

# Global View of the Rare Diseases Field

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# Today's Discussion

**Historical and Current Background of Rare Diseases**

**Global Activities and Needs of the Rare Diseases Community**

**Meeting the Needs of the Community**

**Translating Research Discoveries to Diagnostics and Treatments**

**“Coming Together Is A Beginning, Staying Together Is Progress,  
And Working Together Is Success.” — Henry Ford**

# **Rare Diseases - Addressing Real and Perceived Problems**

- **Very Few People Have the Condition – Patients and Families Attempt to Avoid Stigmatization, Personal Growth, Underemployment, Loneliness, Isolation, and Lack of Social Interactions (Dating, Marriage)**
- **Obtaining the Correct Diagnosis is Very Difficult with Limited Access to Rare Disease Specialists**
- **Little or No Information Available About the Rare Diseases**
- **Little or No Research Interest**
- **No Approved, Investigational or Repurposed Treatments are Available**
- **Increased Risk Acceptance/Risk Tolerance with More Risk/Benefit Assessment by Patients, Families, and Health Care Providers**
- **Little or No Hope for the Future**

# Orphan Product and Rare Diseases Legislative Activities and Considerations

- 1983 USA
- 1991 Singapore
- 1993 Japan
- 1997 Australia
- 1999 European Union, Kazakhstan,
- 2000 Taiwan
- 2008 South Korea
- 2010 Colombia
- 2011 Argentina, Chile, Peru, Russia
- 2012 Mexico, Canada
- 2013 Ukraine
- 2014 Brazil
- 2015 Philippines ( India – Interest) (China Host of IRDiRC 2015, ICORD 2017)
- 2016 Turkey, Malaysia, (Interest from Indonesia, Thailand, Vietnam)

# Background

- **> 8000 Genetic and Acquired Rare Diseases (Many More with Genetic Variability); ~ 250 New Rare Diseases Identified Each Year**
  - **~ 80% of Rare Diseases Have a Genetic Origin ( 4500 Have Known Molecular Basis of Disease or Genetic Etiology)**
  - **15% of Rare Diseases Represented by Patient Advocacy Groups**
- **Rare Disease Defined with Prevalence < 200,000 People in the USA; Prevalence < 5 in 10,000 People in the EU; <50,000 People in Japan; 0.1% of Population of Taiwan; 20,000 in South Korea; 1 in 2000 in Australia**
- **~ 4%-8% of Population Have a Rare Disease (Current Global Population - 7.4 Billion People or 296 – 592 Million People Worldwide; ~ 12 – 25 Million People in the USA; ~ 30 Million People in European Union**

# Background

## ■ Orphan Drug Act Incentives

- Research Grants, Protocol Assistance, Open Protocol for Treatment Purposes
- 7 or 10 (5+5) years Marketing Exclusivity
- Tax Credits for 50% of Clinical Trial Expenses and IND/NDA Request for Waiver from User Fees [Prescription Drug User Fee Act (PDUFA)] ~ \$2 Million USD for 2015
- Rare Pediatric and Tropical Diseases Priority Review Vouchers Available (Market Price ~ \$350 Million USD)

## ■ Average Time to Diagnosis

- USA – 3.9 - 7.6 years (4 Primary Care Physicians, 4 Specialists and 2-3 Misdiagnosis During the Diagnostic Odyssey)
- UK – 5-6 years

## ■ Reduced Trial Size – Median Trial Size for Regulatory Decision-Making

- Non-Orphan Product – 1558 Patients (Average Phase 3 = 3,549)
- Orphan Product – 538 Patients (Average Phase 3 = 761 Patients)

## ■ Average Review Time at FDA

- Orphan Drugs - 10.1 Months (Have a 27% Higher Approval Rate)
- Non-Orphan Drugs – 12.9 Months

## ■ Current Sales and Anticipated Sales of Orphan Products

- 2015 = \$102B (Non-Orphan = \$559B (15.5% of All Rx Sales))
- 2020 = \$178B (Non-Orphan = \$701B) (20.2% of All Rx Sales)
- Average Cost of Orphan Product to Patient in 2014 = \$111,820 (Median Cost = \$66,057)
- Average Cost of Non-Orphan Product to Patients in 2014 = \$23,331 (Median Cost = \$4,775)

