29 April 2016
EMA/155560/2016
Stakeholders and Communication Division

Report on the 10th anniversary of the SME initiative

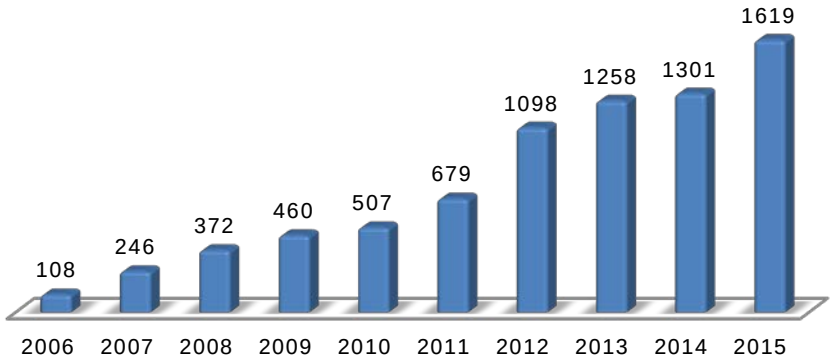
The SME Regulation[1] was adopted in December 2005 to promote innovation and the development of new medicines by SMEs. Its main objective is to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs) through a dedicated instrument, the SME Office, addressing the needs of smaller companies in the pharmaceutical sector.

This report reviews the experience with the SME initiative on the occasion of the 10 year anniversary of the SME Regulation.

1. An overview of the registered SMEs

At year-end 2015, the number of companies with an assigned SME status stood at 1,619, the highest figure ever recorded since the introduction of the SME initiative. The number of SMEs registered with the Agency at the end of year 2015 was 15 times higher than in 2006 and increased by 24% compared to the previous year. Significant increases in 2012 and 2015 were due to companies registering respectively for MedDRA fee incentives and for Pharmacovigilance fee incentives.

Number of companies registered (2006-2015)



Since the launch of the SME Office, the process for applying for SME status has been simplified in order to reduce the administrative burden on applicant companies. An automated electronic SME declaration form which calculates the headcount, annual turnover and balance sheet total in line with the ownership structure of the enterprise was launched in 2011. A risk-based approach to the Agency's

[1] Commission Regulation (EC) No 2049/2005

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5550
Send a question via our website www.ema.europa.eu/contact

review process was also introduced in order to facilitate and speed up the SME qualification renewal process.

Back in 2011, the large majority of SMEs registered were research and development stage companies. Conversely in 2015, a high proportion (56%) of the companies which were registered with the Agency were marketing stage companies. The shift can be explained by the introduction in July 2015 of fee incentives for SMEs in relation to pharmacovigilance activities[2] for medicinal products for human use approved centrally and at the national level (e.g. for periodic safety update reports and annual pharmacovigilance fees).

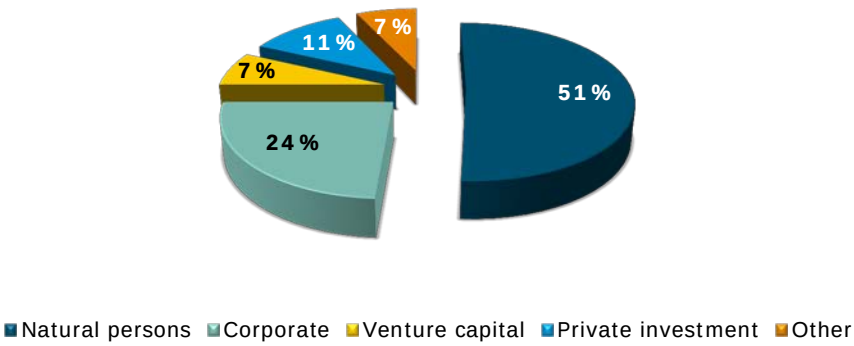
The relative size and ownership structure of registered companies have also changed over the years. Most of the companies in 2006 were medium-sized (< 250 staff), linked companies whereas most of the companies registered with the Agency in 2015 were micro-sized (< 10 staff) and autonomous enterprises[3].

In terms of geographical distribution of SMEs, a slight shift can be noted over the last ten years. The top 3 countries remained the same in 2015 (the United Kingdom, Germany and France) followed by Italy and Spain, whereas Denmark and Sweden stood 4th and 5th in 2006.

In 2015, the large majority of registered companies were developing products for human use (76%), 5% were developing both human and veterinary products and 4% were developing veterinary products only. Service providers to the pharmaceutical industry represented 15% of companies; the majority of them were regulatory consultants (86% of all service providers).

Of those registered SMEs, 14% were created in the last 3 years (since January 2013) and 10% of these newly created enterprises were academic spin-offs, underlining the importance of this stakeholder group in pharmaceutical innovation. 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 accounts for 7% of companies' capital share.

Profile of shareholders of registered SMEs (2006-2015)



Therapeutic medicines account for the highest proportion of products in the pipelines (84%), with vaccines representing 5%. When looking at the types of products under development, the breakdown into chemical entities vs. biologics is 67% and 33% respectively. The proportion of advanced therapy medicinal products that are being developed by SMEs stood at 7% in 2015, and have remained at a similar level since 2010.

