



World Orphan Drug Congress, Geneva – Report 28 November – 1 December, 2010

Oxford PharmaGenesis™ was represented at the Congress by David Bennett. A summary of points based around several commonly asked questions is now available.

Based on presentations and private discussion, David noted the following keenly debated questions and the points that were raised. This report does not pretend to be representative of the consensus of the delegates, but is an honest attempt to set out the issues which are being discussed by the various stakeholder organizations involved in rare and orphan disorders (ODs). You may identify many contradictions! Again, these reflect the discussions that took place.

There was a clear sense of common purpose arising from the meeting and the impetus was captured by the acknowledgement that this is a golden age of genetic discovery, with the majority of OD targets being genetic – often monogenic – diseases.

But first, some top line messages:

- There may be several thousand rare diseases, but companies are often focussing on many of the same disorders.
- The rare end of the OD spectrum is over-represented.
- To ensure that patients benefit from the latest breakthroughs, the relevant community of interested parties – patient organizations, regulators, payers, clinicians and industry – must collaborate far more closely than has been the case in traditional medicine development.
- For industry, significant adaptation of traditional business practice, internal organization and culture is necessary.
- Risk reduction is a strategic goal for industry and for payers – the term ‘de-risking’ became a common theme.

What is the working definition of an OD?

- More than simply a matter of the incidence specified in OD legislation.
- Different national healthcare systems apply their own cut-offs for defining reimbursement.
- Companies active in the field consider a cluster of characteristics:
 - Highly personalized approach, especially putting the patient first – this can no longer be a cliché but central to the thinking
 - Concept of the disease community frequently highlighted

- Although the term 'niche buster' has been applied to ODs, in the context of working with the community of interested parties, including patients and their families, this term is considered inappropriate, even offensive
- If a company 'gets it right' for the patient, then the sales will follow.

What are the specific hallmarks of an OD?

Not all of the following apply to every OD but they tend to be characteristic:

- Low awareness of the OD, particularly by non-specialist healthcare providers
- Limited knowledge of natural history
- Few clinical experts
- Unclear clinical endpoints for treatment

Why is 'big pharma' suddenly interested in the OD area?

- The view that big pharma's interest is new was challenged; with some of the largest pharmaceutical companies able to claim a significant number of OD designations and approvals (for example, GSK has 14 US Food and Drug Administration [FDA] approvals for OD indications).
- Trends in the pharmaceutical industry do, however, strengthen the interest in this sector:
 - Increasing R&D expenditure not matched by the output of approved new chemical entities
 - Strong downward price pressure on many treatments for common disorders.
- ODs offer clear attractions:
 - High and currently unmet patient needs – only approximately 1% of rare disorders have a specific drug treatment
 - Shorter development times/lower costs
 - Support of regulatory and political bodies
 - Less competition, fewer high barriers to entry
 - Patients concentrated in few centres of clinical expertise.
- As a result, existing players and new entrants are applying a more systematic approach to evaluating orphan drug opportunities.
- Rare, monogenic diseases offer opportunities to understand disease pathways, which may lead to treatments for more common disorders.

Is the OD area easy for traditional pharma?

- In a word – no.
- The statistics show:
 - Increasing number of OD designations but a plateau in approvals/reimbursement.
 - Severe challenges in conducting clinical trials. ([Click here for link to 'Clinical development – what are the special issues in the OD area?'](#))
- Long timelines in the clinical development of follow-on compounds (e.g. a 15-year gap between the first enzyme replacement therapy for Gaucher disease and the follow-on product).
- Outcome studies are very difficult to conduct pre-marketing and this affects the company's ability to build Health Technology Assessment (HTA) needs into the drug development process.
- Difficulty of establishing incremental value in absence of existing treatment.

What does big pharma need to do to adapt to working successfully in the OD area?

