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Human Medicines Development and Evaluation

Report from SME Office on its 5th Year of Operation

The European Medicines Agency launched an initiative to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs)[1] on 15 December 2005. The SME office has now completed its fifth year of operation. This year's report focuses on the launch of the SME office's public register and SMEs experience to date with paediatric investigation plans/deferrals and waivers.

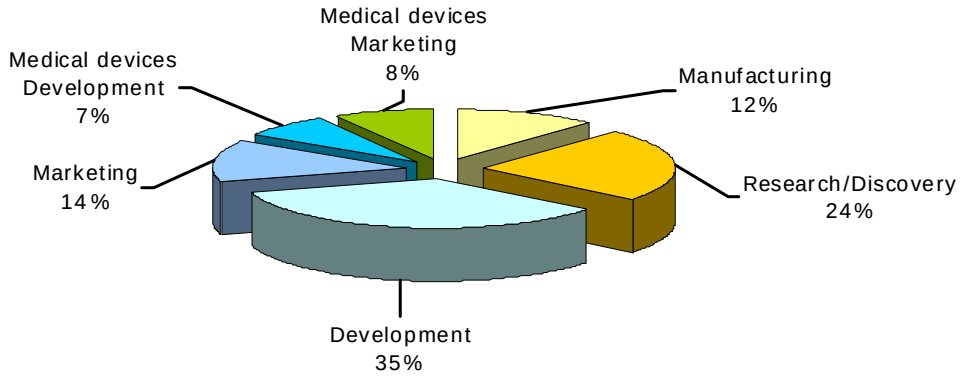
An overview of registered SMEs

In 2010, the number of companies assigned SME status by the agency increased by 10% compared to the previous year. Currently, 507 SME companies are registered with requests from a further 58 companies under review.

The relative size of registered companies and their geographic distribution remained similar to previous years, with the highest proportion of companies being based in United Kingdom, France, Germany, Sweden and the Netherlands. Currently 36 % of companies are micro, having less than 10 employees and not more than € 2 million of assets or turnover. Around 21% are academic spin-offs.

Of the assigned companies, the large majority (69%) are developing products for human use, 12% are veterinary companies, 7% companies are developing products for both human and veterinary use and 12% are regulatory consultants [2]. 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. 2010



[1] Pursuant to Commission Regulation (EC) No 2049/2005
[2] 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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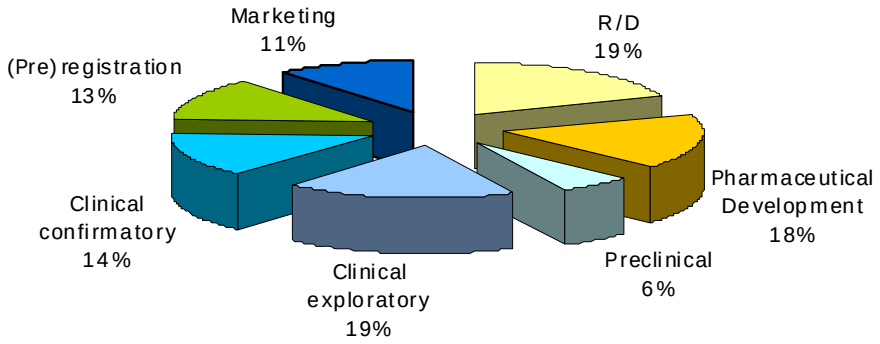
Launch of public SME Register

This month sees the launch of the 1st phase of the SME public register which provides further information on SME companies that are registered with the EMA. In the past public information on SME assigned companies has been limited to the company name and country of origin. Now additional information on companies with medicinal products under development, including contact details, and domain (human /veterinary), is available online and will be updated quarterly.

The SME database is searchable and has been designed to address the increasing demand for information and interaction from SMEs, their stakeholders and national competent authorities. Information in the database will be expanded in the first quarter of next year to include high level information on the company pipeline and product profile.

Information gathered from companies to date on the phase of product development shows that the large majority of companies registered with the Agency are yet to place a product on the market, approximately a third of them have reached the clinical phase of development – with some 14% in late phase clinical trials (Figure 2).

Figure 2: Phase of Product Development of SMEs – Dec. 2010



Looking at the types of product under development, the broad breakdown into chemical entities vs. biologics is 66% and 32% respectively. Of those companies developing biologics, 65% are developing recombinant DNA derived products and 35% advanced therapy medicinal products (ATMPs): cell therapy – 46%, tissue engineering – 29%, and gene therapy – 25%. A small proportion of companies are working in the field of pharmacogenomics/biomarkers (4%) and nanotechnology (5%).

The year at a glance

In 2010, 81 SMEs developing medicines for human use sought scientific advice or protocol assistance from the Agency. For veterinary medicines, 7 requests for scientific advice from SMEs were received this year, representing 33% of all veterinary scientific advice requests. For human medicines, the proportion of SMEs to all applicants remained at the same level as last year (20%). Clinical advice was sought in the majority of cases (47%), with preclinical and quality requests featuring in 32% and 21% of cases respectively. Many companies (63%) are still seeking advice rather late in development (phase III), with 17% in phase II and 20% in phase I.

