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Regulatory Dialogue to Optimise Orphan Drug Development: Patients' Experience and Perspectives

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To achieve the quickest access to as many safe, efficient and affordable medicines with a real therapeutic added value, for all rare disease patients in the European Union.
BACKGROUND
EURORDIS Position Paper on Rare Disease Research 2012
(based on broad consultation of patients/members):

- **Translational research** that leads to developing **therapeutics** for rare diseases = the **most urgent** action is needed

- Main suggested actions:
  - Supporting pre-clinical therapeutic research and proof of concept studies on orphan medicinal products and other rare diseases therapies
  - Continuing support to clinical development of designated orphan medicinal products
  - **Repurposing** existing drugs marketed but not in orphan indications with potential benefit for rare diseases (analysis of off-label uses)
  - **Training therapy developers** – reducing risk of failure
  - Supporting national and international networks organising clinical trials.
Focus on Orphan Designated Products

1. Orphan Designated Medicinal Products

- Targeting the group of products with highest chances of development: Orphan Designated Products (US and EU)
- Medical plausibility/scientific rational and development plan discussed by relevant scientific committee
- Existing regulatory advantages (protocol assistance, ...)
- Selecting best candidates by defining selection criteria:
  - Therapeutic potential
  - Degree of innovation
  - Number of existing products for the concerned condition
  - With no resources for development and no incentives
2. Preclinical research for rare diseases with no designated products

- Supporting **Phase I trials** for products with potential therapeutic benefit for rare conditions for which no orphan medicinal products have been designated – address unmet medical needs

- To generate preliminary evidence to obtain orphan designation at preclinical and in some cases clinical level

- Make it conditional to Protocol Assistance/Scientific Advice
Regulatory international cooperation – how?

• Using existing regulatory tools and mechanisms such as:
  – Parallel scientific advice & protocol assistance
  – Qualification of new methodologies for drug development
  – Qualification of biomarkers

• Harmonising procedures where they are not yet harmonised

• Developing mechanisms to adapt regulatory procedures to the evolution of science and shared them at an international level
THE CONCEPTS
FIVE CONCEPTS

• **Evidence Generation** for Rare Disease Treatments is a continuum between **pre- & post- marketing** authorisation research activities.

• **Evidence generation** is global as clinical trials and data collection both pre- & post-marketing are international.

• **Regulatory flexibility** is needed for rare diseases therapies: experience shows **EMA & FDA** are flexible but need to be more predictable, more flexible and more coordinated.

• **Focus on Effectiveness** Beyond Quality, Safety and Efficacy.

• **Enhancing the Dialogue between all Stakeholders** all Along the Product Development & Life Cycle.
Marketing Authorisation is no longer an on/off switch or a magic moment. Even less so for Orphan Medicines.

We need better and broader collection of relevant data all along the life cycle of the medicine on benefits as much as on risks, pre- & post- marketing:

- Clinical trials
- Compassionate use & Pre-Approval Patients’ Access
- Real-life studies (heterogeneous populations and real-life constraints beyond clinical trials)
- Off-label use
Focus on Effectiveness beyond Quality, Safety and Efficacy

- Anticipate more the demonstration of the therapeutic value (ex: Registries, Natural History, Good Clinical Practice Guideline on Diagnostic & Care, choice of comparator) and do it through Protocol Assistance (EMA) – Parallel to FDA? And EUnetHTA?

- Early dialogue between EMA, sponsors, medical experts, patient representatives on the Clinical Trial design to optimise resources allocation (number of patients, R&D investment, time of development) in a more proportionate manner to the expected level of evidence. This dialogue should take place as early as possible (ex: adaptive design in small population, surrogate endpoints, de-link efficacy trials and safety trials, historical control)

- Key Success Factor: Interface and dialogue between regulators (EMA & FDA) and EMA & HTA (EUnetHTA) before and after MA
Enhancing the Dialogue between all Stakeholders all Along the Product Development & Life Cycle contributes to:

- **Corporate Responsibility** = unmet medical needs, improved patient access, certain degree of transparency on cost

- **Shared-Value for all stakeholders** – companies & shareholders, patients & physicians, payers & society

- **Economic Sustainability** & Public Perception
PROPOSALS
1. Call for an Official Regulatory Flexibility
2. Common “Guidelines” or “Points to consider”
3. Scientific Advice & Protocol Assistance
4. Progressive/Adaptive Licensing / Stepwise Access for Patients
5. Stronger FDA – EMA Collaboration
6. Early dialogue
1. Call for an Official Regulatory Flexibility

- **Regulators’ decisions shows flexibility** – supported by:
  - Retrospective analysis for last 10 years experience of FDA (F.Sassinowski study for NORD, 2011 based on 135 OD MA)
  - Retrospective internal analysis by EMA for last 10 years of the types of design, number of patients recruited, etc..

- **Regulators have tools for flexibility** – supported by:
  - USA: Breakthrough Designation / Accelerated Approval (2012)
1. Call for an Official Regulatory Flexibility

- Regulators need to change and have a supportive approach: Being a “Gate Keeper” is not good enough. Regulators should become “Partners for Successful Development of Innovative Medicines”

- More intense roll-over process of Scientific Advice & Protocol Assistance before & after MA involving all stakeholders

- We need an “Official Policy on Regulatory Flexibility” from EMA and FDA to send the right message, have better visibility, predictability, attractivity for drug developers and consistency of scientific opinions

- No compromise of Q / S / E criteria, however open to adaptive design for small populations and new ways of looking at Benefits / Risks from the rare disease patients perspective – what is a meaningful benefit? what is an acceptable risk?

