EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Annual Report from the SME Office 2012

The European Medicines Agency launched an initiative to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs) in December 2005.

An update on SME related activities in 2012 is provided here, together with an overview of experience with application for centralised marketing authorisations.

An overview of registered SMEs

In 2012, the number of companies assigned SME status by the agency increased by 62% compared to the previous year, with a total of 1098 SME companies registered with the EMA at year end. The significant increase was primarily due to companies registering for the submission of electronic submission of product information[1] and for MedDRA fee incentives.

Companies applying for assistance benefitted from a streamlined SME validation process introduced in November 2011. As such the average time taken for the Agency to review SME declarations remained at a similar level to 2011 (21 days). Simplification of SME assignment remains a key challenge and to further ease the administrative process, an electronic SME declaration form is currently being piloted for rollout in 2013. Furthermore, the SME Office has initiated a dialogue with other EU agencies to exchange best practice.

The large majority of companies registered with the EMA are developing medicinal products for human use (76%), 4% are veterinary companies, 6% companies are developing products for both human and veterinary use and the remaining 14% can primarily be categorised as service providers. The relative size of registered companies remained the same as previous years with around 41% of micro-sized companies (<10 staff). The geographic distribution changed slightly in 2012 with the highest proportion of companies being based in the United Kingdom, Germany, France, Spain and Sweden.

The large majority of SMEs are research and development stage companies. Thirteen percent (13%) are academic spin-offs, and 8% (80 enterprises) were created in the last two years. The majority are privately owned either by natural persons such as founders or employees, or owned by private corporations through partnership or majority holdings. Funding by venture capital, or other private investments (e.g. business angles, institutional investors) accounts for 18% of companies' capital share (see figure 1).

[1] Article 57(2) of the new pharmacovigilance legislation (Regulation No 1235/2010)

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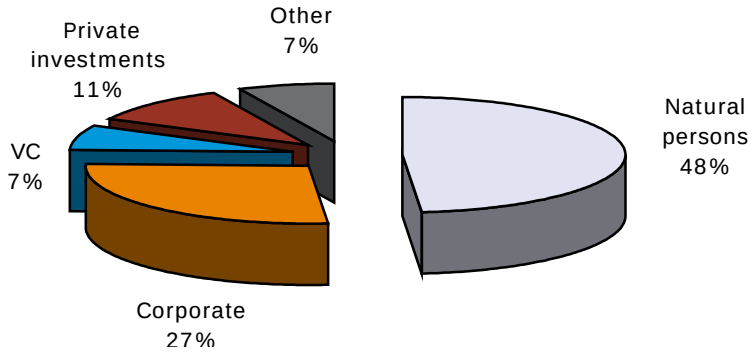
Figure 1: SME ownership (2006-2012)



Access to capital remains a key concern for SMEs and, to raise awareness of the various financial instruments available at EU level, an updated overview of initiatives to support financing of SMEs and research funding opportunities from the European Commission has been published on the EMA website[2].

Scientific advice and regulatory assistance

In 2012, the percentage of SMEs seeking scientific advice for human medicines (28%) increased compared to the previous year (20% of all applicants). One of the seven biomarker qualifications and two of the six scientific advice with Health Technology Assessment bodies were sought by SMEs. Clinical advice was sought in the majority of cases (49%), with preclinical and quality requests featuring in 34% and 17% of cases respectively. The number of scientific advice for veterinary medicines also increased (13 requests representing 46% of all requests) compared to 2011 (38 %).

Overall the number of companies active in the field of advanced therapy medicinal products (ATMP)[3] stood at 7% this year. Specific incentives for ATMP such as certification on quality and non-clinical data, available exclusively to SMEs, continue to show a low uptake however. SMEs are encouraged to approach the SME office to discuss the certification process and overall regulatory support available to development.

This year's SME workshop focused on pharmacovigilance, in view of the new legislation entering into force in July 2012. The meeting enabled SMEs to acquaint themselves with key aspects of the legislation whilst also providing an opportunity for regulators to obtain valuable feedback on the implementation of the legislation.

