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Stakeholders and Communication

Annual report from the SME Office - 2014

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 2014 is provided here, together with an overview of experience with applications for centralised marketing authorisations.

An overview of registered SMEs

A total of 1301 SME companies were registered with the EMA at year end, an increase of 3% compared to 2013. A streamlined SME validation process introduced in 2011-2012 had a significant impact on the time taken for the Agency to issue SME qualifications, which now takes an average of 12 days (vs. 21 days in 2012). Revised processes for SME assignment and renewal will be rolled out in 2015 to further ease the administrative burden of applying for SME qualification. The SME Office also continues to engage with other EU institutions and agencies to develop synergies and exchange best practices on the EU SME definition, the SME qualification process, financing and support to innovation.

The large majority of companies registered with the EMA are (bio)pharmaceutical companies developing medicinal products for human use (72%), 5% are veterinary companies, 6% are companies developing products for both human and veterinary use, and the remaining 17% are service providers to the pharmaceutical industry. About 20% of registered SMEs perform their activities in the medical device and technology fields. 17% are biopharmaceutical companies developing or marketing biologicals and advanced therapies.

The relative size of registered companies remained the same as previous years with around 45% of micro-sized companies (<10 staff; turnover and balance sheet < € 2 mil). The geographic distribution remains unchanged in 2014 with the highest proportion of companies being based in the United Kingdom (19%), Germany (13%) and France (9%).

An increasing number of SMEs holders of marketing authorisations have started to register with the EMA in order to benefit from incentives, which will apply to micro, small and medium sized enterprises further to implementation of the pharmacovigilance fee regulation.

11% of registered companies are academic spin-offs, and 9% were incorporated in the last three years. The majority of registered SMEs are privately owned either by natural persons or owned by private corporations through partnership or majority holdings. Funding by venture capital and other

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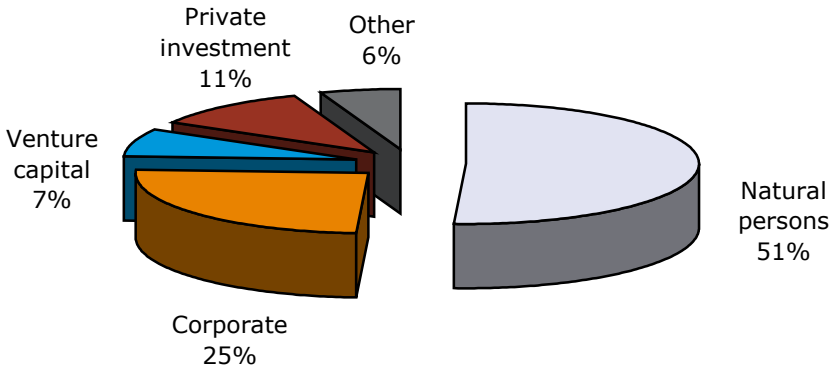
private investments (e.g. investment firms, institutional investors, business angels) accounts for 18% of companies' capital share (see figure 1).

Figure 1: SME ownership (2006-2014)



Regulatory assistance, scientific advice and new targeted incentives

Assistance and support during drug development is important as 56% of registered SMEs are research and development stage companies with a limited number of products in their pipelines. These include predominantly medicinal products containing chemical entities, biologics and advanced therapies, while vaccines and diagnostic and imaging products represent a limited number of products in the pipelines.

In 2014, the number of scientific advice by SMEs for human medicines stood at 121, which represents 24% of all requests for scientific advice and protocol assistance. Biomarker qualifications (6) were also sought by SMEs (40% of all requests), whereas parallel scientific advice with health technology assessment (HTA) bodies were not submitted by SMEs. The number of scientific advice for veterinary medicines also increased (16 requests representing 46% of all finalised requests) compared to 2013 (41%).

Specific incentives for advanced therapies such as the certification procedure, which enables early review of quality and non-clinical data and is available exclusively to SMEs, showed an upturn with 5 certification procedures finalised–2 of them in 2014. A new CVMP Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT) has been established in 2014. It provides support to developers of novel veterinary medicines such as stem cell-based therapies or monoclonal antibodies during the early stages of development.

Regulatory assistance, including SME briefing meetings, are routinely provided with 163 direct assistance to SMEs on different topics such as administrative or regulatory aspects of the pharmaceutical legislation. SME briefing meetings (15) provide assistance to enterprises which are unfamiliar with the EU regulatory approval process. Experience has shown that it allows companies to have an early dialogue with the EMA on their planned regulatory strategy or discuss how to prioritise regulatory procedures to support the development programme, dossier preparation and submission.

Fee incentives covering the overall medicinal product life cycle are now in place for SMEs having centrally authorised products. Fee incentives apply to centralised marketing authorisations for human and veterinary products during the initial authorisation and, since April 2014, for post authorisation activities, such as variations or extensions. The total budget for SME incentives in 2014 was €7.5 mil with scientific advice accounting for the majority.

Pharmacovigilance fee incentives (e.g. periodic safety update reports, post-authorisation-safety-studies) also apply to SMEs which have centrally and/or nationally authorised products for human use.