Seventeen centralised marketing authorization applications (MAAs) were submitted by SME applicants in 2010, 13 for human medicinal products and 4 for veterinary medicinal products. For veterinary medicinal products there were 2 positive outcomes (both generics) and for human medicinal products, 4 positive outcomes (3 orphan medicinal products, & 1 generic) and 1 negative (withdrawal of an ATMP). Currently, 22 centralised applications from SMEs are ongoing (including 2010 and earlier submissions). Further information on SMEs experience through the centralised approval process will be released next year when further procedures are finalised.

In May, the EMA finalised its first ATMP certification procedure for a suspension of mononuclear cells under development by an SME in the cardiovascular field. Through certification, SMEs can obtain feedback from the Agency's Committee for Advanced Therapies early in development on the extent that quality and where available non-clinical data generated with an ATMP comply with MAA review

standards. Interest in the certification procedure to date has been surprisingly low and SMEs are strongly encouraged to contact the SME office for more information on this important new service.

Throughout 2010 requests for regulatory assistance from SMEs remained high (102), with a 10% increase compared to 2009. The SME office held briefing meetings with 7 companies to discuss regulatory filing strategy. In addition, a further 5 requests for translations were processed by the Agency in 2010, bringing the total of companies that have benefited from this service to 21.

This year's annual SME workshop was organized in May in co-operation with the Clinical Trials Facilitation Group (CTFG) and focused on regulatory considerations in initiating clinical trials. Attendance was high with more than 150 SME representatives and their stakeholders participating. The next SME workshop, which will take place in May 2011, will focus on scientific and regulatory procedural advice. Further information will be published early next year on the Agency's web-site.

A Frequently Asked Questions document on the SME assignment process and an update of the SME User Guide were both published in December. The User Guide includes an update of SME incentives available at national level. SME/Innovation offices have recently been launched by AffSAPs in France and by the Paul Ehrlich Institute in Germany, and contact details are provided in annex to the Guide.

In September, the SME office opened up a dialogue with the Small Business Assistance group within CDER at the US FDA to exchange views and experiences. The two agencies look forward to continued collaboration on SME related issues in the future.

In June, the SME Office received the 2010 Mediscience award for 'Most significant contribution to mediscience sector'.

PIPs/deferrals/waivers

EU paediatric legislation, which entered into force in January 2007, brought with it new obligations for companies to agree paediatric development plans with the Agency early in development. As almost 4 years have now passed, it is of interest to report on how SMEs are coping with the new paediatric investigation plan (PIP) requirements generally.

Between July 2008 and September 2010, the EMA received 912 valid applications for PIP/deferral/waiver from all companies (non-SME and SME). Of those, 74 (8%) applications were from SME applicants. The following observations can be made on the applications received from SMEs:

- 52 of the requests had outcomes and 22 were ongoing. Of those with outcomes, forty were positive (77%) i.e. 23 PIPs and 17 waivers adopted. Twelve were negative (23%) i.e. 2 negative opinions and 10 withdrawals after procedure start. For all companies over the same period, 84% had positive outcomes and 16% negative.
- The average active time from submission to opinion is 210 days for SMEs which is marginally shorter than for non-SMEs (217 days). The average response (so-called "clock-stop") time is around 120 days for both SME and non-SME companies.
- 7 requests for PIP were withdrawn at validation and never started.
- Since the beginning of 2010 EMA has offered pre-submission meetings to SMEs. To date, only 3 meetings have been held with SMEs.

The SME office received many requests for regulatory assistance on paediatric issues, such as: timing of scientific advice vs PIP, clarification on PIP requirements for a particular product, PIP vs. waiver, queries relating to the submission process, proposals for Paediatric Use Marketing Authorisation (PUMA), and PIP modification/compliance issues.

Closing remarks

From the limited experience to date with the paediatric initiative, smaller companies appear to have similar PIP outcomes and timelines to all companies. There is a need, however, to raise SMEs awareness of the requirements of the paediatric legislation, which if not addressed may delay validation of the MAA. Companies unfamiliar with the PIP approval process are encouraged to approach the SME office to request regulatory assistance and should consider requesting a pre-submission meeting prior to filing the PIP.

The uptake of SMEs into scientific advice and regulatory assistance remains at a high level. This is encouraging and financial provisions to support SMEs applying for scientific advice will be maintained in the future. Companies are also reminded that once initial advice has been sought, follow-up advice is recommended particularly if major changes in development are considered.

The same, however, cannot be said for the new ATMP certification procedure. SMEs have been slow to benefit from this incentive aimed at supporting the development of ATMPs. Detailed guidance documents have recently been released and companies developing ATMPs are encouraged to contact the Agency to discuss how certification might benefit their product development and how different regulatory pre-authorisation support measures might be prioritised.

As the SME initiative has now been in place for 5 years, in 2011 the SME office will undertake a survey of SME companies and stakeholders on the various incentives and support measures in place.

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