SME outcomes through the centralised procedure

From December 2005 to December 2012, 98 marketing authorisation applications (MAAs) were submitted by SMEs, 83 for human medicinal products and 15 for veterinary medicinal products.

To date, for veterinary medicines, there have been 10 positive and 2 negative outcomes (withdrawals), with three applications currently ongoing.

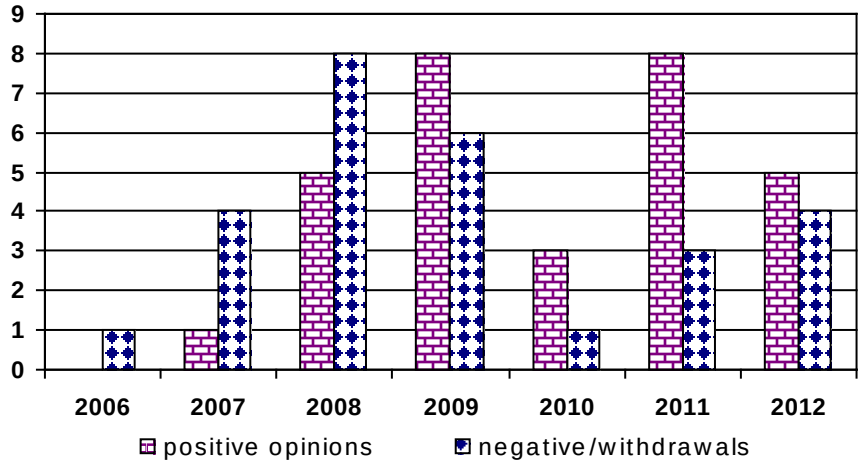
The following observations can be made on the applications from SMEs for human medicines that have received an outcome to date:

- There have been 30 positive and 27 negative outcomes (negative opinions or withdrawals), with 26 MAAs currently ongoing.
- Although the success rate for SMEs over this 7 year period (53%) remains lower than the average for all applicant companies (78%), it is encouraging to see that over the last 4 years the number of

[2] www.ema.europa.eu Regulatory / Human Medicines / SME office / Related information
[3] Gene therapy, somatic cell therapy and human tissue engineering

positive outcomes has exceeded the negatives with a success rate of 63%. Furthermore, it is important to highlight that these figures relate solely to MAAs where the applicant is an SME at the time of filing and do not take into account of mergers/acquisitions or out-licensing prior to filing.

Figure 2: SME applicants - MAA outcome by year for human medicines (2006-2012)



- The last 2 years has seen an increase in SMEs seeking scientific advice prior filing for marketing authorisation applications (64% compared to 41% in previous years).
- Although the quality (module 3) documentation continues to be a problem area for many SMEs, in 2011-12 there was a decrease in the number of major objections raised in this area (figure 3). Particular problem areas relate to the manufacturing process validation, the setting of specifications, and stability data.
- With regard to the preclinical data (module 4), the percentage of major objections remained unchanged with issues being most frequently raised on pharmacodynamics, pharmacokinetics, and toxicity study design.
- For the clinical documentation (module 5), major objections related mainly to the effect size or the need for additional clinical data, the robustness of pivotal data and pharmacokinetic and pharmacodynamic studies. A detailed breakdown is provided in figure 4.
- Finally regarding clinical safety, the issues raised most frequently related to methodological concerns (size/quality/duration of safety data), the adverse event profile of the product, and the lack of specific interaction studies.

