New Pathways to Breakthroughs for Progress & Patient Access

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What do we plan to cover?

1. Introduction
2. Analysis of the Rare Disease Field
3. Impact on Healthcare System Innovation
4. Involvement of Patients
5. Accelerated Pathways
6. Novel Developments on the Horizon
7. Collaboration between Stakeholders
8. The Role of Philanthropy
9. Hurdles and Challenges ahead
1. Introduction & Facts about ‘Rare’ Diseases

General public + politicians must understand: all rare diseases together are one of the Largest Global Public Health Issues!
There are over 7,000 rare diseases

- Rare diseases make up ~25% of all human diseases
- Only 5% have an on-label treatment, 95% haven’t
- >50% of rare disease patients are children, 35% of deaths in the 1st year of life
If all rare disease patients lived together in one country, it would be the third largest in the world; Imagine Patients’ Island!

RARE is defined as fewer than 5/10,000 suffering from any one rare disease

- the genetic causes for >4,000 are known, still only 400 have a treatment
- rare and complex often go together
Rare means Difficult Diagnosis too

• Without a correct diagnosis first
  • no effective treatment for the patient;
  • no development of a therapy for a group of patients.
• Time from clinical symptoms to diagnosis has been taking very long (up to 30 years+) – this is changing for the better...
• Human, financial and societal benefits in doing diagnosis right
  • Study of autopsies in New York found 30% of people treated for diseases they didn’t have;
  • Consequences of wrong diagnosis: 16% unnecessary surgery, 33% unadapted treatments, large numbers of unnecessary psychological treatments.
2. Analysis of the Field: Investment & Research Climate
Investment Climate for UMN intact

• Unmet Medical Needs incl. Rare Diseases remain an attractive target for financing and dealmaking, investors became more sophisticated.

• Much potential left in rare diseases (95% no on-label therapy).

• Growing attention for neglected diseases (e.g. Gates Foundation, Medicines for Malaria, etc...)

• Even with changing politics, little macro-economic pressure on health care field → further growth potential for stocks.

• With exceptions, small companies take on preclinical development. Large pharma look for proof-of-concept.

• Payers don’t shut the door, require more evidence. Orphan medicines to plateau at 10% of medicines budget (still far)?
Highlights in Rare Disease Research

• European orphan medicine designations using *significant benefit criterion* make up >70% of total. No such criterion in US.

• At EU designation ➞ *assumption* of significant benefit sufficient.
  
  At MAA ➞ assumption no longer enough, need *confirmation* (most often comparative data required!).

• For similar products & for non-similar alternatives in same indication: *not easy to obtain orphan designation*!

• **Cell therapy** for life-threatening or very serious diseases slowly getting more traction – but not for other indications.

• **Gene therapy** continues to be of high interest, it will be coming...
3. Impact on Health Care System Innovation
Orphan Medicines Continue to be Societal Laboratory

• It took some time to interest large biopharma, but now it is massive.

• ‘Orphan Space’ has been the laboratory to develop and test new approaches in health care for some time.

Examples:

• Combined diagnosis and therapy: testing ground for personalized health care; patient registries.

• Gene therapy: pricing a one-shot therapy?

• International Reference Networks: from diagnosis to treatment to care → research, collective clinical expertise, knowledge and innovation essential for well-functioning health care systems of the future.
Incentives Intact & Growing for UMNs:

• **Large pharma** no longer considering orphan medicines too complex or with too little ROI.

• With exceptions, they rather scout for **proof-of-concept**, leaving much promising science unused – **too risky**.

• Developments for **Unmet Medical Needs** encouraged by accelerated approvals, fast tracking, tax incentives, & first-to-market opportunity.

• **Orphan drugs**: increasing % of approved new medicines
  
  • In 2014: 41% of all novel FDA-approved drugs are for rare diseases
  
  • In 2015, **47%** or 21/45 orphan drugs
4. Involvement of Patients in Medicines Development & Regulatory System
Patients are important partners in health care, not just as users or in clinical trials!
Partnering with patients in research, preclinical development*, regulatory & access issues.

