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Jan Regnstrom, Franz Koenig, Bo Aronsson, Tatiana Reimer, Kristian Svendsen, Stelios Tsigkos, Bruno Flamion, Hans-Georg Eichler, Spiros Vamvakas

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SPECIAL ARTICLE

Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency

Jan Regnstrom · Franz Koenig · Bo Aronsson · Tatiana Reimer · Kristian Svendsen · Stelios Tsigkos · Bruno Flamion · Hans-Georg Eichler · Spiros Vamvakas

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Abstract
Purpose To identify factors associated with success of Market Authorisation Applications (MAAs) for pharmaceutical drugs submitted to the European Medicines Agency (EMEA), with an emphasis on the Scientific Advice (SA) given by the Committee for Human Medicinal Products (CHMP).
Methods MAAs with a CHMP decision (outcome) between 1 January 2004 and 31 December 2007 were included in the analysis. Factors evaluated were: company size, orphan drug (OD) status, product type, existence of SA, compliance with SA, therapeutic area and year of outcome. Compliance with SA was retrospectively assessed with reference to three critical clinical variables in pivotal studies: choice of primary endpoint, selection of control and statistical methods.
Results Of 188 MAAs with an outcome, 137 (72.9%) were approved, whereas 51 (27.1%) were not approved or were withdrawn by the company. In the simple logistic regression analysis, company size [odds ratio (OR) 2.96, 95% confidence interval (CI) 1.92; 4.56, $p<0.0001$) was positively correlated with a positive outcome, whereas OD status (OD vs. non-OD: OR 0.38, 95% CI 0.19; 0.77, $p=0.0067$) was negatively correlated. A total of 59 (31.4%) MAAs had obtained SA related to one or more of the three critical variables. Thirty-nine of these were assessed as being compliant with SA. Obtaining an SA per se was not associated with outcome (SA vs. no-SA: OR 0.96, 95% CI 0.49; 1.88, $p=0.92$), but complying with SA was significantly associated with positive outcome (compliant with SA vs. no-SA: OR 14.71, 95% CI 1.95; 111.2; non-compliant with SA vs. no-SA: OR 0.17, 95% CI 0.06; 0.47, $p<0.0001$). Stepwise regression analysis revealed that company size and SA compliance were independent predictors of outcome. The proportion of the MAAs that had received SA increased from 22% in 2004 to 47% in 2007. Company size and product type were associated with the frequency of requesting SA (26, 33 and 46% for small, medium-sized and large companies, respectively; 16, 39 and 48% for known chemical substances, new chemical substances and biologics, respectively). Factors related to compliance with SA were company size and OD status (25, 60 and 84% for small, medium-sized, and large companies, respectively; 77 and 38% for non-OD and OD status, respectively).
Conclusions The strong association between company size and outcome suggests that resources and experience in drug development and obtaining regulatory approval are critical factors for a successful MAA. In addition, obtaining and complying with SA appears to be a predictor of outcome. Based on this analysis, companies, particularly smaller ones and those developing orphan drugs, are recommended to engage in a dialogue with European regulators via the SA procedure. Obtaining SA early in development and at major transition points as well as compliance with the advice given by the CHMP are recommended.

Keywords Drug approval · Drug development · Regulatory · Scientific advice

Jan Regnstrom and Franz Koenig contributed equally to this paper

J. Regnstrom (✉) · F. Koenig · B. Aronsson · T. Reimer · K. Svendsen · S. Tsigkos · B. Flamion · H.-G. Eichler · S. Vamvakas
European Medicines Agency (EMEA),
7 Westferry Circus—Canary Wharf,
London E14 4HB, UK
e-mail: Jan.Regnstrom@emea.europa.eu
URL: http://www.emea.europa.eu

Introduction

In recent years, great progress has been achieved in basic biomedical sciences, but so far the translation from new discoveries into innovative therapies reaching the market has been limited. There is a perceived inefficiency in pharmaceutical drug development. While money spent on drug development keeps increasing, the number of newly approved innovative drugs remains constant or has even declined over time. This phenomenon is sometimes referred to as the "pipeline problem" of the pharmaceutical industry. Multiple factors may contribute to this situation, including the development of more complex drugs (i.e. biologics) and high regulatory demands. These demands have particular consequences for the design of and the adequate enrolment of patients into Phase III confirmatory trials, making such trials costly to perform. Consequently, only medicines intended for large markets will give the necessary return on investments, and products with a more narrow indication may not qualify for inclusion in pharmaceutical portfolio management strategies. Consequently, interaction between regulators and drug developers is important to avoid unnecessary use of resources during the most costly phase of drug development. Stakeholders have identified various aspects of drug development to be improved, including use of new statistical methodology, such as adaptive designs [1–4], and biomarkers. Continuous discussions and interactions between regulators, the pharmaceutical industry, patient organisations and academia, have helped to foster a better mutual understanding of the benefits and limitations of using new methods and technologies in drug development. Workshops are now organised by industry and/or regulators, such as the EMEA/EFPIA workshops on adaptive designs [5, 6] and the workshops on monoclonal antibodies [7] and on advanced therapy medical products.

