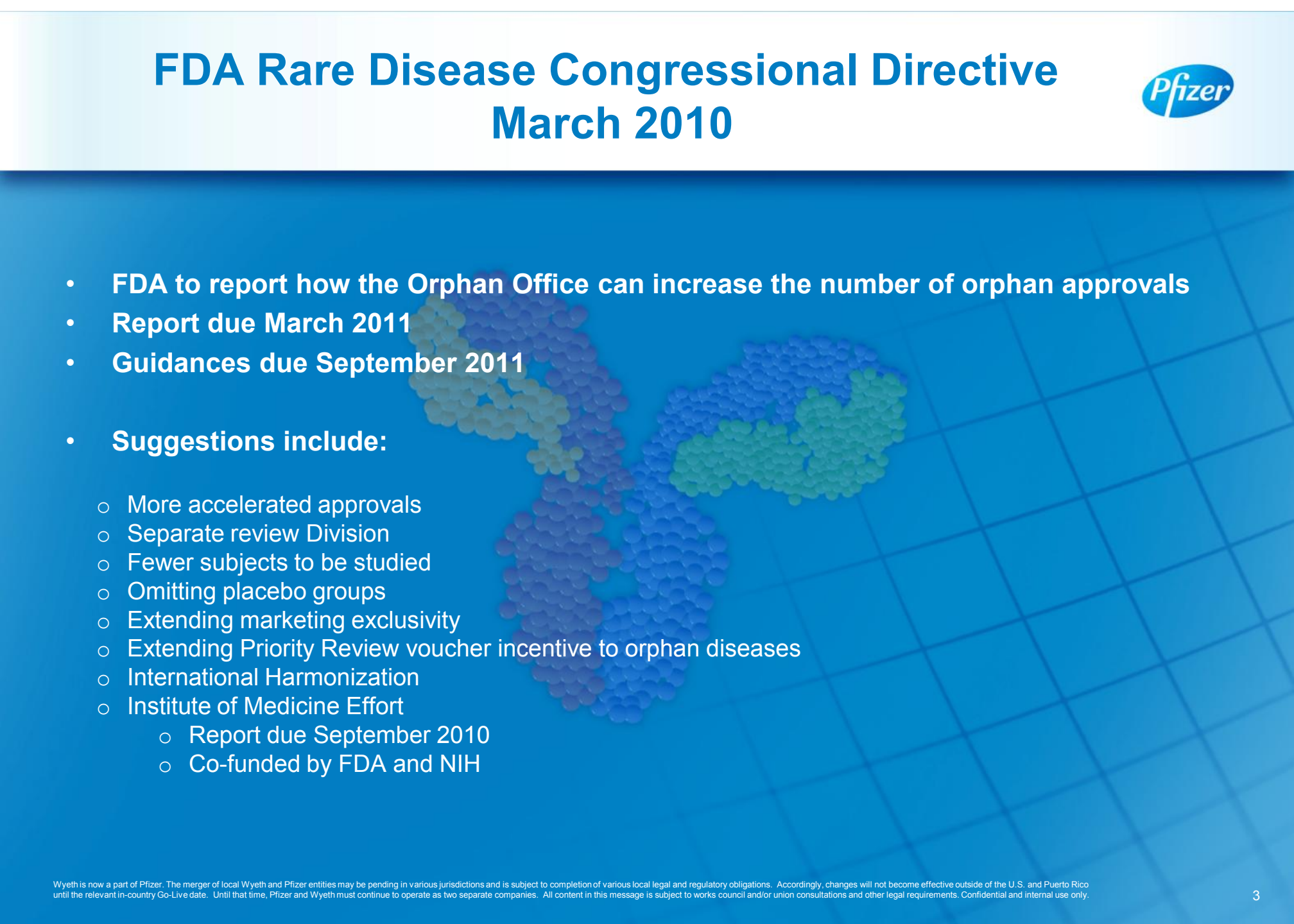
- "Orphan" Disease defined as afflicting <200,000 Americans

