The quantity and quality of evidence supporting European marketing authorisation of orphan drugs: Comparison of rare oncology versus rare disease

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Background

The quality and quantity of evidence for orphan drugs is often variable for rare disease and rare oncology and poses challenges for rigorous assessment.

Objective

To evaluate evidence for orphan drugs supporting European marketing authorisation (EMA) for rare disease and rare oncology.

Methods

Comprehensive review of orphan drugs with EMA on the community register of orphan medicinal products up to June 1, 2018.

Results

102 36 RO 66 RD
medicines

121 44 RO 77 RD
orphan indications

59
manufacturers

Only nine indications achieved peadiatric extension of market exclusivity.

139 46 RO 93 RD
identified main studies

28% 37% RO 24% RD
28% (39) were single-arm cohort studies

309 vs **142**
Average sample size was more than double for RO (309) versus RD (142)

100
controlled trials

38% 62% RO 28% RD
active control

72% 38% RO 86% RD
double-blind

Full EMA
39 14 RO 25 RD
medicines

Conditional EMA
16 8 RO 8 RD
medicines

Exceptional EMA
13 2 RO 11 RD
medicines

Commitment to a registry specified
23 2 RO 21 RD
medicines

Conclusions

Although orphan drug (OD) development is challenging, incentives have enabled a diversity to achieve EMA, typically from manufacturers of a single OD with a single indication. Rare oncology (RO) approval is frequently supported by a single, large, pivotal RCT often open-labelled with active control. In contrast, rare disease (RD) have multiple, smaller studies often double-blinded with placebo. Conditional EMA is more common for RO whereas exceptional EMA is more common for RD. Conditional EMA often occurred for RO with ongoing phase-three pivotal studies. In the absence of ongoing studies for RD, exceptional EMA was often granted with the requirement to establish a registry. This review demonstrates a flexible, diverse approach to the evidence and regulatory approval of ODs, with stark differences between RO and RD. Subsequent assessment of the evidence for access should adopt a bespoke approach with a framework beyond standard quality criteria.

Table 1: Data extraction for orphan drugs on the community register

up to June 1, 2018

	All			Rare Oncology			Rare Disease		
	n	N	%	n	N	%	n	N	%
Orphan Indications	121			44	121	36.4%	77	121	63.6%
Paediatric Extension	9	121	7.4%	1	44	2.3%	8	77	10.4%
Orphan Medicines	102	121	1.19%	36	44	1.22%	66	77	1.17%
Manufacturers	59	102	1.73%	21	36	1.71%	48	66	1.38%
PASS Requirement	36	102	35.3%	13	36	36.1%	23	66	34.8%
Conditional MA	16	102	15.7%	8	36	22.2%	8	66	12.1%
Exceptional MA	13	102	12.7%	2	36	5.6%	11	66	16.7%
Conditions for Safe and Effective Use	11	102	10.8%	4	36	11.1%	7	66	10.6%
Registry Commitment	23	102	22.5%	2	36	5.6%	21	66	31.8%
Trials	139	121	115%	46	44	105%	93	77	121%
Randomised Controlled	100	139	71.9%	29	46	63.0%	71	93	76.3%
Double Blind	72	100	72.0%	11	29	37.9%	61	71	85.9%
Placebo Controlled	66	100	66.0%	13	29	44.8%	53	71	74.6%
Active Controlled	38	100	38.0%	18	29	62.1%	20	71	28.2%
Cohort	39	139	28.1%	17	46	37.0%	22	93	23.7%
Dose Comparison	7	139	5.0%	1	46	2.2%	6	93	6.5%
Crossover	3	139	2.2%	0	46	0.0%	3	93	3.2%
Parallel RCT	90	139	64.7%	28	46	60.9%	62	93	66.7%
Open Label RCT	22	90	24.4%	17	28	60.7%	5	62	8.1%
Parallel DB RCT	68	90	75.6%	11	28	39.3%	57	62	91.9%
Parallel DB PC RCT	60	68	88.2%	10	11	90.9%	50	57	87.7%
Parallel DB AC RCT	6	68	8.8%	1	11	9.1%	5	57	8.8%
Parallel DB PC + AC RCT	2	68	2.9%	0	11	0.0%	2	57	3.5%
Sample Size	**Low**	**High**	**Average**	**Low**	**High**	**Average**	**Low**	**High**	**Average**
	9	792	197	32	792	309	9	742	142