# A Global Approach to Rare Diseases – Assessing and Addressing the Needs in Each Country

- **Identify Needs of Patients, Advocacy Groups and Foundations, Health Care Providers, Research Investigators, Industry, Payers, Government Regulatory and Research Agencies.**
- **Determine Family and Societal Needs Across the Lifespan**
- **Complete Inventory of Current Rare Diseases Activities of ALL Stakeholders in Public and Private Sectors – Many Surprises Occur at High Level of Activities with Little or No Coordination**
- **National Government Decisions to Emphasize Needs and Develop Incentives to Meet Needs of All Patients Regardless of ...**
  - **Prevalence of Diseases**
  - **Severity of Diseases in All Age Groups**
  - **Expected Lifespan of Patients with Rare Diseases**
  - **Availability of Less than Optimal Treatments or Supportive Care**
  - **Cost of Treatment**

# **Keys To Policy Formulation from National Governments in Each Country**

- Acknowledge Public Interest**
- Develop Commitment at All Levels**
- Identify Responsible Program Officials to Contact**
- Provide Adequate Financial and Personnel Support to Succeed**
- Facilitate Collaboration of All Partners in Your Country and Global Collaborations**
- Require Sharing of Resources and Data**
- Be Aware of Increased Risk Acceptance /Risk Tolerance with More Risk/Benefit Assessment by Patients, Families, and Health Care Providers**

# Various Paths to Policies

- **Legislative Mandates, Implementing Regulations and Resulting Initiatives**
- **Research, Regulatory, Health Care Services Agency Decisions and Emphasis**
- **National and Strategic Plans**
- **Administrative Initiatives and Directives**
- **Utilize Existing Programs**
- **Public Health Concerns and Priorities**

# **The Keys to Global Collaboration**

- **Develop Collaborative Efforts - Participation in Consortia, Networks, Federated Platforms of Data Gathering and Sharing and Interoperability of Data Systems**
- **Find the Gaps in Research Continuum and Close Them by Identifying Funding Streams**
- **Emphasize Rare Diseases Community and Public-Private Partnerships Including Patient Advocacy Groups**
- **Develop and Maintain Trust Among All Investigators and Research Team and With Regulatory Agencies – Visit Early and Visit Often**
- **Publicize Planned, Ongoing and Completed Research Studies and Research Advances in ClinicalTrials.gov and WHO Database of Clinical Trials**
- **Expand Disease-Specific Knowledgebase in GARD, Orphanet, and Patient Advocacy Groups.**
- **Education of Policy Makers, Regulatory Agencies, Grant Making Organizations in Private Sector and Government Agencies**

# Why The Increased Activities in Rare Diseases and Orphan Products?

- **Increase in Scientific Opportunities Identified in Basic Research and at Scientific Conferences**
- **Public Recognition that Rare Diseases Represent Global Public Health Issues**
- **Partnerships and Individual Commitments and Accomplishments Exceeded Expectations**
- **Expanded Role of Patient Advocacy Groups as Research Partners with Improved Patient Recruitment with Access to Critical Mass of Patients**
- **Increased Number of Research Investigators (Reaching a Critical Mass) Experienced in Study Design of Rare Diseases with Multi-Center (Consortia, Networks), International Clinical Trials with Small Patient Populations**
- **Increase in FDA and EMA Emphasis and Flexibility in Regulatory Decisions and Approvals (FDA Approved Products from 2008-2015= 86%(77/90) Orphan Products Used Expedited Programs vs. 39% (69/177 Non-Orphan Products)**
- **Increase in Informational Technology Use - Internet Access, Expansion of Digital Technology and Social Media, Crowdsourcing, Blogs, and Mobile Apps, All Leading to Increased Public Interest**
- **Publicity about Undiagnosed Diseases, Genetic Testing, Gene Therapy, Stem Cells, Gene Editing and Personalized (Precision) Medicine**
- **Good Business Models Exist for Rare Diseases and Orphan Products Development in Niche Markets**