  Orphan drug designation under the statutes of the 1983 Orphan Drug Act (ODA) confers several advantages:

- 7 year market exclusivity upon approval, during which the FDA cannot approve another company with the same drug for the same condition
- Research grants – only ~$4M new funding per year
- Waived PDUFA fees
- Federal tax credits amount to 50% of the cost attributed to human trials

- ~7000 rare diseases
- FDA Orphan Drug Designations >2250
- Orphan Drug Approvals 359
- Orphan Diseases Treated ~ 200
- 10 % of U.S. population has an orphan disease

FDA Rare Disease Congressional Directive March 2010



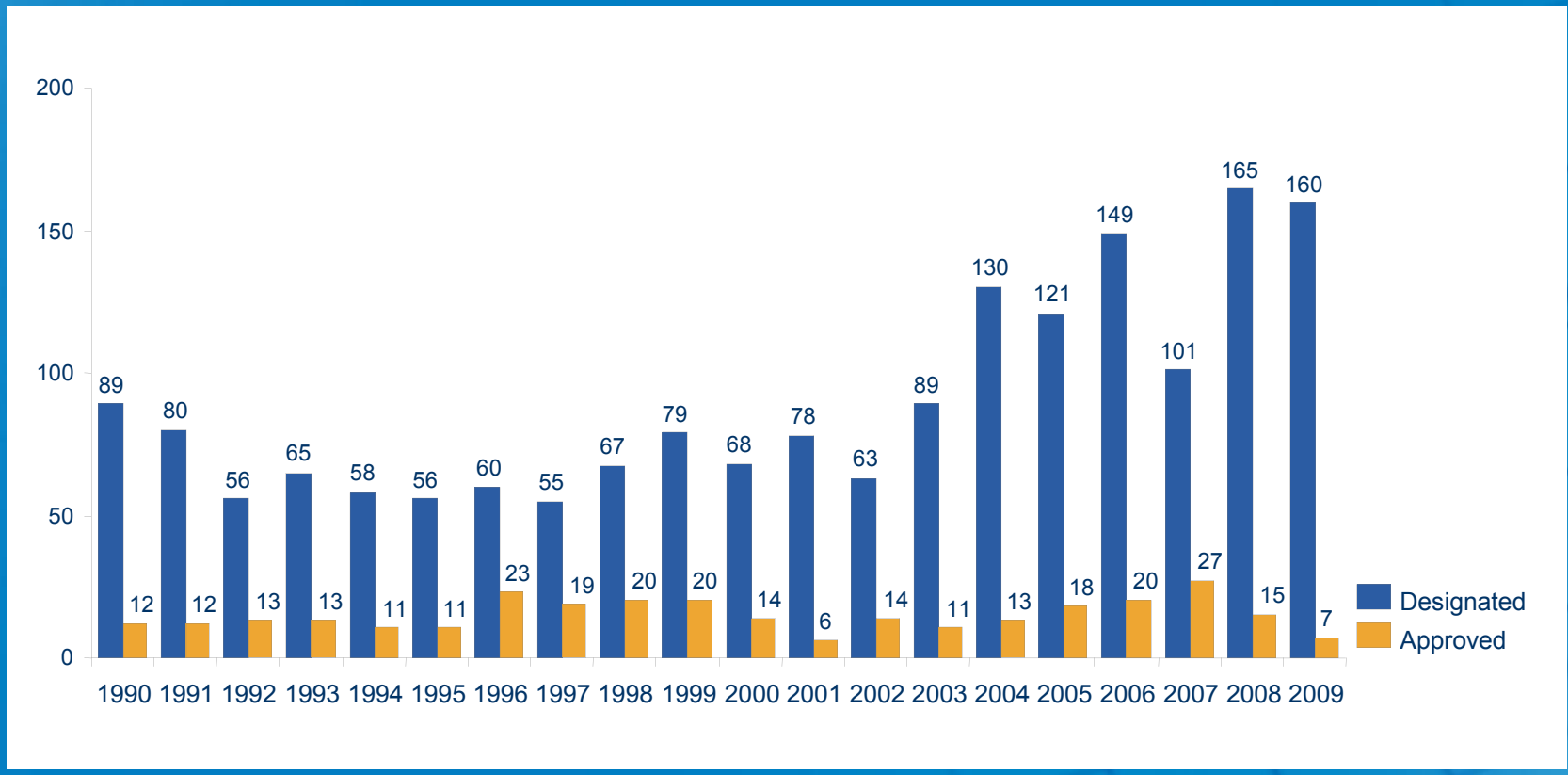
- **FDA to report how the Orphan Office can increase the number of orphan approvals**
- **Report due March 2011**
- **Guidances due September 2011**