SME outcomes in the centralised procedure

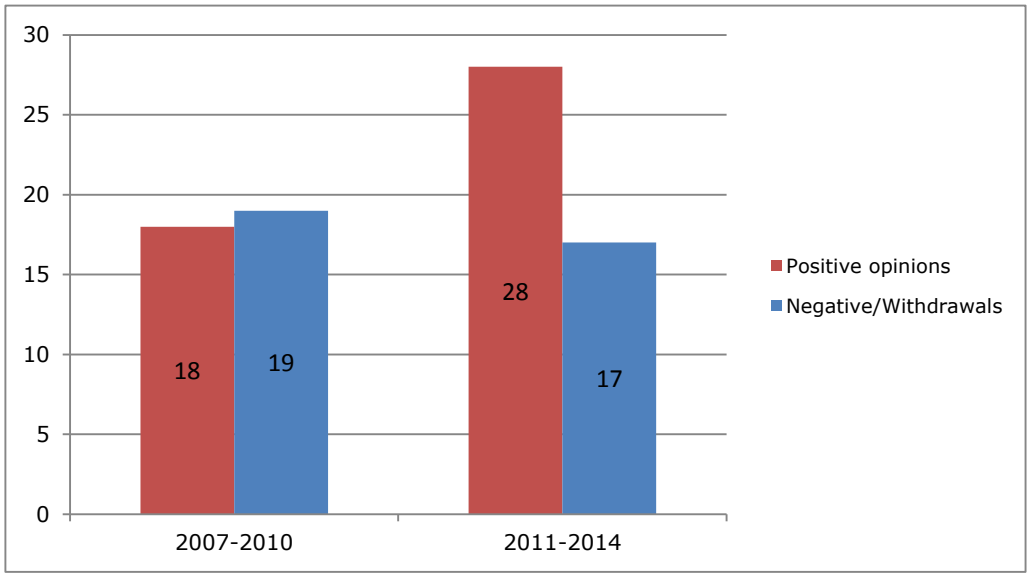
From December 2005 to December 2014, 127 marketing authorisation applications (MAAs) were submitted by SMEs, 107 for human medicinal products and 20 for veterinary medicinal products. To date, for veterinary medicines, there have been 14 positive and 3 negative outcomes (negatives/withdrawals), with 3 applications currently ongoing.

For human medicines, outcomes by SMEs showed over the last four years improvements compared to the preceding four year period (success rates of 62% vs. 49%; see figure 2).

It should be noted that the reported success rate might be confounded by the fact that mergers, acquisitions or out-licensing prior to filing are not taken into account[1].

Scientific advice was requested in an increasing number of marketing authorisations dossiers, the figure reached 64% over 2010-2014 compared to 40% during the 2007-2010 period.

Figure 2: SME applicants – CHMP outcome by year for human medicines (2007-2014)



[1] 'Where do new medicines originate from in the EU?' Nature Reviews Drug Discovery; Lincker et al. Volume: 13, Pages: 92–93 Year published: (2014), Link

The SME office conducted a follow-up analysis on the issues encountered in applications from SMEs for human medicines during 2011 and 2013 at day 120 of the evaluation process. Compared with earlier findings, the analysis revealed the following:

- Deficit areas in the quality and clinical modules of the dossiers continue to be identified. Approximately 46% of major objections were on the quality documentation, 47% on the clinical efficacy and safety documentation and 7% on the non-clinical development. Positive dossiers experience an average of 6 major objections (range: 0-18) and negative/withdrawn files, an average of 12 (range 18-24).

- When comparing outcomes for biologics and chemical entities, an increase in the average number of major objections is noted, with biologics experiencing an average of 15 major objections per dossier vs. 6 for files containing chemical entities. 51% of objections encountered in MAAs for biologics were on quality topics vs. 41% in dossiers for chemical entities.

- The most frequent problem areas in the quality documentation related to manufacturing process validation, control and/or characterization data of active substance/finished product, stability/compatibility data/shelf life and pharmaceutical development.

- Deficits in the pre-clinical development programmes were identified on toxicity study design, pharmacodynamic and pharmacokinetic studies, and reproduction toxicity. Toxicity study design and pharmacodynamics were more frequently raised in biologics applications than in dossiers for chemical entities.

- Major deficiencies in the clinical documentation related to the analysis/robustness of pivotal data, inconsistent data on clinical efficacy, study design and safety issues.

Closing remarks

SMEs applying through the centralised authorisation procedure seem to have been experiencing more favourable regulatory approval rates in the past four years. Deficit areas in the quality and clinical modules of dossiers however continue to be identified.

The uptake of scientific advice by SMEs is now significant and it is encouraging to note an increased number of SMEs utilising a broader range of regulatory scientific advice services such as biomarker qualification. There is need to increase awareness of other incentives such as parallel scientific advice with health-technology-assessment bodies.

Initiating dialogue early and repeating it at major milestones is important to decrease the quality and clinical failure rate at time of marketing authorisation review. Compliance with the advice should also be emphasized as an important factor in increasing the outcomes of regulatory submissions.

Major research and financing initiatives have been launched at the EU level to support SMEs during the research and development phase and updated briefing notes on these programmes are available on the EMA website[2].

[2] Summary of EU Initiatives for Research Update 2014 EMA/748291/2014 (Link)
Summary of EU Initiatives for Financing Update 2014 EMA/748284/2014 (Link)

Over the course of 2014, EMA expanded its array of incentives to support SMEs through the regulatory process. It broadened its fee incentives to the post-authorisation phase and continues to reach out to SMEs and their stakeholders to identify and address the concerns of SMEs in relation to EMA's regulatory processes from development to marketing.

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