# Global Needs

- **Develop Better Tools for Web-Based Recruitment and Develop Reliable Prevalence Data for Rare Diseases**
- **Identify Role of Telemedicine, TeleHealth, and Mobile Health Devices – Sensors, Wearable Devices, Mobile Apps with Smart Phones**
- **Emphasize Transitional Care from Pediatric to Adult Clinics**
- **Increase Quality of Care, Diagnostic Capabilities, and Research Infrastructure in Tertiary Medical Centers in Each Country**
- **Improve Health Literacy of Populations to Enable Information-Based Decision Making**
- **Expand Use of Consortia and Networks to Develop Natural History Studies, Pilot or Demonstration Projects with Appropriate Biomarkers, Clinical and Surrogate Endpoints for Safety and Efficacy**
- **Question of Sustainability of Emphasis with Increasing Costs of Orphan Products - > \$700,000 USD/Year; Gene Therapy Estimate of \$1 Million USD**
- **Review Beta Version of International Classification of Diseases 11 - > 5400 Rare Diseases**  
<http://apps.who.int/classifications/icd11/browse/f/en#/>

# Global Needs

- **Expand Global Collaborative Drug Development and Discovery Efforts to Span Research Continuum from Basic > Clinical > Translational Research Efforts at Industry, NCATS, NIH ICs, and Academic Centers**
- **Increase Public Private Partnerships: Utilizing Strengths of Academia, Government , PAGs, and Industry with Translational Research Emphasis to Develop Interventions – IRDiRC and ICORD**
- **Utilize the Capabilities of the Social Media Network, Facebook, Twitter, Instagram, Blogs to Connect with the Rare Diseases Community**
- **Increase Health Care Provider/Public Education in Genetics, Genomic Medicine, Pharmacogenomics with Interpretation of Genetic Testing and Sequencing Results**
- **Provide More Training Funds for Programs to Increase Number of Clinical Geneticists and Genetic Counselors**
- **Reduce Health Disparities and Provide Worldwide Access to Information and Safe and Effective Products for the Diagnosis, Prevention, and Treatment of Rare Diseases**

# Developing a Realistic Optimism

- **Expanding Pipeline with Multiple Therapies in R & D:**
  - **Small Molecules**
  - **Enzyme Replacement Therapies, Antibody Immunotherapy, Therapeutic Proteins, Gene Therapy, Stem Cells, Regenerative Medicine, RNA-based Therapies**
  - **Repurposing of Approved Products**
  - **Tissue/Organ/Bio-Systems/Body/Clinical Trial on a Micro-Chip for Safety and Efficacy**
  - **Nanotechnology**
  - **CRISPR Cas9 Gene Editing Technology**
- **Personalized or Precision Medicine Leading to Patient Stratification Through Genetic Analyses and Genetic Mutation Differences - Multiple Cancers; Cystic Fibrosis Ivacaftor (Kalydeco) and Lumacaftor/Ivacaftor (Orkambi) - Vertex; and Duchene Muscular Dystrophy – Exondys 51 (Eteplirsen) – Sarepta.**
- **Best Pharmaceuticals for Children Act – 6 months Extension To Exclusivity (Since 1998 ~ 425 Drugs have Received Pediatric Labeling Changes)**
- **Expanding Bio Pharma Commitments, Open Innovation Approaches to Drug Development Arrangements**
  - **49% Licensing**
  - **25% Co-Development**
  - **24% Mergers and Acquisitions**
  - **2% Joint Ventures (Vaccines, Oncology, Immunotherapy, Epigenetics, Tumor Microenvironment)**
- **Improving Diagnostic Capabilities with Molecular Classification of Disorders and Sequencing Results Leading to Quicker and More Accurate Diagnosis – Undiagnosed Diseases Network International and Matchmaker Exchange (Global Alliance for Genomics and Health and IRDiRC)**

# Providing Hope - Filling the Pipelines

## ■ 3876 Orphan Product Designations

- 354 in 2015 (262 in 2016)
- 287 in 2014,
- 26 in 1983

## ■ 579 Approved Orphan Products/Indications by FDA

- 42 in 2015 ( 29 in 2016 )
- 46 in 2014,
- 2 in 1983

<https://www.accessdata.fda.gov/scripts/opdlisting/ood/>

## ■ PhRMA ~ 650 Compounds in Development for Rare Diseases and 836 Compounds and Vaccines in Clinical Trials for Common and Rare Cancers