- **Suggestions include:**
  - More accelerated approvals
  - Separate review Division
  - Fewer subjects to be studied
  - Omitting placebo groups
  - Extending marketing exclusivity
  - Extending Priority Review voucher incentive to orphan diseases
  - International Harmonization
  - Institute of Medicine Effort
    - Report due September 2010
    - Co-funded by FDA and NIH

Genetic Basis of Disease

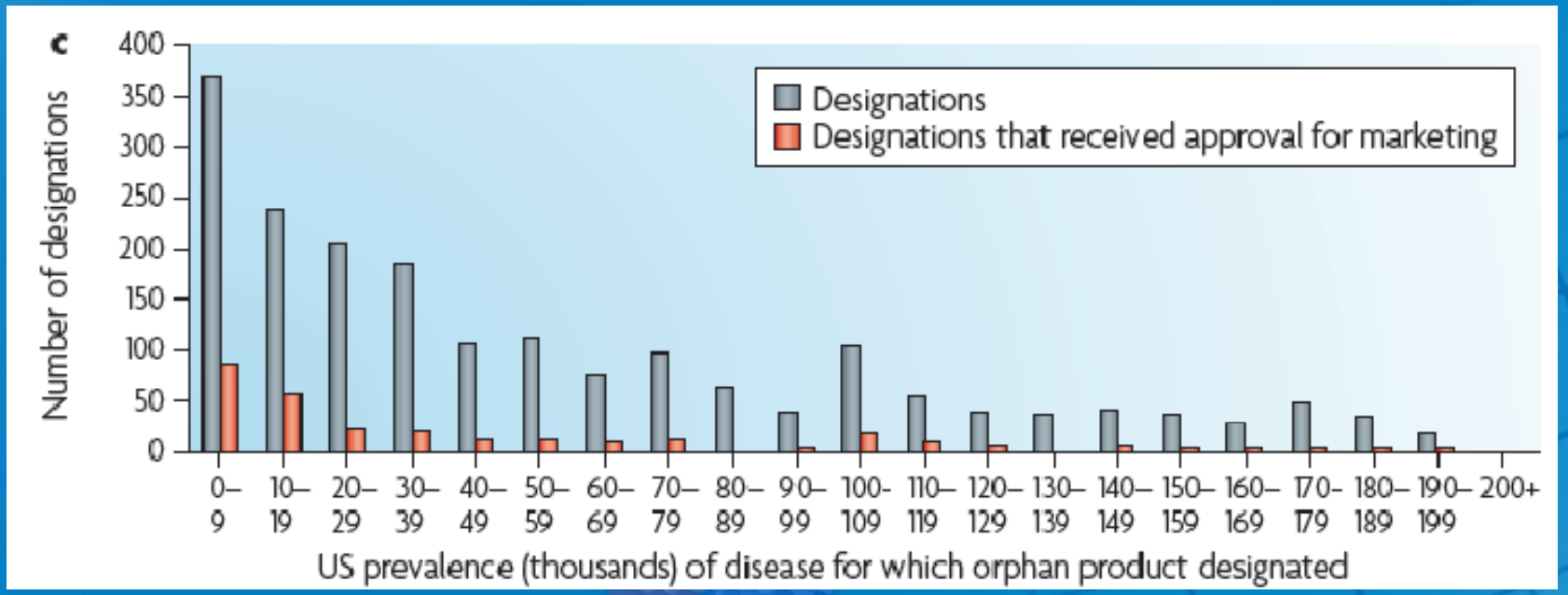
- Monogenic diseases are caused by single gene mutations
- These provide an entry point into the disease's biochemical pathway
- Target / pathway pharmacologic correction yields a higher expectation of a positive and meaningful clinical effect
- Greater probability of development success

