Regulatory Strategies and Practical Aspects for the Development and Authorisation of Orphan Drugs in the EU

12th DGRA Annual Congress 2010
Bonn, 15 June 2010

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Orphan Drugs in the EU

- Regulation (EC) No 141/2000 (16 December 1999)
  - Regulation (EC) No 847/2000 (27 April 2000)
- Aim: Stimulate research and development of medicinal products for orphan diseases
  - Incentives
- Products intended for treatment, prevention, or diagnosis
- Orphan designation → Development → Authorisation

EU Orphan Criteria

- Rare: Prevalence ≤ 5 in 10,000
  - De facto < 5.0 in 10,000
  - No return on investment
- Severe: life-threatening, seriously debilitating or serious and chronic condition
- No adequate treatment […] available or medicinal product offers significant benefit for the patient

Structure of the Analysis

1. Orphan Designation
2. Development of Orphan Drugs
3. Authorisation of Orphan Drugs

Survey on Orphan Designation

- Questionaire on the orphan designation process was designed
  - Identification of issues during procedure
- 103 companies who had recently obtained orphan designation were contacted
  - 91 successful enquiries
- 28 (31%) answers were obtained in total

Results Survey (I)

- EMA Validation
  - Validation issues in 74% of all cases
  - A.3 (Medical Plausibility): 42%
  - D.3 (Justification of Significant Benefit): 37%
- COMP List of Questions
  - 43% all projects
  - 42% medical plausibility, 58% significant benefit
  - No risk factor identified (clinical data, etc)

Results Survey (II)

- Orphan disease
  - Applications with products on recognized orphan diseases receive less frequent LoQ (29% vs 57%)
  - 19% particular discussion on the definition of the disease
- 71% of application comprised clinical data
  - 65% phase II or phase III

Development / Authorisation

- 48 Orphan drugs authorized at time of completion of the Master Thesis
- Analysis of data published in the EPARs
- Comparison of orphan and matched non-orphan drugs
  - Therapeutic class (e.g. oncology, CNS, …)
  - Small molecule/biological
  - Authorisation year ($\Delta \leq 3$)
- 17 matches pairs identified
  - 35% of all authorized orphans

Clinical Development of Orphan Drugs

	ORPHAN	NON-ORPHAN	STATISTICS
Main studies (No)	1.8 ± 1.2	4.4 ± 4.2	P = 0.02
One main study	41%	13% (n=2)	n.s.
Control group	70%	88%	n.s.
Active control	8%	53%	P = 0.0003

Patients in Development vs Prevalence (1)

- Prevalence of oprhan diseases published
- Number of patients included in development can be derived from EPAR
- But authorized indication frequently smaller than designated orphan condition
- E.g. Yondelis:
  - Designation: Treatment of soft tissue sarcoma
  - Authorisation: Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents

Patients in Development vs Prevalence (2)

- Nine orphan drugs have similar designated and authorized condition
- Ratio of number of patients and prevalence was calculated
- Range: 0.3% - 16%
  - High figures for very rare severe but not lethal metabolic diseases
- Meta-analysis: 1.2%
  - Fraction of all available patients included into development

Authorisation of Orphan Drugs (1)

	ORPHAN	NON-ORPHAN
Review Time [d]	197 ± 16	192 ± 19
List of Questions	1.8 ± 0.4	1.9 ± 0.8
Answer Time [d]*	128 ± 89	95 ± 56
Negative Opinions#	13%	4%

* First list of questions
# All products Jan 2000 – Jul 2008

Authorisation of Orphan Drugs (2)

	ORPHAN	NON-ORPHAN
Total authorisations	39	121
Conditional	4 (10.3%)	6 (5.0%)*
Exceptional	8 (20.5%)	1 (0.8%)

* 2 HIV, 4 oncology

(new products authorized under the centralized procedure since Q3/2005)

DANKESCHÖN

Markus Ambrosius
(Kanzlei Sträter)

Dr. Ulrich Granzer
(Granzer Regulatory Consulting & Services)

Prof. Rembert Elbers
(BfArM)

Dr. Ted Drell
(Bayer HealthCare)