There is evidence that a good line of communication between sponsors and regulators throughout the drug developmental process may increase the chance of market access. Further initiatives from the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA) to facilitate efficacious drug development include scientific interactions between sponsors and regulators. To support the development and availability of high-quality, effective and safe medicines for the benefit of patients, the EMEA has been offering sponsors of medicinal products scientific advice (SA) since 1996. SA is given by the Committee for Human Medicinal Products (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP; for further description of EMEA terms, see Table 1). Within the European Union (EU), it is not mandatory for sponsors of medicinal products to request SA; additionally, the SA provided by the CHMP is not legally binding with regard to any future Market Authorisation Application (MAA) of the product concerned, either for the regulatory agency or for the company. The SA can be requested on all aspects of drug development, including quality and non-clinical and/or clinical issues, either during the initial development of a medicinal product or later on, during the post-authorisation phase. Sponsors may ask for "follow-up" to the initial request for SA. The SAWP also provides advice on broad, product-unrelated questions and on the qualification of novel methodologies for drug development [8], such as whether a specific biomarker can be used as primary or secondary endpoint in a clinical trial. The current SA procedure is streamlined to allow finalisation within 40 or maximally 70 days and includes the involvement of CHMP, which formalises the peer review before final adoption of the SA letter, thereby maximising the clarity and ensuring consistency. A total of 1333 SA letters had been finalised by the SAWP–CHMP by the end of 2007.

Marketing authorisation of a medicinal product for the entire EU is granted via the centralised procedure. This procedure involves the EMEA with its Scientific Committees and Working Parties for scientific evaluation of the application. The centralised procedure is a 210-day evaluation procedure resulting in a scientific opinion by the CHMP—i.e. the recommendation, or not, to authorise the MAA. The final decision is then taken by the EU Commission (DG Enterprise). There is an option for the applicant to withdraw an application prior to the CHMP decision.

In a previous analysis of MAAs submitted to the EMEA with an outcome between September 1997 and May 2001 ($n=111$), failure to establish clinical efficacy due to lack of adequate randomised controlled trials (identified and raised as a major objection during the review process) was the single most important independent predictor of negative outcome [9]. The study reported here was designed to further identify factors associated with the outcome of MAAs submitted more recently and places more emphasis on the potential impact of the SA given by the CHMP and sponsor compliance with the SA received. Factors associated with sponsors requesting SA and factors associated with sponsor adherence to the SA given were also analysed.

Methods

Data sets and analysis

The EMEA Scientific Memory Database [9, 10], which includes all MAAs submitted to the EMEA that have reached an outcome since January 1995, was used to identify and characterise the MAAs in this study.

Table 1 A short description of European Medicines Agency terms, including weblinks