Number of Designated and Approved Orphan Drugs in the US, 1990 – 2009



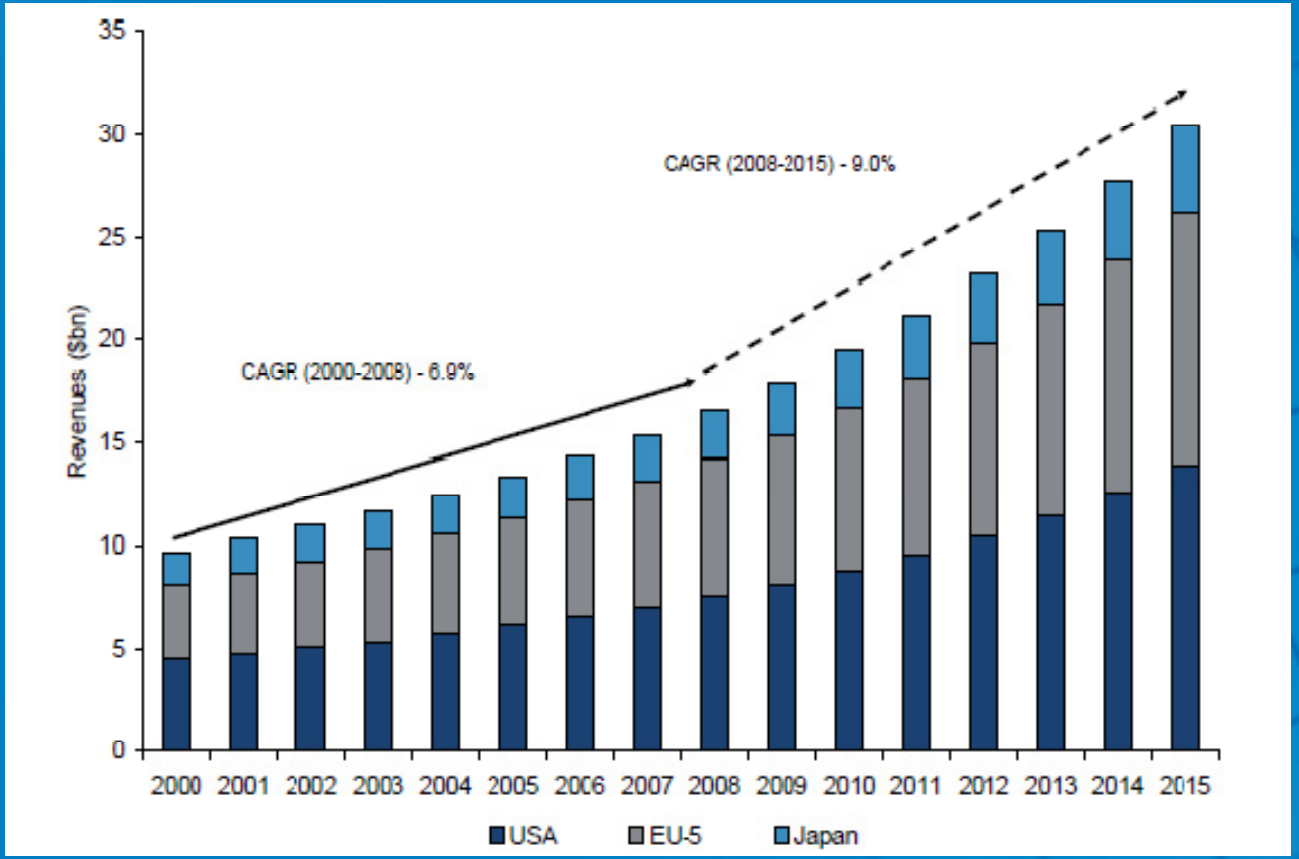
From Nature Reviews 2010

Orphan Drug Designations and Approvals by Disease Prevalence



From Nature Reviews 2010

Expected Worldwide Revenue Growth



From GBI Research Dec 2009

Inborn Errors of Metabolism – One Category of Genetic Diseases

- Genetic etiology is often a single enzyme deficiency
- Accumulation of metabolites preceding defect in the respective pathway
- Reduction in metabolites downstream of defect in the respective pathway
- Individual incidences range from ~40 to 200 per million births, or collectively 1 per 1000 births
- Presentations often neurologic or gastrointestinal
- Abnormal tone, lethargy, coma, seizures, psychomotor delay, ataxia, neuropathy
- Vomiting, hepatic dysfunction, hepatosplenomegaly, jaundice, cardiomyopathy
- Dysmorphic features

Inborn Errors of Metabolism - IV

Lysosomal Storage Disorders

- Normal function is degradation of mucopolysaccharides (glycosaminoglycans, sphingolipids, glycoproteins)
- With enzymatic deficiency, see accumulation of substrate
- Mucopolysaccharidoses – e.g. Hurler's, Scheie, Hunter, Sanfillippo, Morquio
- Sphingolipidoses - e.g. Fabry Disease, Gaucher Disease, Krabbe Disease, Niemann-Pick Disease, multiple sulfatase deficiency
- Glycoproteinoses – mannosidosis, sialidosis
- Lysosomal enzyme transport disorders – e.g. mucolipidoses
- Lysosomal membrane transport disorders – e.g. sialic acid storage disease, cystinosis

Inborn Errors of Metabolism - II

- **Amino acidemias, amino acidurias**