* [http://biopontisalliance.org](http://biopontisalliance.org)
Inventing the Wheel per Rare Disease?

• Rare Disease patients’ organizations to invent their own pathway and bridge over the gaps?
  • Some e.g. Cystic Fibrosis or the Duchenne Muscular Dystrophy PO’s were able to develop own pathway to therapy;
  • Most lack expertise and resources;
  • Researchers would like their work to benefit patients, but most don’t know how;
  • Why do it for each disease independently again?

• Pharma begins connecting with patients at clinical trial phase...

• Integration of patients’ organizations into early preclinical phases improves outcomes of therapy development, avoiding potential late stage failures.

• BioPontis Alliance has developed the Research Readiness Tool for Patients’ Organizations (see website).
Drug Discovery With Patients, For Patients

We are walking the talk!

BioPontis has organized Patients Integration Workshops

See http://biopontisalliance.org
Early Access to Medicines *

- Still a long way to go for rare disease patients to experience health care standards comparable with common conditions.
- Regulations have advanced, but current decisions in context of greater uncertainty, causing reservations about conclusions based on early data.
- Shifting the current paradigm of regulatory approval and access requires mutual understanding, reliable data & early inclusion of patients’ views in benefit–risk and HTA assessments.

* Pauline Evers, Lesley Greene, Mario Ricciardi, Reg. Rapporteur - Vol 13, No 2, Feb 2016
5. Accelerated Pathways
Accelerated Pathways

• An opportunity for patients because shorter clinical development/review times → faster access.
• An opportunity for developers because earlier revenues, support for post-approval collection of real-life evidence & first-to-market.
• But opportunities don’t come with guarantees
  • similarities and differences between regulations in different geographies;
  • Potential consequences of early data and regulatory review times on reimbursement potential.
• *Compassionate Use Programs* (CUPs): access to medicines without MA (patients with no treatment & unable to enter clinical trials); CUPs sometimes conditional in early access programs.
EU Accelerated Pathways

- Two pathways, discussed at Scientific Advice/Protocol Assistance:
  - **Conditional Marketing Authorization (CMA) pathway**: for seriously debilitating or life-threatening diseases, or emergencies. Sponsor to demonstrate favorable benefit-risk and yearly provide EMA with additional clinical data **up to a full dossier**.
  - **Exceptional Circumstances Marketing Authorization pathway**: reduced dataset in MAA; annual review of data, **without the need to reach a full dossier**.

- **PRIority MEdicines (PRIME) pathway** consolidates APs: reduces review time within the centralized procedure for medicines of ‘major public interest or a therapeutic innovation’, as designated by EMA.

- **ADAPT SMART** (existed before PRIME) facilitates MAPPs (**Medicines Adaptive Pathways to Patients**): experimental pilot program to MA with fewer data → **CMA for a small patient population**, later widened with real-life data; patients and HTAs take part in early review dialogue. **NOT lowering evidence standards.**
US Accelerated Assessment Pathways

- **Breakthrough therapy**: drugs with substantial benefit to patients over existing treatments (shown for clinically significant endpoints with existing clinical data)—access to senior FDA officials, if success: entrance into *Fast Track Pathway*; comparable to PRIME in Europe.

- **Fast Track**: medicines addressing UMN or improving existing treatments—more access to FDA experts to review development & rolling review of data for NDA or BLA; success means: qualified for AA or PR.

- **Accelerated Approval (AA)** since 1990; as of 2012, surrogate endpoints allowed, then with Phase IV confirmatory trials (outcome may alter approval).

