Orphan Drug Development – Strategic considerations

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Orphan Drug Development – Strategic considerations
Topics to discuss

• Introduction
• Understanding rarity
• EU Orphan Legislation
• Experience to date
• How to obtain orphan designation
• Drug development in rare disorders
• Transparency
• Other considerations
• Summary and conclusions
Drug Development Considerations

- Increased costs for R&D
- Time to market is getting longer
- Clinical development pressures:
  - Increased complexity of products prolonged clinical development process
  - Increased burden on and from regulators
  - Balancing risk and return in drug development

⇒ Looking for new R&D models as well as increased interest in unmet medical needs and orphan conditions
Understanding Rarity

Patients (000) Treated (US 2006)

Nexium: 17,635
Lipitor: 6,038
Singulair: 2,314
Fosamax: 2,155
Zoloft: 1,917
Plavix: 1,896
Advair-Diskus: 1,724
Celebrex: 1,213
Aranesp: 294
Epogen: 192
Gleevec: 23

Orphan Drug (<200,000 prevalence in US, < 250,000 in EU)
Understanding Rarity

Patients Treated (US 2006)

- Gleevec: 22,744
- Avastin: 20,302
- Pegasys: 18,691
- Erbitux: 10,353
- Tracleer: 6,946
- Recombinate: 2,947
- Advate: 1,907
- Cerezyme: 1,524
- Flolan: 1,497
- Remodulin: 1,377
- Tysabri: 1,069
- Fabrazyme: 702
- Soliris: 200
- Myozyme: 131
- Aldurazyme: 120
- Elaprase: 59
- Zavesca: 48
- Naglazyme: 34
EU – Rare Conditions at a glance

• Estimated 6,000 – 8,000 rare diseases exist
• Affecting approximately in total 27 to 36 million people in the EU
  - Is approx. 6-8% of the total EU population
• ~ 80% of rare diseases have identified genetic origins
  - Medical and scientific knowledge often minimal or lacking
EU Orphan Legislation
Why develop EU Regulations for Orphan Medicinal Products?

Regulation EC/141/2000:

• “Some conditions occur so infrequently that the cost of developing a medicinal product would not be recovered by the expected revenues. Therefore industry is unwilling to develop these medicines under normal market conditions”.

• “Patients suffering from these conditions should be entitled to the same quality of treatment as exists for other diseases”
History Regulation EC/141/00

- Aug 96: first draft
- Dec 99: unanimous EP acceptance
- Apr 00: entry into force
- Jun 00: first applications for OMP validated by COMP
- Jul 00: first MAAs submitted
- Aug 01: first approvals
- Mar 02: Public Summaries of Opinion
- Sep 07: 500th COMP positive opinion
- Q4 09: first time more than 100 positive opinions
- < 2014: 100th marketing authorization for an orphan designated product

Note: ~ 70 marketing authorizations with orphan designation approved in EU, but this is not equal to ~ 70 orphan indications
Orphan Designation Criteria - EC Regulation EC/141/00

- Intended for diagnosis, prevention or treatment of a life-threatening or chronic debilitating condition:

  and

  - Prevalence should be less than 5 in 10,000

  or

  - Financial - unlikely to generate sufficient return to justify investment

  and

  - No other method authorised in EC for this condition or if it is available the product has “significant benefit” for patients
Subset of a condition

• Medically plausible subset
  – Usually defined by characteristics of the drug that limit the use of the investigational medicinal product in only the subset of the patients with the disease
    – Subset is medically recognizable
    – Drug will not be effective/safe for the rest of patients population not included in the subset
EC Regulation EC/141/00

• For medicinal products only, based on the definition in Directive 2001/83 EC:
  − no devices
  − Impact advanced tissues regulations

• Sponsor should be established in the European Community; application can be made through a CRO/Consultant

• No retrospective designation
EC Regulation EC/141/00

• Market exclusivity (Article 8)
  – 10 years (Article 8.1)
  – No MAA will be accepted for the same therapeutic indication for a “similar medicinal product” (Art. 8.1)
  – Reduction in exclusivity to 6 years if criteria in Article 3 are not longer met (Art. 8.2)
EC Regulation EC/141/00

• Derogations (Article 8.3)
  – Consent of sponsor to second applicant
  – MA holder cannot supply sufficient product
  – Second OMP is “clinically superior”:
    – greater efficacy
    – greater safety
    – major contribution to patient care
Designation - When to Apply

• Application:
  − At any stage of development...
  − ... but prior to MAA submission
  − Free of charge
  − What basis

But be aware of trade name challenges
  − Orphan and non-orphan indication can not have same trade name
Designation - When to Apply

