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Human Medicines Development and Evaluation

Report on the SME Initiative 2006-2011

The European Medicines Agency launched an initiative to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs)[2] on 15 December 2005. As the SME office completes its sixth year of operation, this year's report reviews the experience with the SME initiative, including the 2011 survey and the stakeholder meeting organised by the SME Office.

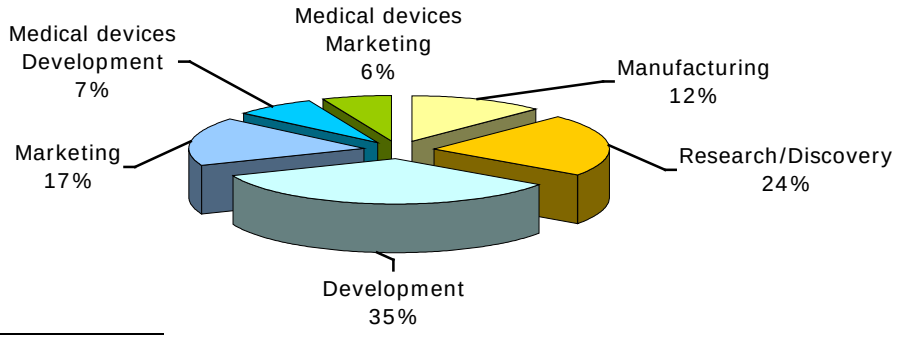
An overview of registered SMEs

In 2011, the number of companies assigned SME status by the agency increased by 34% compared to the previous year. Currently, 679 SME companies are registered with requests from a further 80 companies under review.

The geographic distribution of companies remained similar to previous years, with the highest proportion of companies being based in United Kingdom, France, Germany, Sweden and the Netherlands. There was an increase in the number of micro-sized[3] companies in 2011, with around 41% of all registered companies now falling into this category. Approximately one quarter (23%) of the registered SMEs were created during 2008-2011 and around 17% are academic spin-offs.

Of the assigned companies, the large majority (73%) are developing products for human use, 6% are veterinary companies, 7% companies are developing products for both human and veterinary use and 14% are regulatory consultants[4]. Information on the profile of registered companies is provided in figure 1 below.

Figure 1: Profile of companies with SME status assigned by EMEA – Dec. 2011



[1] Correction of figures in overview of SME outcomes through the centralised procedure.
[2] Pursuant to Commission Regulation (EC) No 2049/2005
[3] Micro-sized companies have less than 10 employees and not more than € 2 million of assets or turnover
[4] Regulatory consultancies, which fulfil the definition of an SME and are established in the Community, may benefit from the provisions of the SME Regulation on behalf of SME clients. It is necessary for the regulatory consultancy to obtain SME status, and the client to fulfil the definition of an SME within the meaning of Recommendation 2003/361/EC.

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Further information on registered companies is available in the public SME register, which was expanded in 2011 to include high level information on the company pipeline and product profile.

In November this year, SME office rolled out a simplified process for handling requests for assignment and renewal of SME status. The new process, which is expected to reduce the administrative burden on companies and speed up the SME assignment/renewal process includes: a move to electronic-only submissions; introduction of an ownership checklist to improve accuracy of submissions; a risk-based approach to the Agency's review process, reducing the number of submission that need to be checked; and replacement of formal SME qualification documents with electronic versions.

SME Office survey and feedback from stakeholder roundtable

A survey was launched in March 2011, to obtain detailed feedback on the SME initiative, 5 years following its implementation. It also aimed to gather information on how successful (or not) the measures introduced to support SMEs have been, and to identify current and future challenges faced by SMEs in the pharmaceutical sector. More than 220 responses were received from SMEs, stakeholders and interested parties. The large majority of respondents were operating in the pharmaceutical field (74%), 12% medical devices and 15% service providers. A full report of the survey is available on the EMA website.

The results indicated the general level of awareness of the SME regulation to be good and the practical implementation of the programme, thus far, to have been highly successful, with 89% of respondents rating the initiative as very relevant or relevant. Of the specific support measures available, the SME User Guide rated the highest followed by the financial incentives, the SME news bulletins, regulatory assistance, workshops and the public SME register.

The measures that respondents considered would benefit from some further reinforcement were the financial incentives, regulatory assistance and pre-submission support in the run up to a marketing authorisation application.

As far as the SME assignment process itself and the contact with the SME Office, respondents were highly satisfied, with 90% rating it as very good or good.

The survey also attempted to identify current and emerging challenges for SMEs. A meeting with stakeholder organisations was held on 3 October 2011, to present the results of the survey and discuss the challenges identified as well as those reported by SME stakeholders (link to stakeholders meeting report).