Figure 3: Major objections in Day 120 List of Questions for SMEs (2006-2012)

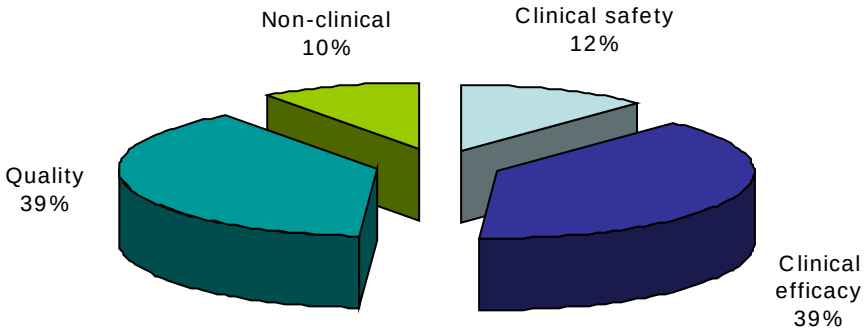
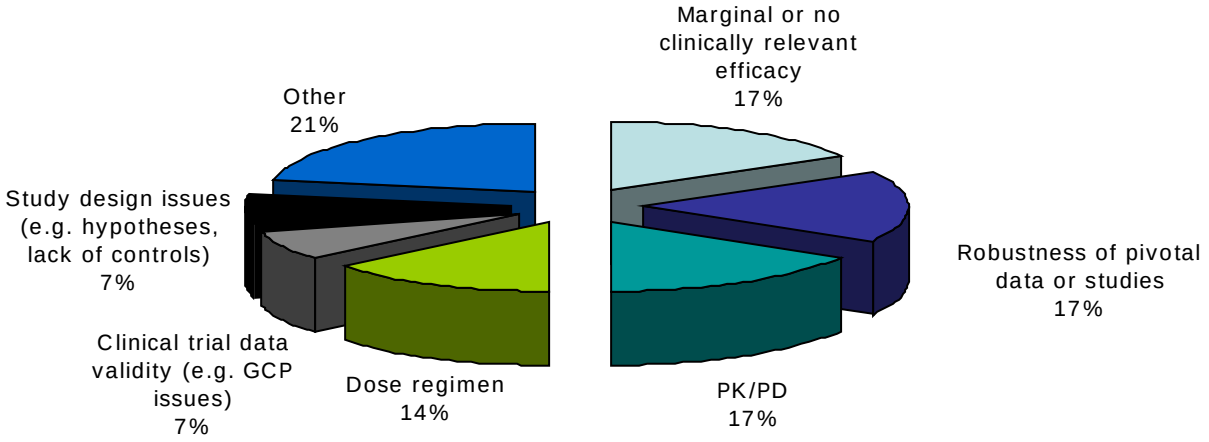


Figure 4: Major clinical efficacy objections in Day 120 List of Questions for SMEs (2006-2012)



Closing remarks

Experience of SMEs applying through the centralised procedure, although still somewhat limited in numbers, provides useful information on the areas where further regulatory assistance and advice should focus. It is encouraging to see that the number of SMEs seeking scientific advice prior to filing has increased. However many companies still seek advice late in development. The importance of opening up an early dialogue with the agency on all aspects of development, including quality, is emphasised as well as following up on the advice received to discuss major changes to development or compliance of the advice received. There is also a need to raise awareness of SMEs to regulatory procedures such as ATMP certification and the possibility for joint EMA and HTA dialogue to encourage uptake.

The 2011 survey highlighted the importance of the SME office as an information provider and the Agency is working hard to reinforce this role. The next version of the SME User Guide is currently being finalised with an overall update and new information including pharmacovigilance requirements, and anti-falsification measures. The Agency will be undertaking a general revamp of its external website which should facilitate access to information by smaller companies. The Agency will also be exploring additional ways of providing training on specific topics of interest through on-line tools such as webinars. Furthermore, there are plans to further simplify the process for assigning and maintaining SME status to decrease the administrative burden on companies.

The EMA remains committed to supporting innovation through the provision of financial and administrative assistance to SMEs. The Agency's SME register, with its growing number of companies, is proving to be a useful information source for EU regulators and will enable more targeted consultation with SMEs on new policies and important regulatory developments in future. Reaching out to all categories of stakeholders in the SME and innovation environment is very important, and the SME office will further develop its interactions with the finance/venture capital community. Interactions with international partners involved in the development of instruments to support SMEs will also continue to be pursued.

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