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Human Medicines Development and Evaluation

Report from SME Office on its 4th 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. To coincide with the fourth anniversary of the Agency's "SME Office", an update on SME related activities is provided here. The focus, this year, is on advanced therapy medicinal products and SME outcomes through the centralised procedure.

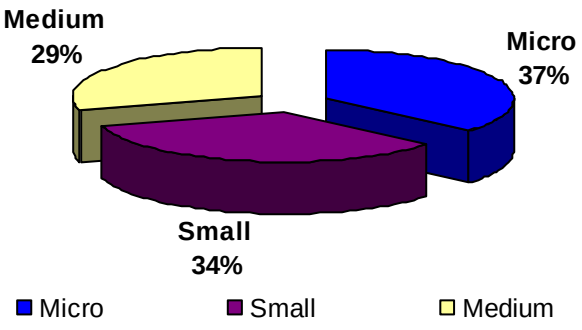
An overview of registered SMEs

In 2009, the number of companies assigned SME status by the agency increased by 24% compared to the previous year. Currently, 460 SME companies are registered with requests from a further 47 companies under review (updated list of companies). Despite the increased workload, the average time taken for the Agency to review SME declarations was maintained at 3 weeks, with companies taking 3 weeks on average to respond to questions.

The large majority of companies are developing medicinal products for human use, 25 are veterinary companies, 16 companies are developing products for both human and veterinary use and 47 are regulatory consultants[2].

The relative size of registered companies (figure 1) and their geographic distribution remained similar to previous years, with the highest proportion of companies being based in UK, Germany, France, Sweden and the Netherlands.

Figure 1: Size of companies assigned SME status by EMEA – Dec. 2009



[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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The year at a glance

The number of SMEs seeking scientific advice (90) remained relatively high in 2009. For veterinary medicines, 7 requests for scientific advice from SMEs were validated in 2009, representing 64% of all veterinary scientific advice requests. For human medicines, the proportion of SMEs (83) to all applicants remained at the same level as last year (21%). Clinical advice was sought in the majority of cases (45%), with preclinical and quality requests featuring in 33% and 22% of cases respectively. The majority of companies (62%), however, are still seeking advice rather late in development (phase III), with the remainder being equally split between phase II (19%) and phase I (19%).

In May 2009, to coincide with the launch of the 1st "SME week" by the European Commission, the Agency hosted a meeting with stakeholder organizations. The aim was to review the SME initiative and discuss how it might be improved in the future. It was agreed that the high uptake of SME companies, to date, into the scheme underlines the importance of existing measures and the significant role the "Office" now plays as a service provider. Proposals put forward for strengthening the initiative, included pre-MAA strategy briefing meetings, eCTD support, and ad-hoc meetings at major milestones in the approval process. Further details can be found in the meeting report.

SMEs participated in three workshops organised by the Agency during the course of 2009, the first on non-clinical aspects of development in February, followed by advanced therapy medicinal products in April and finally paediatric medicines in October. Attendance was high with more than 100 SME representatives attending each meeting. Preparations are now underway for the next SME workshop which will take place in May 2010 and will focus on initiation of clinical trials in the European Union. Further information will be published early next year on the Agency's web-site.

Throughout 2009 requests for regulatory assistance from SMEs remained high (93), with a 10% increase compared to 2008. Further to the recommendations made by stakeholders, the SME office initiated in-depth briefing meetings with 4 companies preparing for MAA submission. These meetings were deemed useful and will be rolled out further in 2010. In addition, a further 8 requests for translations were processed by the Agency in 2009, bringing the total of companies that have benefited from this service to 16.

Advanced Therapy Medicinal Products (ATMPs)

As many SMEs are active in the field of ATMPs[3], this year a number of the registered companies started to benefit from new incentives introduced at the end of 2008 to encourage research and development of ATMP pursuant to Regulation (EC) No 1394/2007.