Term	Description
Centralised procedure	An European Community registration procedure created by Council Regulation (EEC) No. 2309/93 and amended by Regulation 726/2004 for the authorisation of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the European Community. The opinion of the CHMP is transmitted to the European Commission to be transformed in a further 67 days into a single marketing authorisation applicable to the whole European Union. This procedure is compulsory for medicinal products derived from biotechnology and for those in four specific therapeutic areas (products against HIV, cancer, neurodegenerative diseases and diabetes), and is available at the request of companies for other innovative new products. Applications are submitted directly to the EMEA. (http://ec.europa.eu/enterprise/pharmaceuticals/procedure/cproc_en.htm; http://www.emea.europa.eu/index/authorisation.htm)
CHMP	The *Committee for Medicinal Products for Human Use* (CHMP) is responsible for preparing the Agency's opinions on all questions concerning medicinal products for human use, in accordance with Regulation (EC) No 726/2004. (http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP.html)
CHMP opinion	CHMP's scientific conclusions on issues related to medicinal products, such as whether the data submitted allow the conclusion to be drawn that there is an overall positive benefit/risk of a new product in a proposed indication and whether the product should be placed on the market.
EMEA	The *European Medicines Agency* (EMEA) created by Council Regulation (EEC) No. 2309/93 of 22 July 1993, and renamed by Council Regulation 726/2004 of 31 March 2004, is based in Canary Wharf, London. The Agency is responsible for coordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products. (http://www.emea.europa.eu)
European Commission	*Commission of the European Communities*: The "civil service" of the European Union It is the executive organ of the Community. It proposes Community policy and legislation, implements the decisions taken by the Council of Ministers and supervises the day-to-day running of Commission policies.
Follow-up SA	Any application for *Scientific Advice* (SA) following the initial application on the same area/condition. For example, the initial advice can be on the pharmacokinetics and the exploratory Phase II trial; later, the pivotal Phase III trial could be the subject of a follow-up advice.
Informed consent applications	According to Article 10c of Directive 2001/83/EC as amended, following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, non-clinical and clinical documentation contained in the dossier of the medicinal product for the purpose of examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form. (http://www.emea.europa.eu/htms/human/presub/q03.htm)
MAA	*Marketing Authorisation Application*: Across all European markets, plus Australia, New Zealand, South Africa and Israel (exceptions among major markets include USA, Canada, China and Japan), the MAA is a common document used as the basis for a marketing application (an application for approval to market the product based on a full review of all quality, safety and efficacy data, including clinical study reports). In the USA, the New Drug Application (NDA) is the MAA equivalent. In Canada, the New Drug Submission (NDS) is the MAA equivalent. (http://www.emea.europa.eu/index/indexh1.htm)
Medicinal product	A finished dosage form, such as a tablet, capsule, solution, etc., that generally contains an active ingredient, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
Multiple applications	MAAs, where the applicants wish to obtain, either simultaneously or successively, more than one Marketing Authorisation for a specific medicinal product, under different invented names. (http://www.emea.europa.eu/htms/human/presub/q09.htm)
OD	*Orphan Drug*: A drug for the treatment of a rare serious disease (defined in the EU as a condition that affects not more than five in 10,000 persons in the Community; defined in the USA as a condition affecting fewer than 200,000 people in the USA) or for a disease not likely to generate sufficient profit to justify Research and Development costs. (http://www.emea.europa.eu/htms/human/orphans/intro.htm)
Protocol assistance	The process of giving scientific advice for Orphan Drugs. (http://www.emea.europa.eu/htms/human/sciadvice/protocol.htm)
SA	*Scientific Advice*. (http://www.emea.europa.eu/htms/human/sciadvice/Scientific.htm)
SA letter	An official written statement expressing the final opinion of the CHMP on the questions raised by the applicant.
SAWP	The *Scientific Advice Working Party* is a permanent working party of the CHMP, in charge of Scientific Advice and Protocol Assistance for orphan medicinal products. This is the only Working Party of the EMEA established in the EU legislation. (http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_SAWP.html)
Scientific committees	These are composed by experts of all Member States and are established in the legislation. In addition to the CHMP, the Committee for Advanced Therapies is also involved in the evaluation of medicinal products, in particular, gene-, cell- and tissue-engineered medicinal products
Single applications	In the European Union (EU), a company that wishes to bring a medicine to the market may submit a single application to the EMEA for a "marketing authorisation" (licence) that is valid simultaneously in all EU Member States, plus

Table 1 (continued)

Term	Description
	Iceland, Liechtenstein and Norway. This is called the "centralised (or "Community") authorisation procedure" and is mandatory for certain types of medicines and optional for others. (The precise scope is set out in Annex I of Regulation (EC) No 726/2004.) (http://www.emea.europa.eu/index/indexh1.htm)
SMEs	*Small and Medium-sized Enterprises*: Companies are classified according to their size (micro, small or medium) based on the number of employees and annual turnover. (http://www.emea.europa.eu/htms/human/raguidelines/sme.htm)
Variation	Modification to the terms of a marketing authorization application (Regulations (EEC) No 2309/93 and Directives 2001/83/EC and 2001/82/EC). Variations can be minor (type IA and IB) or major (type II), (Commission Regulation (EC) No 1084/2003) (http://www.emea.europa.eu/htms/human/raguidelines/post.htm#type1); (http://www.emea.europa.eu/htms/human/raguidelines/post.htm#type2)
Withdrawal	An applicant withdraws the application for evaluation of a medicinal product. (http://www.emea.europa.eu/htms/human/withdraw/withdrawapp/background.htm)
Working Party	The CHMP establishes working parties which have expertise in a particular scientific field and are composed of members selected from the European experts list maintained by the EMEA. (http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html)

So-called informed consent applications [according to article 10 (c) of Directive 2001/83/EC as amended], and variations to the terms of an existing marketing authorisation, such as the addition of a new indication, were excluded. Applications resubmitted after an initial rejection or after withdrawal by the sponsor were included. Multiple applications for a specific medicinal product under different invented names [according to the article 82(1) of the Regulation (EC) No. 726/2004] were included as a single application.

Positive outcome was defined as a positive opinion by the CHMP. Negative outcome was defined as a negative opinion by the CHMP or withdrawal of the application by the sponsor prior to CHMP opinion. The EMEA scientific advice database was used to retrieve SA reports.