• Strategic considerations:
  – looking for access to national incentives?
  – Competition
  – Marketing considerations
  – Scientific input
  – Stage of development
Orphan designation - Incentives (2012 fees)

• Fee reduction / exemptions
  - 75% fee reduction (100% for SMEs) on Protocol assistance, initial and follow-up requests, 100% for paediatric-related assistance
  - 10% fee reduction (100% for SMEs) on Marketing Authorisation Application
  - 100% fee reduction for Inspections (pre-authorisation)
  - 100% fee reduction for SMEs on Post authorisation applications and annual fee, in the first year from granting of a marketing authorisation

• Fee incentives have been reduced over time, esp. for non-SMEs
Orphan designation - Incentives (exclusivity)

- 10-year market exclusivity (+ 2 if paediatric)
  - Protection from similar products
    - molecular structure
    - mechanism of action
    - for same indication
  - Three derogations (access to market even if similar)
    - Sponsor’s consent
    - Lack of supply
    - Clinical superiority
Orphan Drug / Orphan Medicinal Product Programs


• Not yet available in Canada and CADREAC
Orphan drugs - EU vs US

- 10 years market exclusivity
- clinical superiority clause
- research money from national authorities
- financial incentives on a national basis
- use Centralised procedure obligatory

- 7 years market exclusivity
- clinical superiority clause
- research money by NIH
- tax reduction
Orphan Drugs - EU vs US

- Max ~246,000 pts in EU affected or financially non-viable
- Fee waiver via request
- Development and Regulatory assistance
- Possible access to accelerated review
- Pediatric development obligatory for new MAA

- Max. 200,000 pts in US affected or financially non-viable
- Always fee reduction
- Development and Regulatory assistance
- Access to fast-track
- Pediatric development exempted
Supervising bodies – EU vs. US

- European Commission
- EMA
- COMP
- FDA
Experience to date
EU OMP Status – May 2012

- 1454 applications submitted
- 1021 designations with positive COMP opinion
- 989 designations granted by European Commission
- 18 final negative opinions (1%)
- 360 applications withdrawn (26%)
- Approaching 70 Marketing authorizations

Note: the large majority is based on prevalence criterion

Success rate ~70%
Number of orphan medicines with EU Positive Opinion (May 2012 COMP monthly report)
Cumulative number of orphan medicinal products with CHMP Positive Opinion
EMA Analysis

- Next slides provide data from EMA analysis in 2011
EMA Analysis

Designations per prevalence

- Less than 1 in 10,000: 12%
- Between 1 and 3 in 10,000: 36%
- More than 3 in 10,000: 52%

Source: EMA
EMA Analysis

OD by therapeutic field

Source: EMA
Orphan products authorised per therapeutic area

Source: EMA
How to obtain orphan designation
EC Regulation 141/2000

• General procedure
  - OD designation application must be submitted prior to application for MAA
  - More that one sponsor may obtain designation for the same indication
  - Market exclusivity only for sponsor who first obtains MAA: this still needs to be tested in practice
    - Co-exclusivity
    - Similar active ingredient
EC Regulation EC/847/2000

• Adopted 27 April 2000: Provisions for implementation of the criteria for designation as OMP

• Significant benefit:

  “clinically relevant advantage or major contribution to patient care”:  
  - for OMP well justified assumptions
  - for MAA demonstration needed
    - E.g in head to head clinical studies
Significant benefit and Similar Medicinal Product

• Significant benefit:
  “clinically relevant advantage or major contribution to patient care”:
  – for Orphan designation stage well justified assumptions
  – for MAA approval “demonstration” needed to maintain orphan designation
    and get access to market exclusivity

• Similar Medicinal Product: “Product containing an identical active substance
  or an active substance with the same principal molecular structural features
  (but not necessarily all of the same molecular structural features) and which
  acts via the same mechanism
  – Consider impact of compounds in same class
  – Differences in for example protein glycosylation
Application Procedure for Designation: Submission

• Notify EMEA of intention to submit 2 months prior to submission

• Application should follow European Commission guideline ENTR/6283/00 on format and content for OMPD application

• Application form and supportive documentation to be submitted in triplicate and electronically to EMEA

• No costs involved
Application Procedure for Designation: Submission

- Intent to file letter
- Submission
- Validation
- Evaluation

DAY 1

COMP MEETING

List of questions / oral explanation

Opinion

COMP MEETING

Opinion

Decision

Publication of public summary of opinion (lay language) on EMEA website

Source: EMA
Application Procedure for Designation: Validation and Review

- Application validated by EMA
- Two co-ordinators (1 EMA member and 1 COMP member) appointed for each application
- COMP adopts opinion by consensus or 2/3 majority (14 of 21) within 90 days
- Sponsor can appeal negative opinion
Application Procedure for Designation: Review, Approval, Follow-up