## ■ NIH Clinical Center Hospital

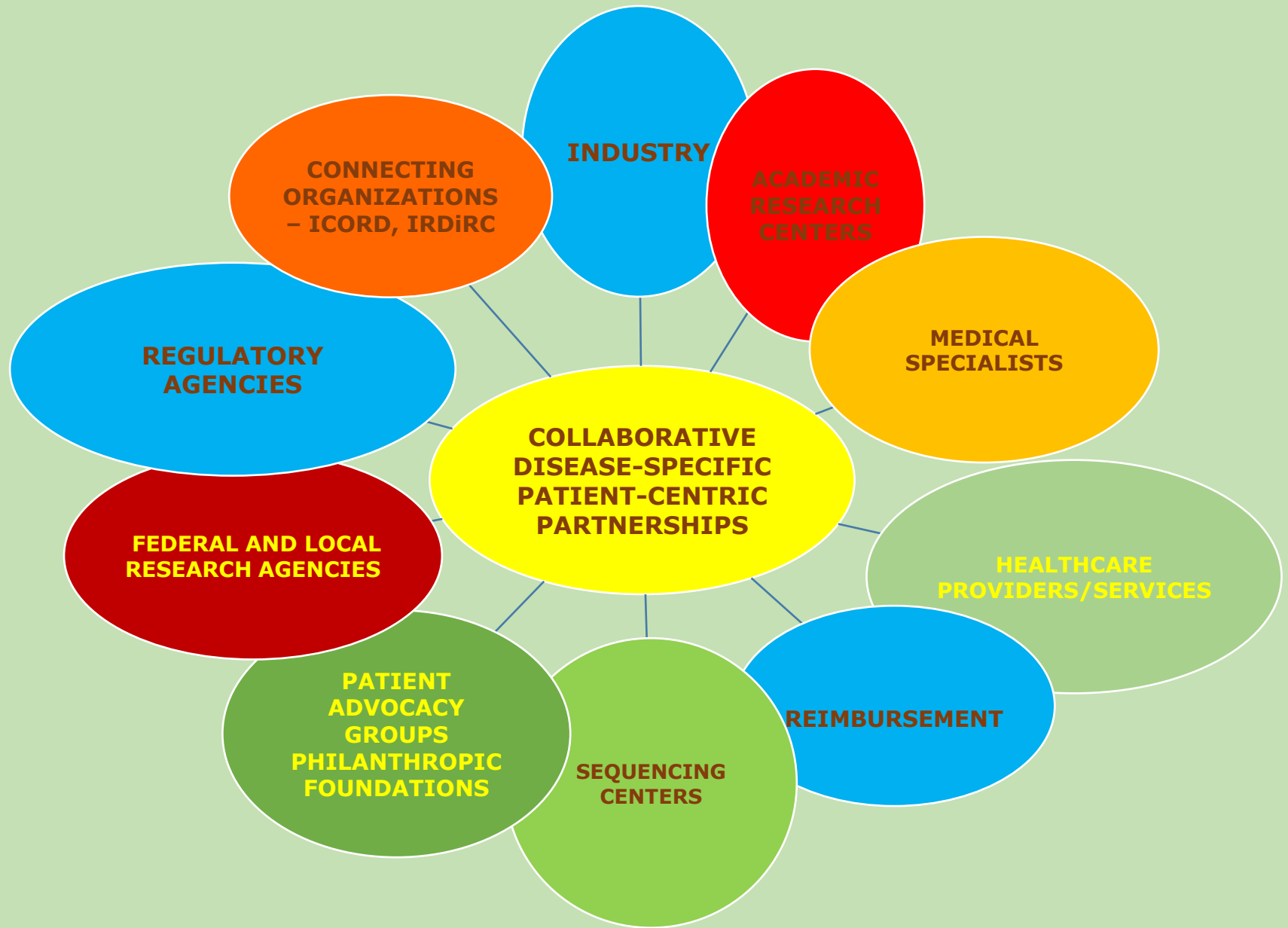
- Number of Rare Diseases – 568
- Number of Rare Diseases Protocols - 799/1,630
- NIH Investigators with Rare Diseases Focus - 315/495
- Patients with Rare Diseases in Studies at NIH – 15,653 (65% of all CC Patients)