The main analysis included all MAAs with an outcome between 1 January 2004 and 31 December 2007. The independent variables used in this analysis included those which could be determined at the time of the MAA, such as company size, orphan drug status, product type, existence of SA, compliance with SA, therapeutic area and year of outcome.

Companies were categorised according to size into small (small pharma, code 1), medium-sized (medium pharma, code 2) and large pharmaceutical (large pharma, code 3). Company size categories were based on ranking by total revenues, as reported in Scrip's Pharmaceutical Company League Tables 2006 [11]. The large pharma category was defined as companies ranked 1–20; medium pharma were ranked 21–150; and small pharma comprised all companies that were not included in the League Tables. This definition is different from the current EU definition of small and medium-sized enterprises (SMEs).

Products were categorised according to type into: (1) known chemical substances (including fixed dose combinations of approved chemical substances and generic or hybrid medicinal products of a reference medicinal products authorised via the centralised procedure); (2) new chemical substances (chemical substances not previously approved); (3) biologics (defined as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins).

For the analyses, the therapeutic areas were defined/grouped as infectious disorders (n=39), oncology (n=35), endocrine and metabolic disorders+inherited disorders of metabolism (n =29), neurologic disorders+psychiatric disorders (n =23) and others (n=62).

Compliance with SA was retrospectively assessed for three variables in pivotal clinical studies: choice of primary endpoint, selection of control (placebo, active comparator, historical control or no control) and statistical methods. These three variables were selected based on their potential importance for predicting a positive outcome of a MAA [9]. Of the 188 MAAs with an outcome between 1 January 2004 and 31 December 2007, 69 had received SA; of the latter, 59 included SA related to at least one of the three variables selected for the assessment of compliance. Compliance was determined independently for each variable by two assessors working at the SAWP secretariat by comparing consistency (yes/no) between the advice given in the SA letter(s) sent to a company by the EMEA and the development programme in the MAA submitted by the company to the EMEA. For example, in a SA letter for an oncology product, the CHMP may have recommended the use of overall survival as primary endpoint in pivotal trial (s). If the review of the documents submitted for MAA found that the company choose overall survival as primary endpoint in the pivotal trial(s), it would be assessed as compliant for that variable. On the other hand, if the company instead selected progression free survival as the primary endpoint in the pivotal trial(s), it would be assessed as non-compliant for that variable. Non-compliance with

SA was concluded based on lack of consistency for at least one of the three variables. For example, the CHMP may have recommended the use of overall survival as the primary endpoint and the use of an active comparator in pivotal studies for an oncology product. If the review of the documents submitted for MAA found that the company selected overall survival as the primary endpoint, but chose not to include any control in pivotal trial(s), it would be assessed as non-compliant to the SA. In the case of any discrepancy in the assessment between the two assessors, the case was brought to two senior members of the SAWP secretariat for a consensus decision.

Statistical methods

For quantitative data, mean and standard deviation (SD) are reported; for qualitative data, absolute frequencies and percentages (%) are given.

Outcome was classified as being positive (positive CHMP opinion) or being rejected (negative CHMP opinion or withdrawal of the application). The probability of a positive outcome was modelled using logistic regression models. 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 (SAS Proc LOGISTIC selection=stepwise), where all variables yielding a p value <0.1 in the simple logistic regression analyses were included as candidate variables. In the stepwise logistic regression model, 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.

In additional explorative analyses, we were interested in identifying factors why companies sought SA. Therefore, the probability of seeking SA during the application was modelled using simple logistic regression models followed by a stepwise logistic regression model as described above.

In the subgroup of MAAs that obtained SA related to one more of the three critical variables (n=59), factors associated with compliance with SA were investigated.

We used the SAS statistical software system (ver. 9.1; SAS Institute, Cary, NC) to carry out the calculations.

Results

Between 1 January 2004 and 31 December 2007 a total of 188 MAAs with an outcome were identified. Table 2 summarises some characteristics of the MAAs.