• Sponsor has to send annual update on development status for the duration of the OMP status:
  – administrative update
  – summary of development
  – Update on regulatory status
Appeal Procedure

• Implemented Feb. 2001

• File intent to appeal to EMA within 15 days of receipt of negative opinion

• Detailed grounds for appeal to be provided to EMA and coordinators by sponsor within 90 days of negative opinion

• Discussed at first COMP meeting after receipt

• Final opinion
Orphan Medicinal Product - MAA

• Orphan designation is reassessed at time of MAA submission

• Report in CTD Module 1.7

• Assessment of similarity if other orphan medicine is previously authorised for same designated condition (market exclusivity)
  − Assessment by CHMP working party competent, final opinion by CHMP

• Maintenance of orphan designation criteria
  − Assessment by COMP; opinion after MA opinion by CHMP
COMP and CHMP roles

Source: EMA
Drug development in rare disorders
Drug Development in Rare Disease – General Considerations

• Often, there are few experts, few treatment centers, and by definition, few patients
• Never underestimate the dedication of the patients
• Early pressure for access
• Due to rarity of disorder need:
  – to develop product globally
  – to take time to develop target product profile early
  – to develop early regulatory strategy including authority interactions
• To consider conditional approval” and/or approval under exceptional circumstances
• Randomized placebo-controlled clinical trials (RCTs) not always possible for rare diseases:
  – currently only RCTs for ~1/3 of the EU orphan drugs.
Regulatory Considerations - Efficacy

• CHMP Guideline on Clinical Trials in Small Populations
  – “in conditions with small and very small populations, less conventional and/or less commonly seen methodological approaches may be acceptable if they help to improve the interpretability of the study results”

• However
  – “most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials that follow generally accepted rules and guidance. Deviation from such standards is, therefore, uncommon and should only be considered when completely unavoidable and would need to be justified”
Regulatory Considerations - Efficacy

• CHMP Guideline on Clinical Trials in Small Populations
  – “Regulatory requirements for licensing ‘substitution products’ (notably recombinant products) may deviate from those for other compounds provided that symptoms related to the deficiency are clearly understood and that the pharmacokinetics and pharmacodynamics of the product are well documented in clinical studies”
  – “Within-patient comparisons in a relentlessly and predictably progressive disorder might provide sufficient data to support a benefit–risk assessment. However, in other situations comparative trials may be needed/expected”
Regulatory Considerations - Efficacy

• CHMP Guideline on Clinical Trials in Small Populations
  – “internal controls are the preferred option for comparative trials”
  – “under exceptional circumstances external controls (historical control) may be acceptable. In general, the absence of any control data is only likely to be acceptable if the natural course of the disease is very well known.”
(Ultra) Orphan Choice of Control Groups

- Internal controls - placebo or active comparator preferred
  - Not always possible
  - “best standard of care”
  - If active comparator does not have good own evidence likely a superiority trial will be required

- External controls – historical may be acceptable
  - Develop historical data early is essential to support control group as well as design of studies (endpoints)
  - Consider matching patients in trials with similar patients from historical database
Regulatory Considerations – Safety

- ICH Topic E1: The Extent of Population Exposure to Assess Clinical Safety
  - A placebo controlled trial allows the adverse event rate in the drug-treated group to be compared directly with the background event rate in the patient population being studied.
  - A study with a positive or active control will allow a comparison of adverse event rates to be made between the test drug and the control drug; however, no direct assessment of the background event rate in the population studied can be made.
  - A study that has no concurrent control group makes it more difficult to assess the causality relationship between adverse events observed and the test drug.
Regulatory Considerations - Safety

• ICH Topic E1
  – Usually:
    – 300-600 patients/6 months, and
    – 100 patients/1 year is acceptable
  – In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small
Protocol Assistance

• Procedure similar to Scientific Advice
• When: after OD designation, before MAA filing and in post-authorisation phase
• Develop prospective questions /answers:
  − MAA: quality, safety, efficacy and clinical superiority
  − OMP: significant benefit
Protocol Assistance

• Pre-submission meeting with EMEA
• Oral explanation “in majority of cases”
• COMP - SAWP - CHMP link to be firmly established:
  – Additional and specific expertise
• Final Advice Adopted by CHMP
• duration: 40 - 100 days.
Protocol Assistance

• 75% (100% SME) fee reduction
• No pre-evaluation of data
• Non binding for CHMP / sponsor
• No link between Coordinators and Future Rapporteur(s)
• Requests on ongoing basis
Transparency
Transparency - EMA