## ■ Research, Condition, Disease Categorization (RCDC) FY 2015

- NIH Rare Diseases ~ 9400 Research Projects (\$3.639 B)
- NIH Orphan Drugs ~ 1650 Research Projects (\$785 M)
- Gene Therapy ~ 615 Research Projects (\$238 M)
- Stem Cell ~ 3900 Research Projects (\$1.429 B)
- Regenerative Medicine ~ 2500 Research Projects (\$862 M)

■ <http://report.nih.gov/rcdc/categories/>

# **A Path to Success: Partnerships and Coordinated Efforts of the Rare Diseases Community**



# Developing Pathways to Interventions Through Partnerships

Bio-specimen  
Repository

Patient  
Registry,  
CDE Portal

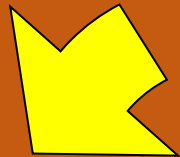
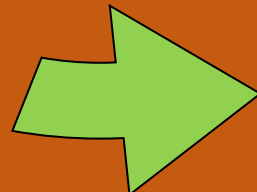
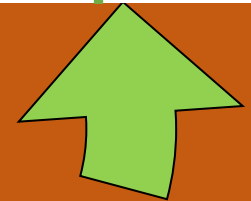
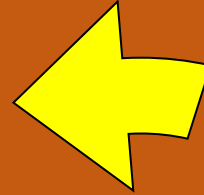
Natural History Studies,  
Clinical Endpoints, Biomarkers,  
ID Off-Label Uses for Studies,  
Big Data, EHR

Phase 4  
Post-Approval  
Studies  
Required

Interventions  
Evaluated

Generate Research  
Hypotheses

Clinical Trials  
Open,  
Recruitment  
Improves



# **Expanding the Role of Social Media/Networking and Mobile Health**

- ~ 6 Billion People Use Mobile Phones ( 87% of World's Population)**
- ~322 Million Mobile Phones in Use in USA (1/2 are Smart Phone Users)**
- Use of Online Patient Communities – Crowdsourcing, Social Media, Facebook, Google, Instagram, and Yahoo Groups, Patients Like Me, Inspire, Rare Connect, Rare Share**
- National Patient-Centered Clinical Research Network (PCORNet) and Patient Powered Research Networks**
- Utilize Patient Advocacy Groups – RDSA, African Alliance for Rare Diseases, NORD, CORD, NZORD, KORD, Genetic Alliance, EURORDIS, Rare Diseases International, Global Genes, Rare Voices Australia, Geiser Foundation, JPA, FEMEXER, Every Life Foundation, Faster Cures, and >1000 Disease-Specific Patient Organizations**

# **3rd International Conference on the Progress of Regenerative Medicine and Its Cultural Impact- Pope Francis Comments on Rare Diseases**

- **Increasing Sensitivity – Must Promote Greater Empathy in Society and Not Remain Indifferent to our Neighbor's Cry for Help When Suffering from a Rare Disease. Patients Should Not Feel Abandoned**
- **Research – Develop Students' Intellectual Abilities and Provide Unwavering Attention to Moral and Ethical Issues to Safeguard Human Life and the Dignity of the Person**
- **Ensuring Access to Care – Oppose an Economy of Exclusion and Inequality When Profit Prevails Over the Value of Human Life**
- **Globalization of Indifference Must Be Countered by the Globalization of Empathy**
- **We Must Nurture These Values and....**
  - **Make Known in the World the Issue of Rare Diseases,**
  - **Invest in Appropriate Education,**
  - **Increase Funds for Research,**
  - **Promote Necessary Legislation and an Economic Paradigm Shift,**
  - **Rediscover the Centrality of the Human Person, and**
  - **Integrate More People and Institutions Throughout the World in Rare Diseases Activities**
- **Thank you to Dr. Domenica Taruscio of ISS, Italy; Dr. Robin Smith from the Stem for Life Foundation; Cardinal Ginafranco Ravasi and Monsignor Tomasz Trafny from the Vatican's Pontifical Council for Culture**

