

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/oopd/>

■ 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

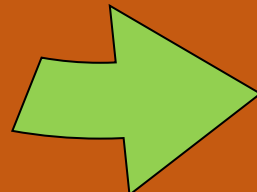
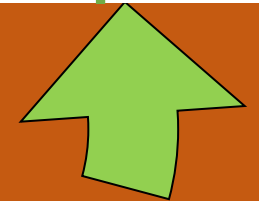
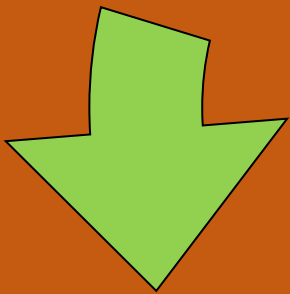
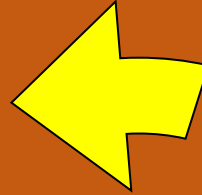
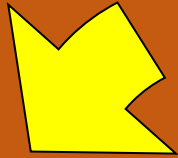
Natural History Studies,
Clinical Endpoints, Biomarkers,
ID Off-Label Uses for Studies,
Big Data, EHR

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**
- **21st 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>
Fast Track (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
Breakthrough Therapy (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
Accelerated Approval (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
Priority Review (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**