Marketing authorisation of orphan medicines in Europe 2000-2013: a *13-year* experience

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1. Objectives:

There is substantial European experience with the authorisation of orphan medicinal products since the adoption of the European regulation on orphan medicinal products (Regulation (EC) No 141/2000) in December 1999.

Objectives of this study:

- Distinguishing the challenges for orphan medicine development;
- Identifying the factors associated with European marketing authorisation application (MAA) success;
- Understanding of the use of EMA Protocol Assistance (PA) as an orphan designation incentive to guide clinical orphan medicine development towards marketing authorisation.

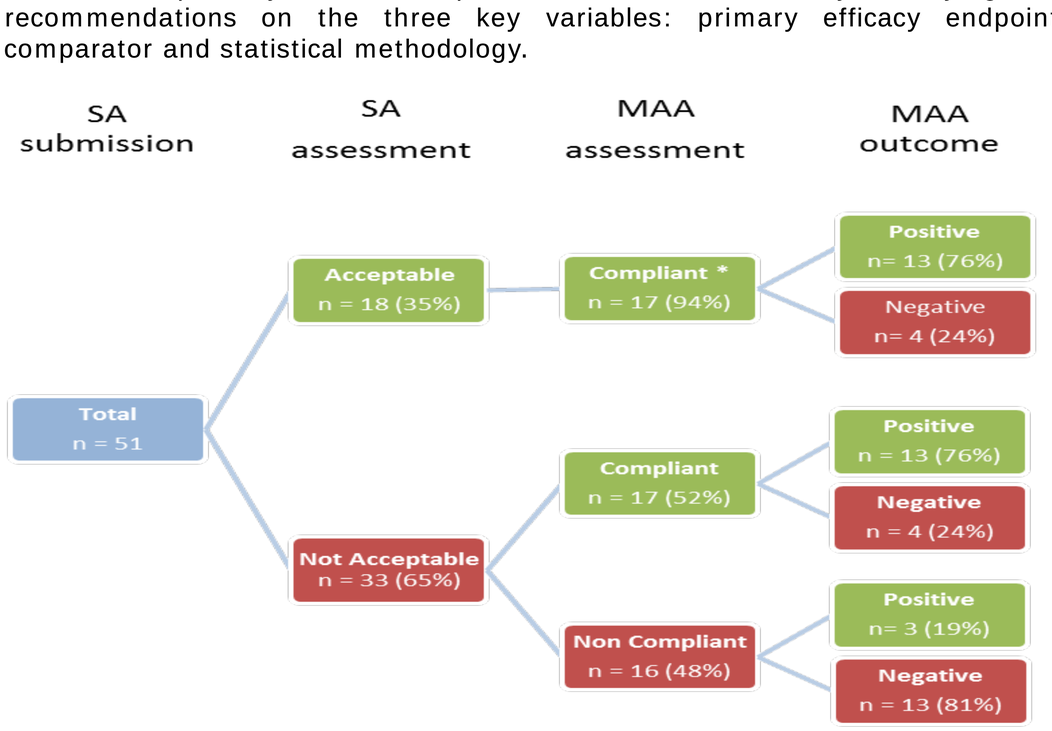
3. Distinguishing challenges of orphan development

- To identify potential challenges major objections (MO) raised at D120 of CHMP assessment in applications with a final positive outcome and applications with a final negative outcome (negative CHMP opinion or withdrawal by the applicant) were collected.
- MOs were first categorised into Quality/ Non-Clinical and Clinical Efficacy/Safety and subsequently in more informative subcategories

Major objection category (at least 5% of total)	total % (n=157)	pos MAA % (n= 104)	neg MAA % (n= 53)
Quality	**46% (73)**	**39% (41)**	**60% (32)**
Quality control of the finished product	13% (21)	11% (11)	19% (10)
Quality control of the active substance	11% (18)	9% (9)	17% (9)
Development of the finished product	8% (12)	6% (6)	11% (6)
Pre Clinical	**21% (33)**	**14% (15)**	**34% (18)**
Toxicity study design	9% (15)	7% (7)	15% (8)
Carcinogenicity	6% (10)	7% (7)	6% (3)
Toxic effects	6% (9)	6% (6)	6% (3)
Specific tests missing	5% (8)	3% (3)	9% (5)
Clinical Efficacy	**77% (121)**	**69% (72)**	**92% (49)**
Study design	32% (50)	26% (27)	43% (23)
Marginal/no clinically relevant efficacy	30% (47)	18% (19)	53% (28)
Selected population	26% (41)	22% (23)	34% (18)
Choice of endpoint	24% (38)	16 % (17)	40% (21)
Analysis/robustness of methodology	23% (36)	17% (18)	34% (18)
Pharmacodynamics, pharmacokinetics	18% (28)	13% (13)	30% (16)
Dose regimen selection	16% (25)	12% (12)	25% (13)
Trial conduct and data validity	9% (15)	5% (5)	19% (10)
Clinical usefulness	9% (15)	10% (10)	9% (5)
Inconsistent data on clinical efficacy	8% (12)	6% (6)	11% (6)
Choice of comparator	8% (12)	7% (7)	9% (5)
Inadequate duration of treatment	6% (9)	7% (7)	4% (2)
Clinical Safety	**49% (78)**	**44% (46)**	**60% (32)**
Serious adverse events	27% (42)	27% (28)	26% (14)
Size/quality long-term data	25% (39)	24% (25)	26% (14)

