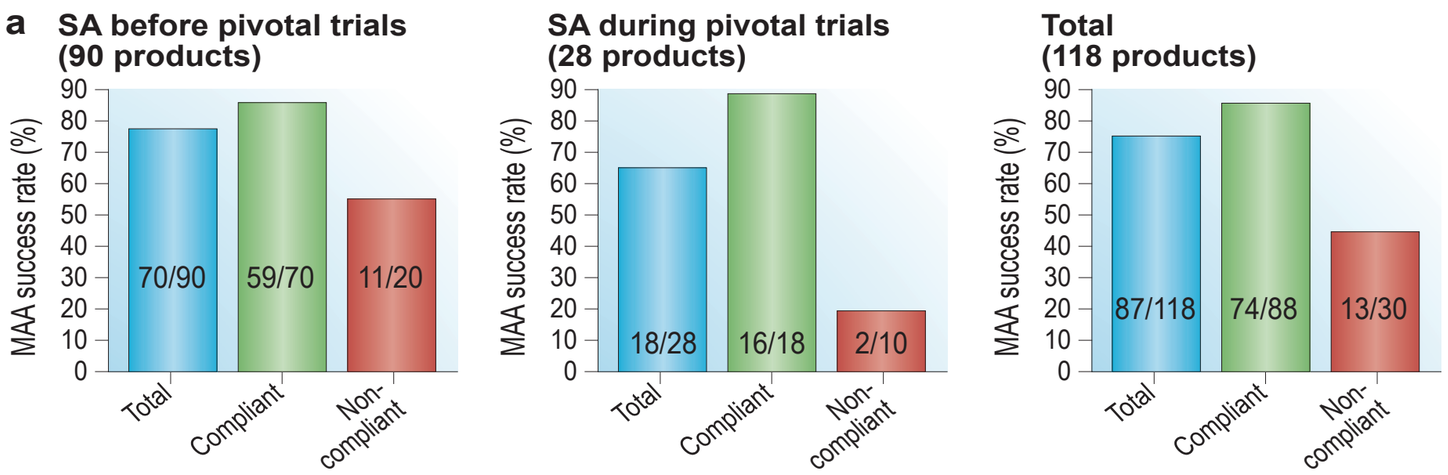
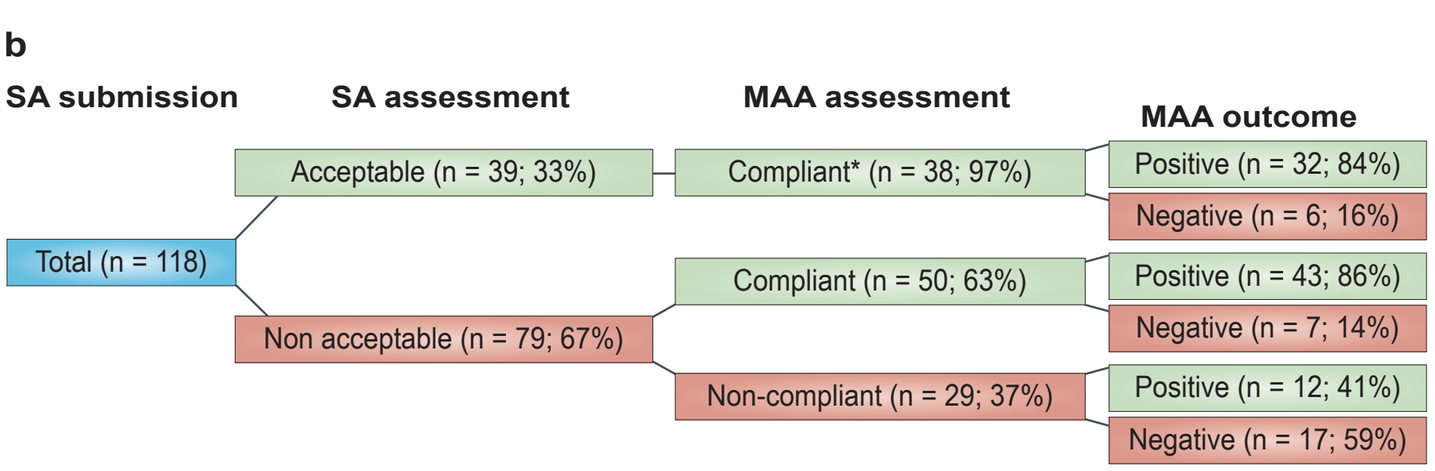
Figure 1 - Impact of scientific advice



Timing of scientific advice (SA), timing of compliance and the relationship with the success of marketing authorisation applications (MAAs) for the 118 MAAs that were submitted in 2008-2012 for which SA had been received and that could be assessed for compliance on the key variables, subdivided into groups depending on whether SA was provided before or during pivotal trial advancement. The number of MAAs as a proportion of the relevant total is shown within the bars.



Evolution of clinical trial design from SA submission to MAA outcome. Clinical trial designs submitted for SA were evaluated for their acceptability at future MAA; their compliance with SA recommendations at MAA; and their ultimate MAA success. The regulatory process from submission of a request for SA to MAA outcome is shown.
*One product was acceptable and non-compliant; the sponsor changed the primary efficacy end point that was originally proposed and accepted by SA, and the MAA outcome was positive.

Table 1 - Summary of marketing autorisation application submissions, scientific advice requests and compliance with scientific advice by year

	MAA applications*		SA requests**		Compliance analysis***	
CHMP outcome by year	Number	Success rate	Number/total (%)	Success Rate	Number/total (%)	Compliance rate
Total 2008-2012	**232**	**168 (72%)**	**143/232 (62%)**	**106 (74 %)**	**118/143 (83%)**	**88 (75%)**
2008	58	37 (64%)	34/58 (59%)	21 (62%)	24/34 (71%)	18 (75%)
2009	57	37 (65%)	31/57 (54%)	21 (68%)	26/31 (84%)	19 (73%)
2010	29	22 (76%)	16/29 (55%)	12 (75%)	13/16 (81%)	11 (85%)
2011	42	35 (83%)	30/42 (71%)	26 (87%)	26/30 (87%)	17 (65%)
2012	46	37 (80%)	32/46 (70%)	26 (81%)	29/32 (91%)	23 (79%)

* The basis of all presented analyses were all MAAs submissions from 2008-2012 and their success rates.
** Also displayed are the procedures with SA requests relevant for the MAA procedure and their related MAA success rate.
*** The number and compliance rates are shown for those procedures that received relevant SA and formed the basis of the compliance analysis, when compliance with SA could be assessed on the grounds of the three key variables: choice of primary efficacy endpoint, choice of comparator treatment, and robustness of chosen statistical methodology.

Table 2 - Marketing autorisation application procedure time and the number of major objections in relation to compliance with scientific advice on clinical trial design

	MAA procedure	Total MO*			
	average days	Quality/Pre-Clinical	Clin. Efficacy	Clin. Safety	Total
Compliance	367	1.64	2.66	0.86	5.16
Non-Compliance	428	4.25	3.91	1.42	9.58

The table shows the average number of days of the MAA procedure (CHMP assessment period and clock-stop period) subdivided by compliance/ non-compliance with SA.
*The individual and total sums of major objections at CHMP assessment day 120 and assessment day 180 are also displayed.

Source: Impact of scientific advice from the European Medicines Agency (Volume 14, p.302, 2015) Nature Reviews | Drug Discovery