Of the 460 SMEs currently registered with the Agency, 80 (17%) are developing ATMPs. Of these, 57% are developing cell therapy, 24% tissue engineering, and 19% gene therapy. In 2009, all 12 requests for classification as ATMP which were processed by the Agency's Committee for Advanced Therapies (CAT) were from SMEs. These companies also benefited from the support of the Agency's Innovation Task Force and the SME office to ease their access into the EU regulatory system.

In 2009, two SME companies with MAAs for ATMPs ongoing already benefited from a new type of fee reduction. An application for marketing authorisation for an ATMP for human use from an SME applicant is eligible a 50% fee reduction (subject to proof that the product concerned has a particular public health interest in the Community) and a 50% fee reduction for post-authorisation activities for the first year after marketing authorization[4].

In December 2009, the first certification request was submitted by an SME and is currently under evaluation by the CAT. The new procedure for certification, available exclusively to SMEs, was introduced in August 2009. Applications for certification will be evaluated to the same scientific standards as an application for marketing authorisation and will provide SMEs with feedback on whether their development is 'on track' and meets current requirements. Although the certificates will not be legally binding, the aim is to facilitate the evaluation of any future application for clinical trials and marketing authorisation based on same data.

[3] Medicinal products for human use which are based on gene therapy, somatic cell therapy or tissue engineering

[4] The fee reductions will be available for a limited period. Fee reductions for applications for marketing authorisation and for the first year of post-authorisation activities apply until 30 December 2011 for advanced therapy medicinal products other than tissue-engineered products, and 30 December 2012 for tissue-engineered products.

SME Outcomes through the centralised procedure

In the four year period since December 2005, forty-five SME companies have submitted MAAs, 37 for human medicinal products and 8 for veterinary medicinal products.

Of the veterinary medicinal products that have been subject of MAAs, four have been authorised: one new chemical entity (Masivet) and 3 generics (Rheumocam, Acticam, and Melovem). Four veterinary applications are currently ongoing.

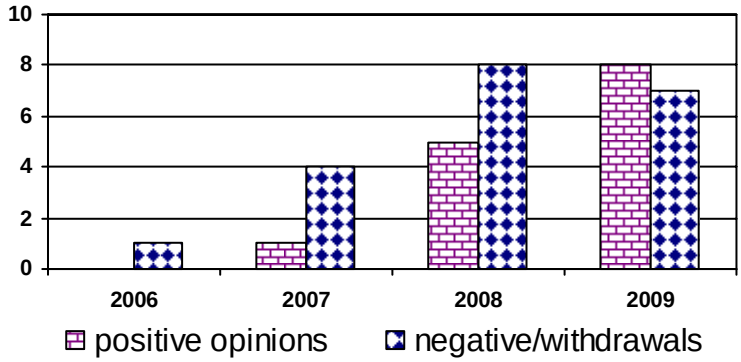
For human medicinal products, 14 have received positive outcomes (12 have been authorised and 2 are currently in the decision-making process) and 20 have resulted in negative outcomes (4 negative opinions[5] and 16 withdrawals). Three applications are currently ongoing.

The 14 positive outcomes (listed below) include 6 orphan medicinal products, 1 advanced therapy medicinal product and one generic. One has been evaluated to an accelerated timetable and 3 have been recommended for authorisation under exceptional circumstances.

- Soliris for paroxysmal nocturnal haemoglobinuria
- Firazyr for hereditary angioedema
- Evicel for improvement of haemostasis in surgery
- Ceplene for acute myeloid leukaemia
- Mepact for osteosarcoma
- Ixiaro for immunisation against Japanese encephalitis
- Qutenza for peripheral neuropathic pain
- Ellaone for emergency contraception
- Vedrop for vitamin E deficiency due to malabsorption
- Grepid for prevention of atherothrombotic events
- ChondroCelect for repair of symptomatic cartilage defects
- Resolor for chronic constipation
- Zenas for Lambert-Eaton Myasthenic Syndrome (LEMS)
- Tepadina for conditioning treatment prior to haematopoietic progenitor cell transplantation

Although, the success rate for SMEs over this 4 year period (41%) is much lower than the average for all applicant companies (75%) for the same period, it is encouraging to see the evolution of outcomes by year (figure 2). The relative proportion of positives vs negatives has increased each year, with the positive outcomes (53%) exceeding the negative (47%) for the first time in 2009.