- Public Summary of the COMP Opinion on EMA website:
  - Orphan indication
  - Current available treatment methods
  - Estimated prevalence or financial information
  - Mode of action
  - Stage of development
  - Sponsor’s contact details

Note: prior to publishing EMA consults sponsor and patient organizations
Transparency - EMA

• MAA submission in monthly report of the CHMP for orphan designated products:
  − Active substance
  − Sponsor/applicant
  − EU designation number
  − Designated orphan indication

• Summary of opinion

• EPAR
  − Module 1.7
Transparency - Community Register

- Community Register of orphan Medicinal products on the European Commission website:
  - Sponsor
  - Product name
  - Orphan condition
Other considerations
Marketing Authorisation but no patient access?

• Reimbursement is a prerequisite for return on investment → not guaranteed upfront.

• Companies would like to file for reimbursement of an approved product speedily, but launch requires manpower, finance, knowhow and skills.

• There are 33 different countries with different reimbursement systems in Europe, not to mention the many regions with reimbursement authority.

• Rare diseases are life-threatening or seriously debilitating:
  − some EU member states reimburse upon approval
  − others wait up to 4 years and require compassionate use product from the company
  − up to 10% of annual turnover in a country can be for compassionate use.

• In some regions, reimbursement is not granted at all, in spite of the definition of an orphan drug

• Or … reimbursement for a smaller subpopulation than regulatory approval…

• Patients with rare disease for which the orphan drug is developed may not always be identified (e.g. in small countries).
Summary and Conclusions
Conclusions

• The Orphan legislation raised awareness and is working

• Very positive for development of treatment for rare diseases but global development is important
  - Significant challenges' for ultra orphan disorders in clinical development
  - Need to be proactive
  - Clinical development present with complex challenges

• Important to consider patient and market access early in development
  - diagnosis

• What is enough for approval and market access remains case to case assessment and is matter of negotiation
Penultimate slide – what have we learned

• What is an orphan disorder
• Learn how to apply for orphan medicinal product designation
• Understand the two basic approaches to support an orphan medicinal product designation application.
• Understand that orphan medicinal products include only medicinal products, not devices.
• What incentives does an orphan provide and how can these be beneficial during development and post approval
• Orphan designation does not imply reduced requirements for quality, safety and efficacy
• Examine the special regulations for rare indications involving small patient populations.
• Obtain a basic understanding of the considerations for orphan medicinal product development for the European market.
• Approval for an orphan is not always immediate patient access.
Questions?
Additional and back-up slides
Legal base

  - Criteria for designation
  - Committee (COMP)
  - Procedure
  - Incentives
- Commission communication July 2003 (2003/C 178/02)
- Commission communication on Art 8(1) and (3) (C(2008) 4077)
Committee for Orphan Medicines (COMP)

- 1 elected Chair (Dr. Kerstin Westermark)
- 1 Representative per Member State
- 3 Patients’ Representatives appointed by Eur Commission
- 3 Members appointed by Eur Commission on proposal from Agency
- one member nominated by Iceland, one by Liechtenstein and one by Norway
- one European Commission representative
Orphan/ultra-Orphan diseases present unique challenges:

- Identifying patients
- Identifying/understanding end points and how the endpoints relate to what is important to patients
- Operating globally
- Understanding the natural history of the disease

Clinical significance vs statistical significance

- Small numbers raise power requirements that can bias against demonstrating efficacy
- Reliance on the p value alone may prevent availability of treatment to patients without therapeutic options
- Support clinical significance with phase 4 studies and registries (long term real world follow up)
- Expert experience may constitute evidence of clinical benefit in rare diseases
Conditional vs Exceptional

**Conditional MA**
- Granted before all data are available
- Valid for 1 year with renewal each year
- Obligations: further clinical studies to confirm benefit/risk ratio
- Final data in dossier: Initial plus obligations makes it a normal marketing authorisation

**Exceptional Circumstances MA**
- Unlikely comprehensive data can be provided
- Valid for 5 years with annual re-assessment
- Obligations: specific procedures in particular concerning safety
- Final data in dossier: Initial plus obligations is less than normal marketing authorisation
Topics for further Consideration

• Pricing and reimbursement at Member State
• Clinical trial applications
• Assumption of Significant benefit at designation stage versus demonstrating clinical superiority concept still vague
  – Some examples e.g. Thelin, Revatio
  – Likely area of more discussion
• Co-exclusivity
• Different trade names for orphans and non-orphans
• Medical plausibility: subset vs indication
• Profitability
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