  - Maple syrup urine disease (elevated branched chain amino acids); phenylketonuria (PKU)
- **Organic acidemias – organic acidurias**
  - Some fatty acid oxidation disorders, ketogenesis disorders, mitochondrial disorders
- **Urea Cycle Disorders**
  - Ornithine transcarbamylase deficiency, citrullinemia
- **Carbohydrate Disorders**
  - Glycogen storage diseases, disorders of galactose, fructose

Inborn Errors of Metabolism - III

- **Mitochondrial Fatty Acid Oxidation Disorders**
  - MCAD deficiency, fatty acid transport defects, β-oxidation defects
- **Mitochondrial Disorders**
  - Cytochrome c oxidase deficiency, Kearn-Sayre syndrome
- **Peroxisomal Disorders**
  - Failure of normal catalytic functions of peroxisomes – very long chain fatty acids, pipecolic, phytanic, pristanic dicarboxylic acids, catalase activity on H2O2
  - Failure of normal anabolic functions of peroxisomes – bile acids, plasmalogen
  - Zellweger syndrome, adrenoleukodsystrophy
- **Purine and Pyridimine Disorders**
- **Porphyrias**
  - Disorders of heme biosynthesis
- **Metal metabolism disorders**
  - Wilson's Disease (copper accumulation)
  - Hemochromatosis (iron accumulation)
  - Acrodermatitis enteropathica (zinc deficiency)

Other Genetic Diseases

- **Hematology**
  - Hemophilias
  - Sickle cell anemia
  - Beta-thalassemia
  - Paroxysmal nocturnal hemoglobinuria
- **Musculoskeletal**
  - Muscular dystrophies, mutations of dystrophin
- **Connective Tissue**
  - Marfan Syndrome, mutations in fibrillin
  - Osteogenesis imperfecta, mutations in COL1A or COL2A

Oncology

  - Li Fraumeni , mutations in p53
  - Adenomatous polyposis of the colon, mutations in APC