- Close contact with patients' issues, but in the context of the regulations governing industry–patient relations.
- Long-term commitment to patient registries – there are examples of industry-supported patient outcome surveys now in their third decade. ([Click here for link to 'What is the value of patient registries/outcomes surveys'](#))
- Strategic focus based on technology platform and/or disease pathway rather than the traditional therapy area categories.
- Culture!
 - Dedicated business units/divisions for rare or orphan diseases
 - Adjust to a commercial strategy based on lower sales turnover for brands, with market share being developed on a patient by patient basis
 - Diverse business models according to each particular OD
 - Need to develop 'companion diagnostics'; some see this as crucial to success in order to gain acceptance of clinical outcomes selected as primary endpoints for studies and for market access (MA).
- Pricing and communications issues
 - Risk identified that big pharma involvement in OD area reduces the willingness of payers to reimburse requested prices
 - Potential conflict facing companies communicating high sales return from brand, at the same time convincing payers of chosen price point for the orphan drug.

What determines which ODs are targeted for drug development? What are the ingredients for success?

Figures quoted for the total number of rare disorders varied, but were within the range 6000–8000. Despite this large number, only in the case of some 200 have treatments been developed, and many companies' pipelines presented at the meeting show similar target diseases (e.g. cystic fibrosis, Duchenne muscular dystrophy).

With the experience of successfully developing and marketing drugs for ODs, certain factors seem to correlate with success, including:

- Critical mass of publications – ODs on which there are more than 600 publications are twice as likely to have a drug in development than diseases with fewer than 200 publications.
- Well-characterized natural history
- Good diagnostic infrastructure
- Treatment guidelines (to reassure payers that product will be used correctly)
- Centres of excellence
- Patient registry/outcomes survey ([Click here for link to 'What is the value of patient registries/outcomes surveys?'](#))
- Centralized, dedicated funding
- Well-developed network of disease experts comprising clinicians, scientists and patients, as well as a strong patient network (offers a huge benefit for clinical study recruitment – ([Click here for link to 'Clinical development – what are the special issues in the OD area?'](#)))
- Compassionate use access
- Monogenic diseases offer particular benefits for OD development:
 - Less variable pathophysiology

- Availability of animal models
- Proof of concept can be demonstrated in a relatively small number of patients
- Biomarkers can be available to confirm the pharmacological effect
- Replacement addresses the root cause of the disease.

There is a role for industry to partner with the community of stakeholders relevant to a particular OD to overcome some of the hurdles in this list. Patient registries in particular are expensive to set up and run. Publication of emerging knowledge of the disease process and the experience of intervention with orphan drugs also needs long-term support.

What is the value of patient registries/outcomes surveys?

- There are many strong reasons to invest effort and budget in these activities:
 - Data from traditional RCTs is often limited in ODs
 - ODs are often poorly understood
 - Patients are not well managed
 - Regulators have a need for risk minimization
 - Clinicians are looking for assurance that a new treatment with limited trial experience has an acceptable safety profile and delivers good clinical outcomes.
- Registries/surveys offer clear benefits:
 - 'Real-world' data to complement traditional clinical studies
 - Creates a network of expertise relevant to the OD
 - Helps build the peer-reviewed literature
 - Generates hypotheses for further studies
 - Data from such a source have previously changed medical understanding and practice.
- What are the important considerations governing the setting up and management of registries/outcomes surveys?
 - Funding
 - Human resourcing
 - Maintaining the quality and completeness of data
 - Performing analyses of the database
 - Preparation of manuscripts.

Clinical development – what are the special issues in the OD area?

- Patient recruitment.
- Patient willingness to accept randomization in a placebo-controlled study.
 - How can placebo-controlled studies be avoided?
 - Robust clinical endpoints
 - Well-characterized natural history.
- During development, drug supplies can be limited. Patient organizations can and do play a role in allocating product.
- Development of techniques to measure endpoints (e.g. robust methods to manage the assessment of dystrophin or measure neurological function in Friedreich's ataxia).
- Traditional clinical trial design and analysis is insensitive when dealing with heterogenous patient cohorts.
- Outcomes that are acceptable to regulatory bodies and payers must be carefully established and possibilities include:

- Slowing of disease progression
- Disease stabilization
- Regression to normal
- Prevention of signs and symptoms.
- Use of multiple endpoints for accelerated development and multiple dose groups.
- Agreement with regulatory authorities on choice of endpoints, measuring outcomes and use of biomarkers/surrogates.
- Usually, comparator treatments are not available.
- Following on from many of these points, the data available pre-MA are limited especially compared with the amount of data generated following launch. ([Click here for link to 'What regulatory incentives most help OD development?'](#))

What regulatory incentives/practices most help OD development?