Figure 2: SME applicants - MAA outcome by year for human medicines (2006-2009)



The following observations can be made on the 34 applications from SMEs for medicinal products for human use that have received an outcome to date:

- Overall 41% (14/34) had previously sought scientific advice. Although this proportion applied equally to those companies with positive and negative outcomes, all but two of the companies with negative outcomes failed to take the advice into account in their development.

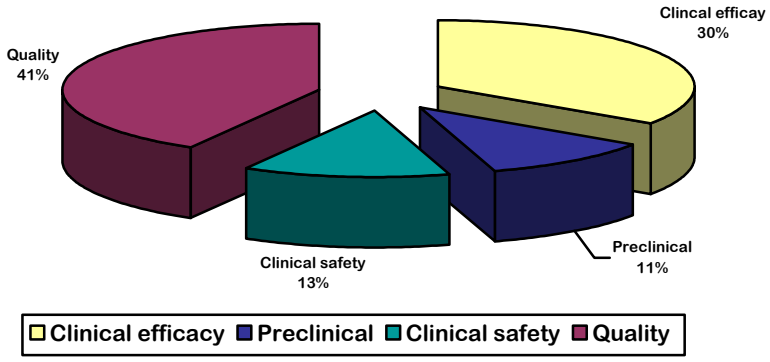
- The average active time for the centralised evaluations remains similar to that reported previously: 222 days, with an average response (so-called “clock-stop”) time for SME companies of around 7 months.

[5] One of the 4 negative opinions is currently under re-examination

- With regard to the clinical documentation submitted, the SME Office reviewed the phase & design of “pivotal” clinical studies in MAAs with outcomes to September 2009. For those with positive outcomes, 83% contained at least one phase III randomised controlled trial considered as pivotal (50% having only one, 33% having 2 or more). For those applications with negative outcomes, a higher proportion was based on non-controlled trials. Furthermore, those companies with negative outcomes were found to be filing earlier in development and only 6% had two or more pivotal phase III studies.

- On average 9 major objections per application were raised by CHMP at day 120 of the procedure. Although, the main reason for negative outcomes is the need for additional clinical data to support the applications, the quality (module 3) documentation continues to be a problem area for a lot of SMEs, with 41% of major objections being raised in this area alone (figure 3).

Figure 3: Major objections in Day 120 List of Questions for SMEs (34 MAAs)



Closing remarks

From the, albeit, limited experience to date with MAAs, there continues to be elements of premature filing. This is evidenced by the number of SMEs, which following negative/opinion withdrawal, are seeking scientific advice and re-submitting applications once further data has been generated. Companies unfamiliar with the EU regulatory approval process are, therefore, encouraged to approach the SME office to request a briefing meeting to discuss their planned regulatory strategy.

The uptake of SMEs into scientific advice and regulatory assistance continues to grow which is a resoundingly positive outcome of the SME initiative. Many companies are seeking advice late in development, however, and the importance of opening up an early dialogue with the Agency on all aspects of development, including quality, is underlined.

Support to innovative SMEs has been further developed in 2009 with the implementation of the major ATMP policy initiative targeting companies developing gene therapy, cell therapy and tissue engineering.

To obtain further information on the various support measures available from the Agency, companies are advised to contact the Innovation Task Force or SME office.

Contacts for further information

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Please note that as of 8 December 2009, the URL of the Agency's website and e-mail addresses has changed from 'emea.europa.eu' to 'ema.europa.eu'. Please update your bookmarks and address books accordingly.