5. Understanding the use of PA/SA and MAA success

- EMA PA fee reduction is an incentive for orphan developments
- This fate map captures the use of EMA PA/SA and identifies clinical development changes after SA/PA assessment and MAA outcome (data source from 2008 – 2013).
- SA/PA acceptability and compliance was assessed by studying SA recommendations on the three key variables: primary efficacy endpoint, comparator and statistical methodology.



2. Data collection

- EMA databases were used for data collection.
- Dataset contained a total of 157 orphan designations, which applied for initial European marketing authorisation to the Committee for Medicinal Product for Human Use (CHMP) between 2000 and 2013.

4. Identifying determinants of MAA success

- Various potential determinants were considered and included into this analysis
- Outcome was classified as being positive (positive CHMP opinion) or being rejected (negative CHMP opinion or withdrawal of the application by the applicant).
- Company size was categorised as per Scrip list
- In a first step, simple logistic regression models were performed to identify variables with a substantial association with the outcome. In a second and final step, a stepwise logistic regression was performed with variables yielding a p value <0.1 in the simple logistic regression analyses. The significance level for entering or leaving the model was set to 5%. Two-sided p values are reported for all analyses. Odds ratios (OR) and corresponding two-sided 95 % confidence intervals [95% CI: lower; upper limit] were calculated. No corrections for multiple testing were performed.

Independent variables	Positive/Total (%), n=104/157	Simple Logistic regression		Stepwise logistic regression	
		Odds-Ratio [95%-CI]	p-value	Odds-Ratio [95%-CI]	p-value
CHMP Date Year		1.028 [0.933;1.133]	0.58		
2001 - 2004	20/31 (65%)				
2005 - 2008	36/59 (61%)				
2009 - 2013	48/67 (72%)				
Prevalence		0.978 [0.730; 1.309]	0.8807		
<0.5	32/44 (73%)				
[0.5-1)	15/27 (56%)				
[1-2)	26/41 (63%)				
[2-3)	14/18 (78%)				
[3-5]	17/27 (63%)				
Product Type			0.2357		
Biologic	23/37 (62%)	1.133 [0.472; 2.7181			
New chemical entity	52/71 (73%)	1.887 [0.870; 4.096]			
Known substance	29/49 (59%)	1			
Signifcant benefit			0.8394		
No	24/37 (65%)	0.923 [0.426;2.002]			
Yes	80/120 (67%)	1			
Therapeutic Area			0.416		
Endocrine and Metabolic Disorders	9/12 (75%)	1.149 [0.279;4.729]			
Infectious Disorders	6/9 (67%)	0.766 [0.173;3.394]			
Neurologic and Psychiatric Disord	4/9 /44%)	0.307 [0.074;1.271]			
Oncology	38/63 (61%)	0.606 [0.288;1.278]			
Other	47/65 (72%)	1			
Company Size		1.896 [1.231; 2.921]	0.0037		0.0273
Small Pharma	41/76 (54%)	1	0.0079	1	
Medium Pharma	29/38 (76%)	2.751 [1.149; 6.588]		2.507 [1.0; 6.286]	
Big Pharma	34/43 (79%)	3.225 [1.362; 7.637]		3.055 [1.193; 7.821]	
SA/PA given			0.8305		
No	47/70 (67%)	1.076 [0.552; 2.094]			
Yes	57/87 (66%)	1			
SA/PA compliance			0.0007		0.0022
Non-Compliant to SA	10/28 (36%)	0.253 [0.103; 0.624]		0.228 [0.089; 0.585]	
Compliant to SA	37/46 (80%)	1.875 [0.791; 4.447]		1.349 [0.540; 3.367]	
No-SA (n=71) & SA not applicable (n=13)	57/83 (69%)	1		1	

6. Summary and conclusions:

- **Section 3:** The analysis on major objections gives an important indication of the main challenges for a successful orphan medicines development. A higher number of major objections are raised on clinical study design, selected trial population, choice of trial endpoint and robustness of trial methodology in applications with a negative MAA outcome.
- **Section 4:** Determinants for successful marketing authorisation of orphan medicines were determined to be company size and compliance to SA/PA recommendations. Smaller companies continue to be less successful at marketing authorisation for orphan medicines. Compliance with SA/PA as one of the factors is of special interest keeping in mind that PA fee reduction is one of the pre-marketing incentives for orphan medicines development.
- **Section 5:** PA/SA provides advice on the development of orphan medicines. The fate map presented identified how this incentive can be successfully used to gain a positive marketing authorisation in showing a positive effect of compliance with protocol assistance on the change of the development programme.

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