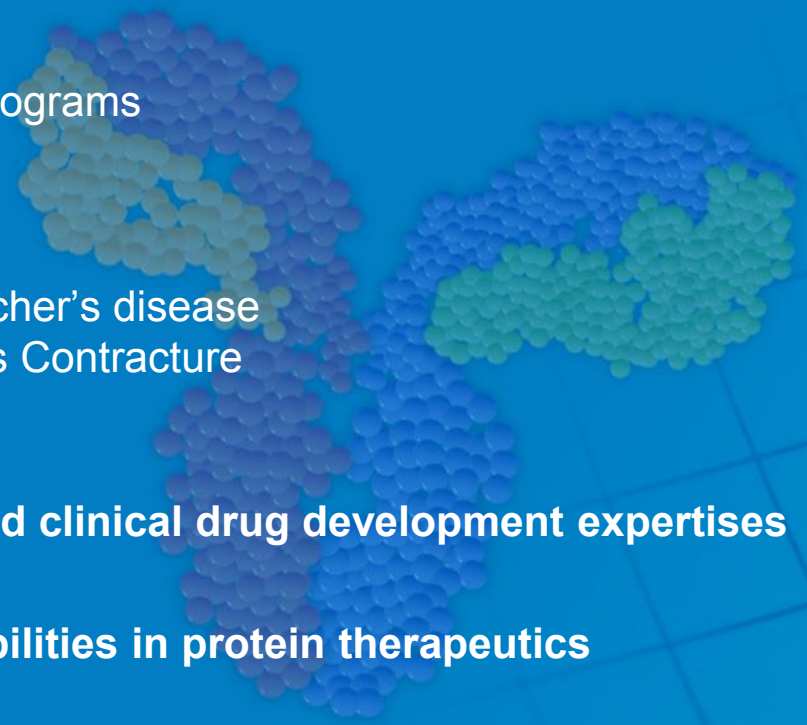
- **Renal**
  - Polycystic kidney disease
- **Pulmonary**
  - Cystic fibrosis, CFTR mutations
- **CNS**
  - Tay Sachs, mutations in hexosaminidase A
  - Huntington's Disease, mutations in Huntingtin

What Value Does Pfizer Provide?

Commercial products in Orphan Diseases

- Xyntha (ReFacto AF®) – Factor VIII – Hemophilia A
- BeneFIX® – Factor IX – Hemophilia B
- Sutent® for gastrointestinal stromal tumor (GIST) (after progression on or intolerance to Gleevec®)
- Revatio® and Thelin® for pulmonary arterial hypertension
- Genotropin® for indications in pediatric populations of Turner Syndrome, Prader-Willi Syndrome, and small for gestational age
- Somavert® for acromegaly
- Rebif® for multiple sclerosis
- Torisel for renal cell carcinoma and mantle cell lymphoma

What Value Does Pfizer Provide?



Pipeline Assets

- Muscular dystrophy programs
- Factor VII
- Factor Xa variant
- Factor IX variant
- Taliglucerase for Gaucher's disease
- Xiaflex for Dupuytren's Contracture

Unmatched preclinical and clinical drug development expertises

Proven world-class capabilities in protein therapeutics

- **Protein design**
- **Crystallography**
- **Structure / activity relationship with complex proteins, e.g. glycosylation patterns**