- **Priority review (PR)**: medicines with benefit to patients; review of NDA or BLA by FDA in 6 months instead of standard 10 months. entrance
Similarities and Differences of APs

- While similarities between US and EU Accelerated Pathways, there are important differences: check them out.
- Pre-approval data requirements for different pathways and number of involved stakeholders add complexity.
- It is a challenge for sponsors to take advantage of the opportunities under different regulations plus fulfill regulatory requirements.
- Approval under an AP based on less (earlier) clinical evidence may create hurdles to obtain HTA/payer approval → may therefore endanger reimbursement!!
6. Novel Approaches & Therapies on the Horizon
Example: unmet medical needs 2016: applications appraisal results

Priority setting by Society for Rare Disease Research Forthcoming

Early temporary reimbursement

- Amyotrophic lateral sclerosis
- Pancreatic cancer BRCA+
- Duchenne muscular dystrophy
- Acute Lymphocytic Leukemia (ALL)
- Acute Myeloid Leukemia (AML) FLT3 +
- Recurrent and/or metastatic squamous cell carcinoma of the head and neck...
- Serious bleedings and coagulopathy with fibrinogen deficiency
- Osteogenesis Imperfecta
- Metastatic breast cancer ER+/HER2-
- Metastatic breast cancer BRCA+
- Recurrent or refractory chronic lymphocytic leukemia (17p del R/R CLL)
- Non-Small Cell Lung Cancer (L2)
- Lysosomal acid lipase deficiency
- Sporadic inclusion body myositis (sIBM)
- Alzheimer
- Chronic hepatitis C with stage 4–5 chronic kidney disease
- Alpha-1 antitrypsin deficiency (AATD)
- Clostridium difficile infection (recurrence prevention)
- Hidradenitis Suppurativa
- Hypoparathyroidism

Life threatening result
QOL result
Opportunities & Potential Developments

• Extending research goals: from a therapy for a single rare disease to a therapy for a group of rare diseases.

• Extending a therapy from one rare to several rare indications or to a common indication.

• More exact definition of prevalence and treatable patient numbers (e.g. by EU Reference Networks for Rare Diseases).

• Repurposing existing compounds, also based on off-label data; already big in oncology.

• Academia-driven comparative clinical trials and their financing.

• Setting up more registries by disease and preferably global.

• Risk-sharing in all meanings of the word.

• Advanced therapies will advance ….
7. Collaboration between Stakeholders
How to create a win-win for all stakeholders
Partnerships are Key

- All indicators to future success point to *more* partnerships.
- Partnerships, not necessarily always within industry, will develop more medicines, *increasing number of investable projects*.
- Such developments must be done *according to industry standards*, and follow regulatory rules!
- This will not only benefit patients, but also *benefit venture capital and industry*, the “sole” source of medicines.
- *Holistic investment* is key, needing multiple partnerships.
Partnerships need Shared Science AND Shared Economics

Economic & IP Sharing  
- Pro rata share in total value created

Partnered Development  
- Original IP
- Improved IP
- New IP
8. The role of Philanthropy: a Unique International New Approach
Scientific progress promises much ……
but *too few bridges to therapy* exist

➢ the gaps are in translation!
Much Progress is Stalled at Leap from Academia to Industry.

Academic researchers unrattle disease mechanisms

Biopharma companies develop & manufacture medicines

BioPontis Alliance Drug Discovery

Basic research → Discovery/Preclinical → Clinic to Market

Biopharma companies need return on investment: rare disease projects need sufficient de-risking

Proof of therapeutic effectiveness and safety (animal models or similar)

✓ Identifying the steps where patients’ input could be impactful by organizing Patients’ Integration Workshops
✓ Developing methods/practices
✓ Broadcasting/sharing with all
✓ Implementing in drug discovery process

we’re listening...
BioPontis/VIB Partnership in CMT

FOR RELEASE: September 2nd, 2016

BioPontis Alliance for Rare Diseases and VIB announce strategic partnership on rare diseases – First project on Charcot-Marie-Tooth Disease.