Access to capital and research funding are a major concern for many companies and stakeholders welcomed the additional support available to SMEs through the European Commission's Seventh Framework Programme (FP7). There is a need to raise awareness of SMEs to the various financial instruments currently available at EU level and, with this in mind, a concise overview of initiatives to support financing of SMEs and research funding opportunities from the European Commission has now been published on the EMA website.

With regard to regulatory challenges, areas where SME stakeholders called specifically for more information and advice include: the clinical trials directive, the variation regulation, post-authorisation efficacy and safety studies, and the provision of product information to the EMA on all authorised medicines in accordance with Article 57(2), second sub-paragraph of Regulation (EC) No 726/2004.

Proposals mooted as points to consider in a future action plan to be developed by the SME Office in the short to medium term include: expanding advice on global development programmes, offering further support in the pre-submission phase, reducing the administrative burden of multiple dossier

preparation, e-CTD support, providing additional training for SMEs through e.g. EMA webinars, reinforcing communication and improving links with National Competent Authorities, and improving impact assessment of regulatory guidance.

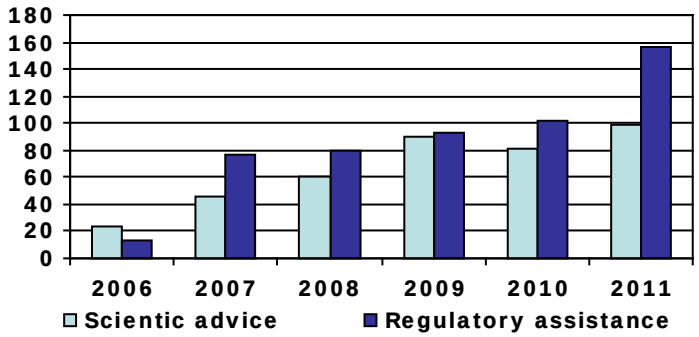
The need to encourage 'early' scientific advice was emphasised, even prior to first in man clinical trials. There is also a need to raise awareness of 'late' stage regulatory activities such as scientific advice cooperation with Health Technology Assessment (HTA) bodies, and advice on post-marketing authorisation issues related to the pharmacovigilance legislation.

Overview of scientific and regulatory assistance

The number of SMEs seeking scientific advice has increased since 2006 with SMEs also benefitting from new scientific procedures such as qualification opinions on novel methodologies and biomarkers (2 in 2011) and the early informal interactions offered by the Agency's Innovation Task Force. For veterinary medicines, the uptake increased significantly in 2011 with 10 requests for scientific advice from SMEs validated in 2011, representing 38% of all veterinary scientific advice requests.

For human medicines, in 2011 the proportion of SMEs (99) to all applicants remained at the same level as in previous years (~20%). Clinical advice was sought in the majority of cases (48%), with preclinical and quality requests featuring in 32% and 19% of cases respectively. SMEs appear to be seeking advice earlier in development as the proportion of companies seeking advice on phase II trials increased to 32% (19% in 2010), while those in phase III and phase I were 52% and 16% respectively. The number of follow-up advice and multidisciplinary requests remains relatively low, however, and companies should be encouraged to contact regulators when major changes are introduced to development programmes.

Figure 2: SME applicants - Scientific advice (human medicines) and regulatory assistance by year (2006-2011)



To date, more than 520 requests for regulatory and administrative assistance from SMEs have been raised through the SME office (see figure 2). Requests increased by 53% in 2011 compared to 2010. Queries related mainly to the marketing authorisation application (MAA) filing strategy (e.g. eligibility to centralised procedure, accelerated review, and conditional approval/exceptional circumstances), MAA presubmission issues (e.g. CTD, and invented name review), and general queries about SME incentives. Assistance was provided through meeting, teleconference, or via email.

As well as having the possibility to seek scientific advice on upcoming development, SMEs developing advanced therapy medicinal products (ATMPs) can request certification from the Agency on the extent that quality and where available non-clinical data already generated comply with MAA review standards. To date, SME uptake of certification has been surprisingly low (1 in 2009) and a short survey has been

launched this year to ascertain the reasons for this. SMEs are strongly encouraged to contact the SME office for information on how to apply.

Workshops for SMEs

The SME Office organizes annual workshops dedicated to addressing the particular needs of SMEs. Workshops to date have covered various topics including: the regulatory framework, quality of medicines, non-clinical data requirements, paediatric requirements, and regulatory considerations in initiating clinical trials.