Table 2 Summary of MAA characteristics (received between 1 January 2004 and 31 December 2007; n=188)

Independent variables	Number of total MAAs (%)
CHMP outcome year	
2004	36 (19%)
2005	36 (19%)
2006	50 (27%)
2007	66 (35%)
Product type	
Biologic	61 (32%)
New chemical substance	84 (45%)
Known chemical substance	43 (23%)
Orphan designation status	
Orphan	50 (27%)
Non-Orphan	138 (73%)
Therapeutic area	
Infectious disorders	39 (21%)
Oncology	35 (19%)
Endocrine and Mmtabolic disorders	29 (15%)
Neurologic and psychiatric disorders	23 (12%)
Others	62 (33%)
Company size	
Small pharmaceutical	54 (29%)
Medium-sized pharmaceutical	51 (27%)
Large pharmaceutical	83 (44%)
Scientific advice	
SA received	69 (37%)
SA not received	119 (63%)

Factors associated with outcome

Of the 188 MAAs with an outcome between 2004 and 2007, 137 (72.9%) received a positive opinion by the CHMP, and 51 (27.1%) received either a negative CHMP opinion (n=10) or were withdrawn by the company (n=41). This observation is in line with the overall EMEA experience regarding MAA outcome between 1995 and 2007 where the approval rate for all MAAs was 350/470 (74%; excluding multiple and informed consent applications). As shown in Table 3, the MAA approval rate did not change significantly over time between 2004 and 2007.

Results of the analysis of factors associated with outcome are summarised in Table 3. In simple logistic regression analysis, company size and orphan designation (OD) status were significantly associated with outcome. The lower approval rate of MAAs involving medicinal products with OD (29/50,58%) versus MAAs with non-OD (108/138, 78%) during the 2004–2007 period is consistent with the overall EMEA experience between 1995 and 2007 where the approval rate for OD status was 52/87 (59.8%)

Table 3 Summary of simple and stepwise logistic regression results of the analysis of factors associated with final outcome

Independent variables	Positive/total, *n*= 137/188 (%)	Simple logistic regression		Stepwise logistic regression	
		Odds ratio[a] [95% CI]	*p* value	Odds ratio [95% CI]	*p* value
CHMP outcome year		0.909 [0.681; 1.215]	0.521		No candidate (NC)
2004	29/36 (81%)				
2005	23/36 (64%)				
2006	39/50 (78%)				
2007	46/66 (70%)				
Product type			0.2992		NC
Biologic	40/61 (66%)	0.577 [0.239; 1.396]			
NCE	64/84 (76%)	0.970 [0.407; 2.309]			
Known substance	33/43 (77%)	1			
OD Status			0.0067		Candidate
Non-orphans	108/138 (78%)	1			
Orphans	29/50 (58%)	0.384 [0.192; 0.766]			
Therapeutic area			0.32		NC
Infectious disorders	30/39 (77%)	1.473 [0.587; 3.696]			
Oncology	22/35 (63%)	0.748 [0.312; 1.790]			
Endocrine and metabolic disorders	22/29 (76%)	1.389 [0.507; 3.803]			
Neurologic and psychiatric disorders	20/23 (87%)	2.946 [0.780; 11.117]			
Others	43/62 (69%)	1			
Company size		2.964 [1.927; 4.560]	<0.0001	2.852 [1.811; 4.490]	<0.0001
Small Pharmaceutical (1)	26/54 (48%)				
Medium Pharmaceutical (2)	37/51 (73%)				
Large Pharmaceutical (3)	74/83 (89%)				
SA-given			0.92		NC
No	87/119 (73%)	1			
Yes	50/69 (72%)	0.968 [0.497; 1.883]			
Compliance[b]			<0.0001		NC
Non-compliant to SA	6/20 (30%)	0.166 [0.059; 0.465]			
Compliant to SA	38/39 (97%)	14.709 [1.946; 111.158]			
No-SA (*n*=119) or SA without a assessment of compliance (*n*=10)	93/129 (72%)	1			
Compliance (conservative analysis)[c]			0.0015		0.0088
Non-compliant to SA	12/26 (46%)	0.315 [0.132; 0.753]		0.267 [0.101; 0.703]	
Compliant to SA	38/43 (88%)	2.795 [1.011; 7.724]		1.658 [0.561; 4.902]	
No-SA	87/119 (73%)	1		1	

CI, Confidence interval

[a] For categorical explanatory variables, the reference group for the calculation of the odds ratio (OR) is indicated by OR=1. An OR>1 means that a positive outcome is more likely in this group compared to the reference group. Otherwise an OR<1 means that a positive outcome is less likely compared to the reference group. Outcome year and company size (small=1, medium=2, large=3) were used as continuous explanatory variables

[b] All MAAs for which compliance could not be assessed either because no SA was given (*n*=119) or because no SA was received for at least one of the three variables assessed for compliance (*n* =10) as variables were pooled in one group

