



Chair Introduction

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MAJOR OBJECTIONS

Impact on timelines

All RANK	% MAA	Categories of major objection	Cerepro-1	Advexin	Glybera	Imlygic	Luxturna*	Strimvelis	Yescarta	Kymriah	Zalmoxis	Altoflisel	Heparesc	Holoclar	Spherox	Provenge	Hyalograft C	MACI	Oranera	ChondroCell	Apligraf**	Approved % MAA	Approved RANK	Failed RANK	Failed % MAA
			1	63%	Comparability and consistency issues	6	7		5	3	5	6	6	5	6	6	5	5	5	8	4				54%
2	58%	Specifications			5																	38%	4	1	100%
2	58%	Impurities, incl. microb. Contamination				1								3								54%	1	4	67%
4	53%	Validation process, assays																				38%	4	2	83%
5	42%	D S and DP characterisation																				31%	6	4	67%
5	42%	Potency assay																				46%	3	8	33%
7	32%	Stability										3										23%	6	8	50%
7	32%	Raw/starting materials																				23%	8	6	50%
7	32%	Viral safety																				31%	8	6	33%
10	11%	Product reconstitution																				8%	10	10	17%
11	5%	Defining DS and DP																				0%	11	10	17%



Major objection categories for 19 ATMP submissions.

Scores are taken from Barkholt *et al.* (1) with the exception of;

*Luxturna, this was scored from the EPAR by the authors,

**Apligraf, this was scored based on the day 120 LoQ obtained under freedom of information from the EMA.

Major objection categories are ranked by frequency over all applications (left, percentage of applications), then by frequency in approved products (right, green, including percentage of applications) and then by failed products (far right, red, including percentage of applications). The categories are divided by dossier section into quality (module 3, blue), nonclinical (module 4, brown) and clinical (module 5, green) issues.

For each product the specific areas of major objection are identified by open circles, for each dossier section the first circle indicates the total number of major objection categories for that dossier section. The overall total number of major objection categories for each submission is shown at the bottom (red, failed applications; green, approved applications).

For full paper see: <https://insights.bio/cell-and-gene-therapy-insights/journal/articles/eu-market-authorisation-strategy-lessons-from-the-first-22-atmp-submitted-to-the-ema/>

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All RANK	% MAA	Categories of major objection	Cerepro-1	Advexin	Glybera	Luxtuna*	Yescarta	Zalmonis	Alofisel	Heparasc	Spherox	Provenge	Hyalograft C	Oratera	Chondrocel	Imlygic	Strimvelis	Kymriah	Holoclar	MACI	Apligraf**	SME % MAA	Large			
																							RANK	RANK	% MAA	
1	63%	Comparability and consistency issues	6	7		5	3	5		6	6	5	5	8	4						5		85%	1	4	17%
2	58%	Specifications			5																4		69%	2	2	33%
2	58%	Impurities, incl. microb. Contamination														1			3				62%	4	1	50%
4	53%	Validation process, assays																					69%	2	4	17%
5	42%	DS and DP characterisation																					54%	5	4	17%
5	42%	Potency assay																					54%	5	4	17%
7	32%	Stability							3														38%	7	4	17%
7	32%	Raw/starting materials																					31%	9	2	33%
7	32%	Viral safety																					38%	7	4	17%
10	11%	Product reconstitution																					15%	10	10	0%
11	5%	Defining DS and DP																					8%	11	10	0%



Major objection categories for SME versus large companies

See Figure 6 legend.

Products to the right of the orange line were submitted by larger companies, those to the left by SME. Major objection categories are recalculated and ranked on the right of the figure to reflect the two groups; all applications are included irrespective of success.

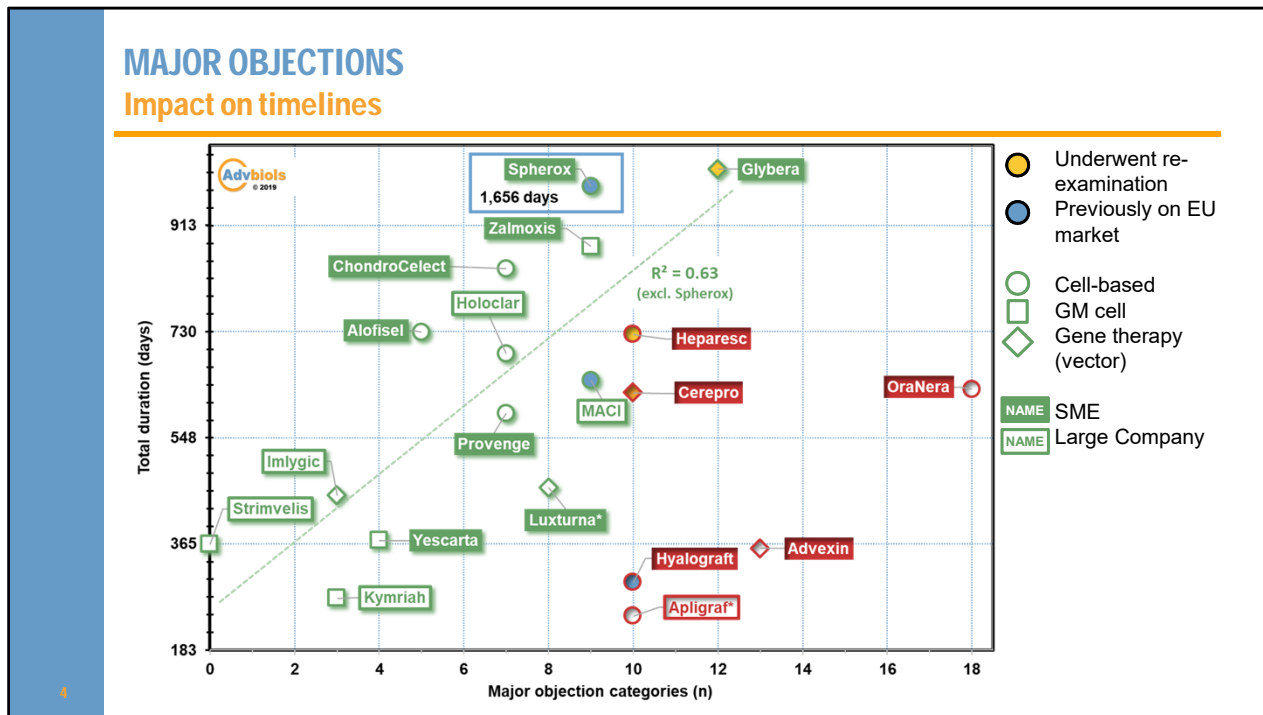


Figure 7: Impact of the number of major objections on procedure duration

Total duration (days): calculated as start of procedure to either, issue of MA by EC, confirmation of negative opinion by EC, or withdrawal of application by applicant. Total duration also includes any time spent seeking a re-examination after a negative opinion (symbols with blue fill).

The number of major objection categories as defined and scored by Barkholt *et al.* (1) except Luxturna and Apligraf which were scored by the authors (see text).

Green, approved; red, not approved; circles, cell-based medicinal products; squares, genetically modified cells; diamonds, gene therapy (vector) products.

Orange filled symbols; products considered on the market prior to the end of 2009.

Company name: white text on coloured background, SME; colour text on white background, large pharma company.

Trendline: linear regression of approved products only, and excluding Spherox as an outlier.