# Moving Towards A Collaborative Global Approach – Your Participation Is Needed



**“Always Dream And Shoot Higher Than You Know You Can Do. Don't Bother Just To Be Better Than Your Contemporaries Or Predecessors. Try To Be Better Than Yourself.” *William Faulkner***

**Thank You!**

**Questions ?**

# Rare Diseases Research and Orphan Products Development: A Collaborative Dynamic Approach in USA

- **Historical Legislative Public-Private Collaborative Alliances of PAGs, Industry, Government Research, Regulatory, and Health Care Services, and Reimbursement Agencies**
- **DHEW Interagency Committee on Drugs of Limited Commercial Value (1974-1975)**
- **Report on Significant Drugs of Limited Commercial Value (1979)**
- **Orphan Drug Act (Public Law 97-414 - 1983 and Amendments)**
- **National Commission on Orphan Diseases(1986-1989)**
- **NIH Special Emphasis Panel on Coordination of Rare Disease Research(1997-1999)**
- **Rare Diseases Act (P.L. 107-280) and Rare Diseases Orphan Product Development Act (P.L. 107-281) (2002)**
- **Institute of Medicine Report Rare Diseases and Orphan Products: Accelerating Research and Development (2010), The National Academies Press**
- **Innovation for Healthier Americans Senate Health, Education, Labor, and Pensions Committee**
- **21<sup>st</sup> Century Cures - House of Representatives Energy and Commerce Committee**
  - [White Paper January 27](#)
  - <http://energycommerce.house.gov/cures>

# Expanded Role of Patient Advocacy Groups

- Establish Global Medical, Scientific, and Patient Advisory Boards
- Support Research and New Investigator Training Programs
- Provide Ready Access to Media and Educate Patients, Public, Media and Health Care Providers
- Identify Research Efforts and Translate Research Results to Communities
- Organize Research Based Conferences and Meetings for Researchers/Patients/Families/Caregivers
- Recruit Patients for Patient Registries, Bio-specimen Repositories Participation, Natural History Studies, and Clinical Studies/Trials

# Expedited Programs for Serious Conditions – Drugs and Biologics (2015 = 21/45 Novel Drugs Approved or 47% for Rare Diseases)

<u>Program</u>	<u>Qualifying Criteria:</u> Serious condition and...	<u>Features</u>
<b>Fast Track</b> (14/45 = 31%)	-Nonclinical or clinical data demonstrate potential to meet an unmet medical need -Or, QIDP (qualifying infectious disease product)	-Actions to expedite development and review --E.g., meetings -Rolling review
<b>Breakthrough Therapy</b> (10/45 = 22%) ( EU PRIority MEdicine (PRIME)	-Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinical significant endpoint over available therapies	-All Fast Track features -Intensive guidance on efficient drug development -Organizational commitment
<b>Accelerated Approval</b> (6/45 = 13%) ( EU Conditional Marketing Approval)	-Provides meaningful advantage over available therapies -demonstrates effect on surrogate or clinical endpoint that can be measured earlier than IMM (irreversible morbidity or mortality)	-Approval based on a surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit
<b>Priority Review</b> (24/45 = 53%) (EU Accelerated Assessment)	-Would provide a significant improvement in safety or effectiveness -Or, other qualifying programs  (* 27/45 =60% Used Expedited Programs)	-Shorter review clock goal for marketing applications (6 months vs. 10 months)

# **If I Am a Patient or Family with a Rare Disease, How Do We Generate Interest in our Rare Disease?**

- **Get Organized and Develop a Plan**
- **Seek Other Patients with Same or Related Disease**
- **Identify ...**
  - **Existence of Patient Advocacy Group(s) - Anywhere**
  - **Ongoing or Planned Research Studies and Clinical Trials (Encourage all Research Studies to be Included in Databases, e.g., ClinicalTrials.Gov)**
  - **Current Information Resources Including Hereditary/Genetic Information**
  - **Identify Industry, Government, Academic Researchers and Healthcare Providers with Interest**