[c] Conservative analysis: Ten MAAs received SA not related to one or more of the three variables assessed for compliance (primary endpoint, comparator, statistical methods) and were treated in this worst case analysis as non-compliant in the case of a positive outcome (*n*=6) and as compliant in the case of a negative outcome (*n* =4). Note that only the conservative one was used as a candidate in the stepwise logistic regression

compared to 340/450 (75.6%) for non-ODs. No significant association was observed for SA per se (OR0.97, 95% CI 0.497; 1.883, $p=0.92$), and only when compliance with SA was taken into account was SA found to be a significant predictor of outcome ($p<0.0001$). The approval rate for MAAs with SA but non-compliant with the advice given was 30% (6/20) compared to 73% (87/119) for MAAs with no SA given and 97% (38/39) for MAAs with SA and

compliant with the advice given. The approval rate among the MAAs receiving SA not related to any of three critical variables (and for which compliance could not be assessed) was 6/10. In the simple logistic regression analysis, this latter group was pooled with MAAs without SA (see Table 2, footnote b). As part of a conservative analysis, these MAAs were treated as being non-compliant in the case of a positive outcome (n=6) and as compliant in the case of a negative outcome (n=4), thereby confirming the statistically significant results (see Table 3, footnote c).

In a stepwise logistic regression analysis using the covariates company size and OD status as candidates, only company size (OR2.964, 95% CI 1.927; 4.560, $p<0.0001$) was a significant predictor of outcome. When compliance with SA (defined conservatively as described in Table 3, footnote c) was included as additional candidate for the stepwise logistic regression model, both company size (OR 2.85, 95% CI1.81; 4.50, $p<0.001$) and SA compliance (p = 0.009; for OR, see Table 3 last column) were significant predictors of outcome. The univariable statistically significant factor OD status did not enter the stepwise logistic regression model because an association between OD status and company size was observed (χ^2-test $p<0.0001$). The proportion of MAAs with OD status decreased with the size of pharmaceutical companies (ratio of MAAs with OD status for small pharma 30/54=56%, for medium pharma 10/51=20%, for large pharma 10/83=12%). Table 4 presents the outcome categorized according to company size and OD status, showing that the influence of OD status on outcome is almost nonexistent within each of the different company size categories.

Scientific advice

Sixty-nine (37%) of the MAAs received SA and 59 (31%) received SA related to one or more of the three variables assessed for compliance (primary endpoint, comparator, statistical methods). The MAAs with SA differed significantly from those without SA in terms of year of outcome, product type, and company size. The detailed results of all simple logistic regression analyses can be found in Table 4 (columns 2–4, Analysis SA). Both the number of MAAs and the proportion of MAAs that had received SA prior to outcome increased over the observation period. MAAs concerning biologics (29/61,48%) and new chemical substances (33/84,39%) received SA more frequently than known chemical substances (7/43,16%). Larger pharmaceutical companies requested SA significantly more often than smaller companies, with 38/83 (46%) of large pharma requesting an SA in contrast to 17/51 (33%) medium pharma and 14/54 (26%) small pharma In the final stepwise logistic regression analysis, all three candidate variables, company size, CHMP outcome year and product type, were found to be statistically significant predictors of receiving SA. They entered the model in the following sequence: Product type (p=0.0221, biologic vs. known chemical substance (OR 3.93, 95% CI 1.48; 10.4); new chemical substance vs. known chemical substance (OR2.81, 95% CI 1.09; 7.24), outcome year (OR1.42, 95% CI 1.06; 1.90, p=0.0184) and company size (OR1.49, 95% CI 1.01; 2.19, p = 0.0439). It should be noted that in all logistic regression analyses company size was used as a continuous explanatory variable (using the code: small=1, medium=2, large=3).

For the 69 MAAs that received SA, the mean number of times the company requested SA was 1.8 (median 2, range 1–6). The mean number (SD) of questions per SA request were 11.6 (9.3), with a dominance of questions relating to clinical issues [mean 9.5 (9.1)], over nonclinical issues [mean 1.4 (2.3)] and quality issues [mean 0.8 (1.4)].

Of the 59 MAAs that received SA related to one or more of the three variables assessed for compliance, 39 (66%) were assessed as being compliant with the SA given. Table 5 (columns 5–7, subgroup analysis compliance) summarises the results of the simple logistic regression analysis of variables associated with compliance with SA. In the stepwise logistic regression analysis using company size and OD status as candidates, both company size (OR 3.62, 95% CI 1.58; 8.29, p=0.0023) and OD status (OD vs. non-OD (OR0.23, 95% CI 0.05; 0.93; p =0.038) were found to be significant predictors of compliance.