The 2011 SME workshop was organised in co-operation with the Scientific Advice Working Party (SAWP) and focused on scientific and regulatory advice. The various opportunities for early dialogue and advice from the Agency were presented, as well as regulatory issues relating to MAA, and national initiatives to support SMEs in France, Germany and in the USA from CDER's Small Business Assistance Division. Presentations from this and all EMA workshops are available online.

The EMA recognises that training opportunities are very important to SMEs and the Agency will continue to run workshops and will explore further ways to build on these. The 2012 SME workshop will focus on Pharmacovigilance and detailed information will be published online early next year.

Overview of SME Outcomes through the centralised procedure

In the six year period since December 2005, seventy-one MAAs have been submitted by SMEs, 59 for human medicinal products and 12 for veterinary medicinal products. Of those 36 have received positive outcomes, 33 of which have benefited from the SME translations service.

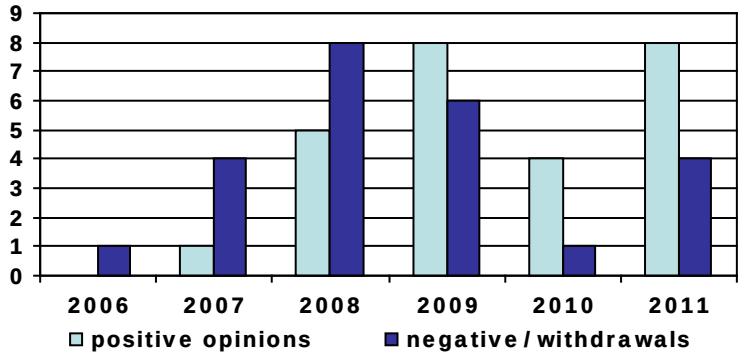
Of the veterinary medicinal products that have been subject of MAAs, ten have been authorised: one new chemical entity, two vaccines, and 7 generics. Two veterinary applications are currently ongoing.

For human medicinal products, 26 have received positive outcomes (21 have been authorised and 5 are currently in the decision-making process) and 24 have resulted in negative outcomes (4 negative opinions and 20 withdrawals). Nine applications are currently ongoing.

The 26 positive outcomes include 10 orphan medicinal products, 1 advanced therapy medicinal product and 4 generics. One has been evaluated to an accelerated timetable and 3 have been recommended for authorisation under exceptional circumstances.

Although, the success rate for SMEs over this 6 year period (52%) is much lower than the average for all applicant companies (73%) for the same period, the evolution of outcomes by year remains encouraging (figure 2). The relative proportion of positives vs negatives has increased each year, with positive outcomes exceeding the negative over the last three years.

Figure 3: SME applicants - MAA outcome by year for human medicines (2006-2011)



The SME Office monitors the progress of SME applications, and reports on the reasons for negative outcomes as evidenced by the types of major objections raised by CHMP during MAA review. Although, the main reason for negative outcomes in 2006-2010 has been the need for additional clinical data to support the applications, the quality (module 3) documentation continues to be a problem area for many SMEs.

At its May 2011 Workshop, the SME office provided a detailed summary of the most frequent objections in each of the four areas, quality, preclinical, clinical efficacy and clinical safety with a view to emphasising the areas where scientific advice is particularly key for SMEs. A copy of that presentation is available online.

Closing remarks

The outcome of this year's survey and stakeholder roundtable confirm that, thus far, the implementation of the SME Regulation has been highly successful in meeting its objectives. The large majority of registered SMEs, which have benefitted from the scheme, rate the incentives as very relevant or relevant.

Access to capital is a key concern for SMEs and, to raise awareness of the various financial instruments currently available at EU level, a concise overview of initiatives to support financing of SMEs and research funding opportunities from the European Commission has now been published on the EMA website.

The uptake of SMEs into scientific advice and regulatory assistance has remained at a high level, which is encouraging. However, for medicinal products for human use the overall results at the stage of the marketing application remain somewhat disappointing. Many companies are still seeking advice at a late stage or are not taking advice into account in their development, and the importance of opening up an early dialogue with the Agency on all aspects of development, including quality, is underlined. Companies unfamiliar with the EU regulatory approval process are also encouraged to seek regulatory assistance and approach the SME office to discuss their planned regulatory strategy.

The Agency is committed to continuing to support SMEs and sustaining the regulatory and scientific support to SMEs in the pharmaceutical sector. Collaboration with SME support structures nationally and internationally will also continue. The SME office will draw up an action plan in 2012 taking into account the valuable feedback received from this year's survey and stakeholder roundtable.

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