- Open dialogue & consultation of experts – patients & doctors
EMA has a track record of organising workshops on disease-specific areas with different stakeholders. Guidances are generated from these workshops that include “Points to Consider” or “Guidelines” for these diseases covering: natural history, trial design, endpoints, registries, comparators.

These are particularly necessary for disease areas where several products are under development or authorised. Collective dialogue between scientific assessors and stakeholders - patients’ representatives, clinicians, academic researchers, sponsor companies and HTA.

Examples: Pulmonary Arterial Hypertension (adopted 2009 + paediatric addendum 2012) or Cystic Fibrosis (adopted 2011) or Duchene and Becker Muscular Dystrophy (EMA Guideline currently available for public consultation and comment) or...
2. Common Guidelines & Points to Consider

- US Food and Drug Administration Safety and Innovation Act (FDASIA) of July 2012 has a provision on “Focused Patient Workshops” to increase inclusion of patient views in medical product regulatory opinions.

- “The new law will allow the agency to develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions.”

- A list of 20 disease areas for public comment to inform planning has been developed.

- First Workshops are taking place in April & September 2013
2. Common Guidelines & Points to Consider

- EMA should expand this successful strategy and significantly increase the number of Workshops and following “Points to Consider” or “Guidelines” in rare diseases

- EMA and FDA should coordinate their planning & topics for such workshops and collaborate in the development of Common “Guidelines” or “Points to Consider” with input from all stakeholders from EU, US and beyond

- EMA-Committee for Orphan Medicinal Products and FDA Office of Orphan Product Development should be involved in such rare disease guidelines, not only EMA CHMP and FDA CDER
3. Scientific Advice & Protocol Assistance

- EMA Scientific Advice & Protocol Assistance success and usefulness have been demonstrated (Regnstrom et al., 2010)

- Rare disease patients are invited to participate in protocol assistance dossiers: **Number of participants increases annually; influence in scientific opinions demonstrated in 50% of cases**

- FDA and EMA offer Parallel Scientific Advice – but limited number. Need more commitment and communication to promote this possibility. Need more support to increase efficiency of organisation and outcomes, which would result in more successful development of products / global orphan product development.

- Need to increase financial support to this process to ensure a roll-over process before and after marketing authorisation involving all stakeholders
4. Progressive Patients Access / Adaptive Licensing

- FDASAI (July 2012) provides “Breakthrough Designation” and “Accelerated Approval”

- EMA needs to take steps for Faster and Progressive Patients Access: for diseases which are severe, with no alternative therapies or non-satisfactory therapies

- Within current EU regulatory framework:
  - Conditional Approval/ an accelerated approval
  - Progressive enlargement of targeted population treated based on hospital prescription & inclusion criteria
  - Collection of real-life data within post-MA research activities (safety, efficacy, effectiveness) including new pharmacovigilance legislation, risk management plan…
4. Progressive / Adaptive Licensing: a pragmatic approach

- Limit “Adaptive licensing” to diseases that are severe, with no alternative therapies or non-satisfactory therapies (use same criteria as Compassionate Use)

- Limit “Adaptive Licensing” to prescription medicines restricted to hospitals: better understanding of trade-off between evidence generation and access + higher chances of collecting robust data rapidly; link to centres of expertise and registries with data reported by physicians along with patients reported outcomes

- Link “Adaptive Licensing” with compulsory Scientific Advice & Protocol Assistance from pre-clinical, phase I, II: continuum of dialogue with a “rolling-on” dialogue between sponsors and regulators on the research plan to generate the level evidence expected. Stop earlier when candidate to failure. Speed up access when promising
5. Need for stronger FDA – EMA Collaboration

- Beyond existing collaboration in Orphan Designation
  - Common Orphan Designation Application dossier
  - Monthly Coordination of Designations by Teleconference

- And in addition to the previously mentioned:
  - Parallel Scientific Advice & Protocol Assistance – more & better
  - Guidelines or Points to Consider for Clinical Trials for specific Rare Diseases or group of diseases – more & co-ordinated

- We need stronger FDA-EMA collaboration on:
  - Greater mutual acceptance of data
  - Sharing of File and Assessment at time of MA
  - Coordination of Post-MA research activities
6. Early Dialogue

- Early dialogue for horizon scanning on an unmet medical need or scoping the main clinical development & regulatory challenges for a product development, and to de-risk any development

- Early dialogue = a dialogue, at a very early stage of development, before orphan designation or protocol assistance, between 1 (or more companies) and all relevant stakeholders - Regulators, HTA, Payers, Medical Experts, Patients - on a specific product (or on a specific rare disease) to discuss “under Chattam House rules” the potential to address an unmet medical need and the optimal research, regulatory, and health policy approach
CONCLUSIONS
Conclusions

- Unilateral or common official policy on regulatory flexibility by EMA and/or FDA on orphan medicinal products would increase the number of products available to patients.

- Increased collaboration between agencies on scientific advice & protocol assistance, development of guidelines & points to consider, sharing of dossiers and data, coordination of post-marketing research activities would increase the number of products available to patients.

- Involvement of patients in all aspects of development of orphan medicinal products for rare diseases would increase the success rate of development up to marketing authorisation.

- Earlier dialogue with all stakeholders including HTA at the stage of scientific advice, would improve post-MA real patients’ access.
THANK YOU