Table 4 Approval rate according to company size and OD status

Company size	OD status	
	Orphan, positive/total, n (%)	Non-orphan, positive/total, n (%)
Small	15/30 (50%)	11/24 (46%)
Medium	6/10 (60%)	31/41 (76%)
Large	8/10 (80%)	66/73 (90%)

Discussion

Transforming discoveries into new medicinal products is a lengthy and expensive process. While the costs of development keep increasing, the number of newly approved medicinal products is remaining constant or even declining over time [12]. There are multiple potential reasons for the perceived inefficiency in drug development as it relates to outcome, including the development of more complex drugs (i.e. biologics), increased regulatory requirements and increased scrutiny regarding safety in the post–Vioxx era. However, there is also evidence that some failures may have been prevented by close communication between

Table 5 Summary of the results of the simple logistic regression analysis of variables associated with having received SA and compliance with SA

Independent variables	Analysis SA			Subgroup Analysis Compliance		
	SA-given/total, n=69/188 (%)	Odds ratio[a] [95% CI]	p value	Compliant/total, n=39/59 (%)	Odds ratio[a] [95% CI]	p value
CHMP outcome year		1.447 [1.093; 1.915]	0.0098		0.742 [0.425; 1.294]	0.293
2004	8/36 (22%)			5/7 (71%)		
2005	11/36 (31%)			7/9 (78%)		
2006	19/50 (38%)			12/17 (71%)		
2007	31/66 (47%)			15/26 (58%)		
Product type			0.0064			0.775
Biologic	29/61 (48%)	4.66 [1.797; 12.085]		14/22 (64%)	1.313 [0.233; 7.409]	
New chemical substance	33/84 (39%)	3.328 [1.326; 8.353]		21/30 (70%)	1.750 [0.323; 9.469]	
Known chemical substance	7/43(16%)	1		4/7 (57%)	1	
Orphan drug status			0.8241			0.0068
Orphan	19/50 (38%)	1.079 [0.553; 2.104]		6/16 (38%)	0.182 [0.053; 0.625]	
Non-orphan	50/138 (36%)	1		33/43 (77%)	1	
Therapeutic area			0.96			0.87
Infectious disorders	14/39 (36%)	0.95 [0.413; 2.184]		6/11 (55%)	0.600 [0.135; 2.673]	
Oncology	14/35 (40%)	1.13 [0.483; 2.645]		7/11 (64%)	0.875 [0.190; 4.030]	
Endocrine and metabolic disorders	9/29 (31%)	0.763 [0.298; 1.954]		6/8 (75%)	1.500 [0.238; 9.438]	
Neurologic and psychiatric disorders	9/23 (39%)	1.09 [0.408; 2.914]		6/8 (75%)	1.500 [0.238 9.438]	
Others	23/62 (37%)	1		14/21 (67%)	1	
Company size		1.566 [1.083; 2.264]	0.0172		3.975 [1.799; 8.781]	0.0006
Small pharmaceutical	14/54 (26%)			3/12 (25%)		
Medium pharmaceutical	17/51 (33%)			9/15 (60%)		
Large pharmaceutical	38/83 (46%)			27/32 (84%)		

[a] For categorical explanatory variables, the reference group for the calculation of the OR is indicated by OR=1. An OR>1 means that an event is more likely in this group compared to the reference group. An OR<1 means that an event is less likely in this group compared to the reference group. Outcome year and company size (small=1, medium=2, large=3) were used as continuous explanatory variables.

sponsors and regulators throughout the developmental stages and by better adherence by sponsors to the advice provided by regulators. Initiatives from the EMEA and the FDA to facilitate efficacious drug development include improved scientific interactions between sponsors and regulators. In the EU, it is not mandatory for sponsors to request SA, and SA provided by the CHMP is not legally binding for regulators or sponsors. Previous studies have shown that formal meetings with the FDA at critical steps during drug development are associated with shorter development and review times [13, 14]. The FDA End of Phase II (EOP2) meetings have had a positive impact on first-cycle approval rate [14]. The fact that 25% of the multiple-cycle applications with an EOP2 meeting had the critical issue preventing first-cycle approval identified at this meeting suggests a failure or an inability by the sponsor to resolve problems prior to submission [14].

Against this background we decided to retrospectively evaluate 188 MAAs submitted to the EMEA between 2004 and 2007 with the aim of identifying predictors of outcome, placing emphasis on the potential impact interaction between sponsors and regulators through the SA procedure. We specifically hypothesised that compliance with a given SA in terms of critical issues in pivotal Phase III studies would relate to outcome.

The results of our study show that company size is an important independent predictor of outcome of a MAA in the central procedure. The MAA approval rate of close to 90% for large pharmaceutical companies compared to 50% for small companies is likely related to overall resources, experience in previous drug development and approval and selection of candidates with a high probability of regulatory success, although these issues have not been specifically addressed in this study.

In a previous study, smaller biopharmaceutical companies were found to be more likely than larger companies to advance drug candidates from Phase I to Phase II clinical trials, but with less promising results. The smaller companies were also less likely to proceed to Phase III and to receive FDA approval [15]. An evaluation of FDA's first

cycle review performance revealed that sponsors with drugs previously approved by the FDA had higher first-cycle approval rates than to sponsors without previously approved drugs. Larger companies had considerably higher first-cycle approval rates than small companies [14]. In our study, large companies not only asked for SA more frequently than medium-sized and small pharmaceutical companies but, importantly, they were significantly more compliant with the SA given than their smaller peers.