PASS = Post authorisation surveillance study; MA = Marketing authorisation; DB = Double blind; PC = Placebo controlled; AC = Active controlled

Figure 1: Proportion of cohort versus randomised trials

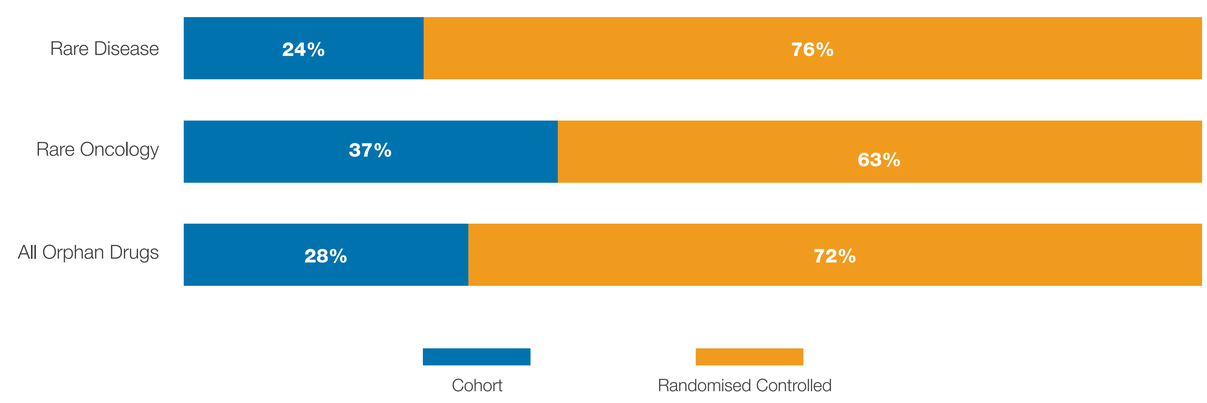
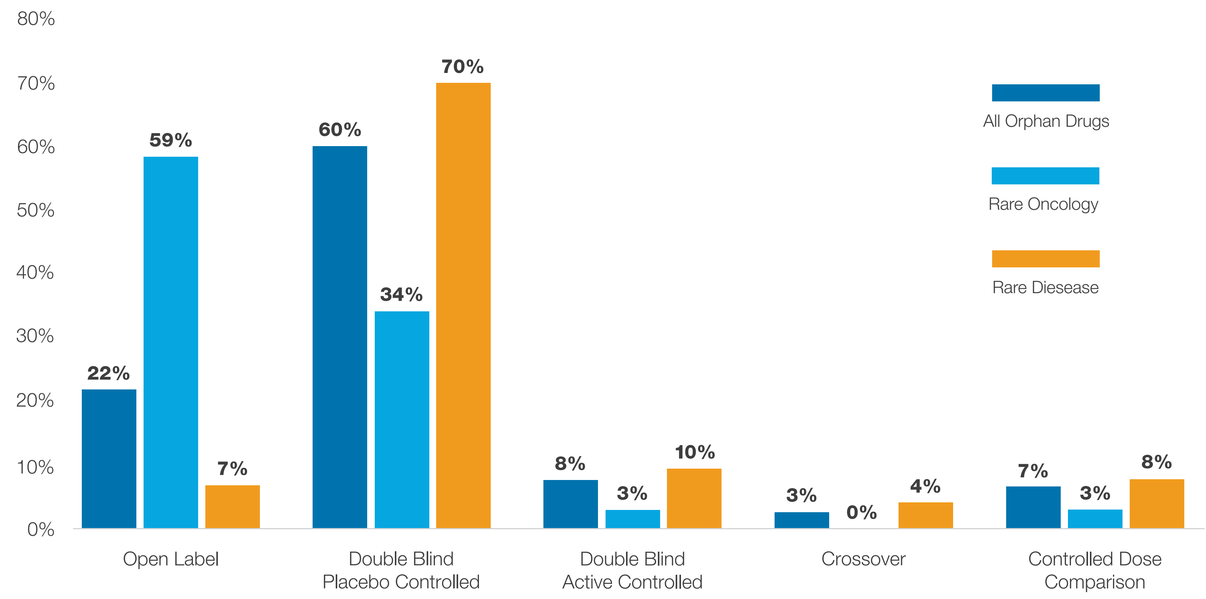


Figure 2: Types of RCT



Abbreviations
ODs = orphan drugs; RD = rare disease; RO = rare oncology; EMA = European marketing authorisation

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