Ghent & Brussels, Belgium and Raleigh, NC, USA.

Today, BioPontis Alliance for Rare Diseases, a unique international nonprofit organization, and VIB, an excellence-based Life Science Research Institute in Belgium, announced a strategic partnership in rare diseases. The first program is aimed at developing a treatment for one type of Charcot Marie Tooth disease (CMT), a rare, progressive and debilitating neuropathy. There are no therapies available for CMT patients today, although it affects 1/2500 worldwide.

The partnership will advance the work of one of VIB’s premier researchers, Dr. Albena Jordanova at VIB-University of Antwerp. Patients with the form of CMT under investigation present symptoms common for many neuropathies and other neuromuscular diseases such as gradual weakness and wasting of the limbs, sensory loss and inability to do daily tasks, but have an earlier onset of the disease. Lessons learned from the research into this specific form of CMT may hopefully help develop treatments for other forms of the disease.

The partnership blends the basic research and early stage translation resources at VIB with the professional therapeutics development expertise in the rare disease field at BioPontis Alliance. The public service missions of both partners enable the combined team to take bold steps in cracking the code to this disease.
BioPontis Alliance Complementary to Other Stakeholders

- We validate feasibility of discovery science together with academic inventor(s), under leadership of industry-trained and regulatory experts.
- We coordinate collaboration with patients’ groups for each project, integrating patients into preclinical development.
- We solicit patients’ input from earliest translational phases; brings real patients’ health outcomes improvements.
- We license proof-of-concepts to biopharma companies, or put them into a NewCo; proceedings are used for new projects.
- *BioPontis funds therapy development through support from philanthropic donors, working with many committed volunteers.*
- Please contact us if you are interested to help with funding, or as volunteer (*email address on last slide*).
9. Hurdles & Challenges
Hurdles and Challenges ahead

- Addressing the clinical evidence issue using international collaboration, international registries, uniformal clinical trial standards, investigator-driven trials, more use of real-life data.
- Getting familiar with the new EU Clinical Trials Regulation.
- Understanding publication of biopharma clinical trial data submitted in MAAs (Europe: EudraCT – US: ClinicalTrials.gov).
- Involve patients through all development and access steps.
- Transparency about pricing; *fairness* is key.
- Cultivating & preserving industry’s fragile image.
- Getting rid of misconceptions...
Transparency & fairness in pricing ‘the elephant in the room’
Comments from Payers

- UK - “There is not a blank cheque. Questions are going to be increasingly asked about justification for price. More and more resistance in the future.”
- ES - “Payers really worry about orphan drugs, particularly pricing.”
- US - “Be very attentive to price because the day is coming. Price concerns are #1 oncology/specialty drugs, #2 orphan … the well is not infinitely deep.”

“Understanding comparative efficacy remains one of the biggest challenges for novel rare disease treatments”

Source: RTI health solutions webinar – Jan 2016
Biopharma Industry’s Fragile Image

• A company’s reputation turning bad does not cause less sales or market capitalisation in the short term for that company (or just a little ... some 1-5% perhaps*)

  *McKinsey’s Vivian Hunt*

  but

• Such reputation, including cases of wrong-doing, erode the total industry’s reputation, and is very rapidly affecting all: all lose collectively.

The challenge: a single company can’t change back the image. That needs to be done collectively, a long time job!
Getting rid of Misconceptions

1. Improve **awareness** about the size of public health issue taking all rare disease together.
2. Improving public understanding of **research versus development**: “patients/society paying twice”?
3. Orphan drug regulations a **success**?
4. **Avalanche** of expensive orphan drugs will bankrupt healthcare systems?
5. **Market exclusivity** for orphan drugs creates long-term rich monopolies?
6. Regulatory **standards** for orphan drugs different?
7. **Rarity valued too highly** to the expense of majority of population? What about **severity**?
Thank You For Your Attention!

Questions welcome 😊!

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