Medicinal products with OD were associated with a significantly lower probability of a positive outcome than non-OD products in simple logistic regression analysis, but this association was not significant when company size was taken into account. Small companies have a larger proportion of medicinal products with OD relative to larger and medium-sized companies. Overall, our findings support the work of Heemstra et al. [16] in showing that OD approval is strongly associated with the previous experience of the sponsor in obtaining approval for another OD.

We found that MAAs with SA did not differ from those without SA in terms of probability of success, but a retrospective analysis of compliance with SA obtained concerning three important variables in pivotal clinical studies—i.e. choice of primary endpoint, selection of control and statistical methods—did find compliance with SA to be an independent predictor of success together with company size. This should not be viewed as a reward for following the regulators' views. When companies come for SA, if the regulators disagree with a proposal, they engage in a face-to-face discussion with the company; consequently, companies have the chance to argue their case and convince the regulators. Furthermore, these same companies have the option to come back to the SAWP to present and discuss modified development plans in a so-called follow-up SA. Thus, the final conclusions of the SA procedure that are included in the SA letter are often the result of these scientific interactions. It is the compliance with these final conclusions which predicts the success. It may be speculated that companies request SA for more challenging medicinal products and development programmes and in situations where regulatory guidance is lacking. This is supported by our observation that MAAs with SA more frequently involved biologics and new chemical substances compared to MAAs without SA, which more frequently involved known chemical substances.

There are several methodological issues in our study that need discussion. Although the three variables in pivotal clinical studies for which compliance was evaluated (choice of primary endpoint, selection of control and statistical methods) were selected prospectively, the actual assessment of compliance with SA was performed retrospectively in a non-blinded fashion when the outcome of the MAA was known. Thus, these findings may formally only be considered as hypothesis-generating. Still, the fact that compliance with SA appears to be a predictor of outcome is not surprising. The SA given by the CHMP reflects evidentiary standards that the CHMP will apply by the time of MAA to establish whether there is a positive benefit/risk or not.

This study did not address compliance with SA given related to quality (CMC) or nonclinical issues. Requests for SA related to quality or nonclinical issues occur considerably less frequently than requests related to clinical issues, and quality and nonclinical issues rarely contribute to a negative regulatory outcome of an MAA. Furthermore, the study did not address compliance with SA related to other clinical issues of potential importance to the outcome, such as selected population, number of patients included, duration of studies and follow-up, dose selection, safety issues, among others.

Our definition of company size has limitations and does not correspond to the current EU definition of SMEs. It was solely based on the ranking of pharmaceutical companies by total revenues as reported in Scrip's Pharmaceutical Company League Tables 2006 [11] and did not take into account previous experience in drug development, previous success in obtaining approval for another medicinal product, potential collaboration with larger pharmaceutical companies, among others.

We did not fully address to what extent sponsors modified their development plan based on the SA given, nor did we address the reasons for non-compliance with SA. Although it is obvious for a non-compliant MAA that the sponsor choose not to/was unable to modify the development plan in accordance with the CHMP's advice, it is unknown for compliant MAAs whether the sponsor choose to modify the development plan according to the CHMP's suggestions or if the development plan was acceptable as submitted to the SAWP and did not require any changes. It is possible that large pharmaceutical companies submit development plans for SA that are considered acceptable by the CHMP and do not require any changes, or that large pharmaceutical companies can modify their development plans more easily and thereby comply with CHMP advice.

Based on our findings, it appears reasonable to further encourage all companies that intend to use the Centralised Procedure to engage in a dialogue with EMEA regarding the development programme via the SA procedure. Optimally, this dialogue should be initiated early during development and continue at the critical development steps. A follow-up SA is strongly recommended when the company subsequently deviates from the SA given or from existing regulatory guidelines, i.e. when there are major changes in the development plan or "state-of-the-art" treatment for the therapeutic indications. The fact that small companies request SA less frequently than their larger peers as well as the poor

compliance with SA by smaller companies and sponsors of orphan medicinal products is of concern, and the reasons behind poor compliance need to be further explored. The EMEA has addressed some of these issues by offering free scientific advice (protocol assistance) to sponsors of designated OD. In addition, SMEs are offered a 90% fee reduction for scientific advice, and the EMEA has created a designated SME office to support the special needs of SMEs. Since the SME regulation came into force in 2006, more than 200 SME companies have requested and received SA. However, it is too early to evaluate the impact of this activity on the outcome of the MAAs.

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