PROTALIX BIOTHERAPEUTICS

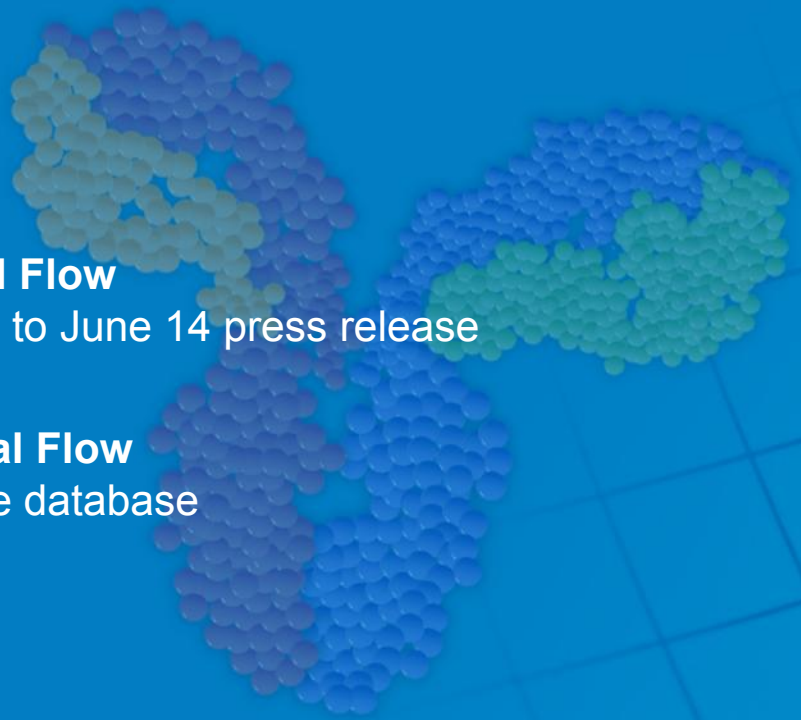
- **Protalix NYSE Amex, PLX**
  - **rhGlucocerebrosidase for Gaucher's Disease**
  - **Known as taliglucerase alfa, has orphan drug designation**
  - **NDA submitted April 2010**
  - **PDUFA date February 25, 2011**
  - **Available through expanded access protocol in U.S.**
  - **Available in Europe under Named Patient Provision**

Competing with Cerezyme (Genzyme) and VPRIV (Shire)

December 2009 publicly announced deal terms:

- **$60M upfront**
- **$55 M regulatory milestones**
- **60/40 expense and revenue split**

Assets for Unit – 3 Sources



- **Internal PFE Assets**
- **External Reactive Deal Flow**
  - Phenomenal response to June 14 press release
- **External Proactive Deal Flow**
  - Screening rare disease database

External Relationships

- **FDA Office of Orphan Product Development (OOPD)**
- **NIH**
  - Therapeutics for Rare and Neglected Diseases (TRND), a congressionally mandated effort to encourage and speed the development of new drugs for rare neglected diseases. TRND will work with internal and external investigators, focusing on preclinical drug development. TRND had a budget of $24M in fiscal 2009 and expects to ramp up its efforts rapidly.

  - Rapid Access to Interventional Development (RAID), a program which is aimed at speeding up translational research that may be commercially attractive. Direct participation by for-profit entities may not be possible, but this program may serve as a conduit for our academic collaborators.

- **NORD and other patient advocacy groups (disease-specific)**
- **KOLs**
- **Academic medical centers**

Cultural Changes for Big Pharma Working in Orphan Diseases

Developmental:

- Open to collaborations in small markets
- Close working relationship with genetically trained MDs
- International clinical trials to recruit sufficient patient subjects

Commercial:

- Little to no reliance on traditional sales forces
- More reliance on KOL networks
- More reliance on connected and proactive patient associations
- Early Access Programs
- ATU – Awareness Trial and Usage
- Patient access programs, registries
- Close relationships with patients
- Much smaller markets
- Higher prices

Business Model Validation

- **Low / absent traditional marketing costs**
- **Potential for indication expansion**
- **Proactive patient groups**
- **Premium Pricing**
  - Meaningful Clinical Effect
  - Often Pediatric Age Groups
  - Often Lethal Diseases

Highest Priced Orphan Drugs

Trade Name	Indication	Company	Launch date	Est. cost per year	2009 revenues
Naglazyme	MPS VI	Biomarin	2005	$500,000	$169M
Soliris	PNH	Alexion	2007	$400,000	$387M
Elaprase	MPS II	Shire	2006	$400,000	$353M
Cinryze	HAE	ViroPharma	2009	$375,000	$97M
Adagen	ADA deficiency	Sigma Tau	1990	$360,000	$32M
Myozyme	Pompe	Genzyme	2006	$300,000	$324M
Arcalyst	CAPS	Regeneron	2008	$260,000	$20M
Aldurazyme	MPS I	Genzyme	2003	$250,000	$155M
Folotyn	T-cell lymphoma	Allos	2009	$220,000	$15M
Cerezyme	Gaucher	Genzyme	1994	$215,000	$793M
Average				$328,000	$235M