1. Market exclusivity is seen as the most attractive incentive.
2. Other incentives would include omission of need for a placebo control group.
3. FDA report due in March 2011 will contain recommendations on ways to increase orphan drug approval. Possible inclusions:
 - Omission of placebo control group
 - Fewer trial subjects
 - International harmonization
4. MA for orphan drugs is often conditional, with manufacturers required to collect and submit post-marketing data. One point of discussion was to formalize this in order to allow earlier access to drugs by patients with ODs.
5. Support of patients in the MA process has a clear role in translating clinical trial statistics into meaningful benefits. Examples given of patients with restricted movement – standard tests of physical function do not tell the full story of how an apparently modest improvement can help patients regain some independence in daily living.

Market access issues

Several drivers were discussed from the perspectives of industry, regulators and payers.

- Decreasing efficiency of R&D in bringing new chemical entities to market.
- Relative reduction in public health funding given increasing demands.
- Fragmentation of payers but centralization of value assessment.
- Insufficient specialized expertise and resources in drug licensing bodies to manage MA applications.
- Difficulties in gaining acceptance of surrogate endpoints for accelerated approvals.

The end result is that, across Europe, patients do not have timely and equitable access to new orphan drugs.

1. What is the budget impact of ODs?

- Small. Typically, in large EU states, the cost of orphan drugs consumes only 2–3% of the total pharmaceutical budget.

2. What is the outlook for reimbursement of orphan drugs?

- No one is suggesting that existing reimbursed drugs should not continue to be reimbursed. In future, newly authorized drugs will be considered in a

more strategic way, with providers needing to show increased cost-effectiveness.

3. How can pricing be agreed with payers?

- Different types of innovative pricing were discussed:
 - i. Outcomes guarantee
 - ii. Capping
 - iii. Rebates

4. What are the predictors of MA success?

The following predictors are based on a study of European Medicines Agency/FDA applications between 2000–2006. If the following criteria apply, granting of MA is more likely:

- Previous experience in OD area
- Large company size
- Primary endpoint positive according to FDA reviewers – if primary endpoint is not met then the chance of being granted MA is zero!
- Interaction with regulatory authorities and taking scientific advice offered.

The following factors make no difference:

- Indication
- The primary endpoint used in the pivotal study
- Number of patients in the pivotal trial
- Rigour of pivotal trial design.

5. What are the predictors of pricing and reimbursement success?

- Global value dossier availability
- Close collaboration between leading clinicians and patient organizations
- Partnering with the best local advisors at national level
- Development of a disease-specific questionnaire
- Development of a patient registry/outcomes survey.

Further reading

Variations in access and use of orphan drugs among EU member states. Heemstra, H.E. 2010. *EJHP Practice* 16 (4), pp. 25-27

Translation of rare disease research into orphan drug development: disease matters. 2009. Heemstra, H.E., van Weely, S., Büller, H.A., Leufkens, H.G.M., de Vruh, R.L.A. *Drug Discovery Today* 14(23-24), pp 1166 – 1173

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Pfizer explores rare disease path. 2010. Catherine Shaffer. *Nature Biotechnology* 28, 881-882. doi:10.1038/nbt0910-881 News

Orphans on the rise. Nadine Kolas. 2010. *Nature Biotechnology* 28, 297-297. doi:10.1038/nbt0410-297a News

Orphan products: an emerging trend in drug approvals. 2010. Timothy Coté, Aditya Kelkar, Kui Xu, M. Miles Braun, M. Ian Phillips. *Nature Reviews Drug Discovery* 9, 84-84. doi:10.1038/nrd2546-c1 Correspondence