[2] Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014.
[3] The EU definition of an SME distinguishes three types of enterprise - autonomous, partner or linked - according to their ownership structure and relationship with other enterprises in terms of holdings of capital or voting rights or the right to exercise a dominant influence.

Information on registered companies is available in the SME register launched in 2010. It addressed the increasing demand for company's information from SME stakeholders, EU Institutions and Agencies and National Competent Authorities. The SME register was expanded in 2011 to include high level information on the company pipeline to facilitate interaction, partnering and networking between SMEs, and to increase transparency on the SME initiative. The SME register has been useful, for example, in partnering SMEs and academic groups within the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).

2. Support received by SMEs to date

2.1. Regulatory assistance and SME briefing meetings

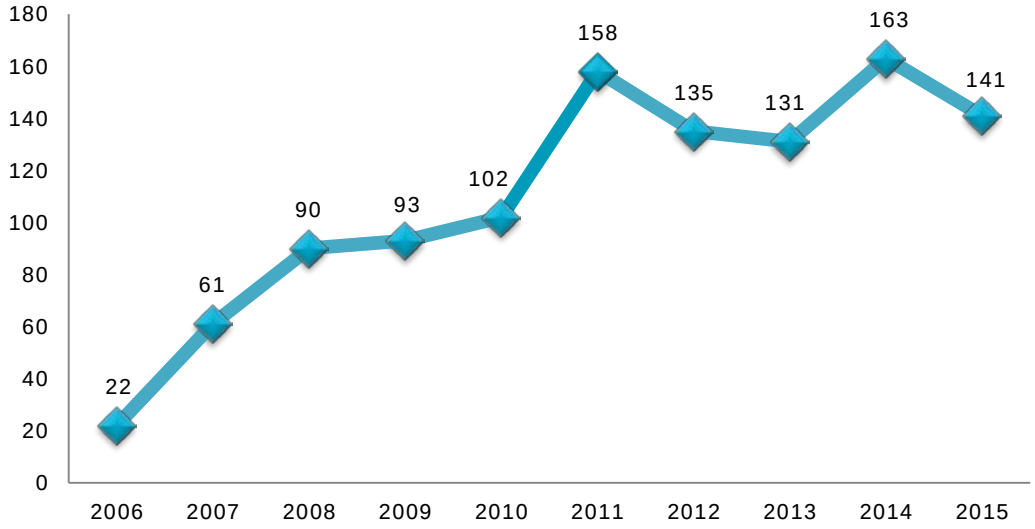
Small enterprises with limited resources often lack experience or are unfamiliar with the regulatory approval process. Opening up early dialogue with the EMA during development, such as scientific advice, and during the pre-submission phase of marketing authorisation application, can be challenging for SMEs which have limited capacity or experience to navigate the regulatory landscape for pharmaceuticals.

The SME Office was set up with the sole remit of offering regulatory or administrative assistance to SMEs, which can be directly accessed via email or telephone. The office offers SME briefing meetings which provide a regulatory platform for a company to discuss its planned regulatory strategy[4]. The early dialogue is particularly important for SMEs as they have limited assets in their pipelines.

Since the launch of the SME Office, 65 SME briefing meetings have been held with companies to discuss topics such as marketing authorisation filing strategy (e.g. legal basis for submission of marketing authorisation application, eligibility to the centralised procedure), orphan drug designation applications, paediatric investigation plan requirements and requests for waiver/deferral, scientific advice, quality aspects and product formulation development.

To date, more than 1000 requests for regulatory assistance, including requests for SME briefing meetings, have been addressed by the SME office. The number of requests for regulatory assistance increased by 34% in 2015 compared to 2010 and is now six times higher than in 2006.

Requests for regulatory assistance from SMEs (2006-2015)



[4] Constantinos Ziogas, 'A regulator's insights for SMEs in the biologics and advanced therapies sector', Regulatory Rapporteur, February 2016, vol 13, pp. 23-25

2.2. Training and regulatory awareness

SMEs have limited resources compared to bigger organisations and find navigating regulatory procedures and performing regulatory intelligence data-gathering exercise more difficult. It is therefore important to provide training and ease the access to information to keep SMEs' knowledge base up-to-date.

The SME Office organises workshops dedicated to addressing the particular needs of SMEs on a yearly basis. Workshops to date have covered various topics such as regulatory requirements of product development, quality of medicines, non-clinical development, clinical trials, scientific advice, pharmacovigilance and regulatory requirements for veterinary products.

Details on the workshops that have been held since the launch of the SME Office can be found under the SME office website (SME workshops).

These events are free of charge and are open to companies that have been assigned SME status by the EMA and to representatives of stakeholders' organisations. A live webcast of each event is also provided so that interested parties can attend the workshop remotely. Video recordings are posted on the Agency's website after the event to support training and increase regulatory awareness.

Over the last 4 years (2012 to 2015), an average of 219 participants have attended the workshops, either in person (54% of participants) or remotely via webcast (46% of participants).

The SME Office also publishes:

- a SME User guide which aims to facilitate the understanding of the main aspects of medicinal product legislation (Link). The relevance and usefulness of the guide have been highlighted repeatedly in SME surveys.
- a newsletter four times a year to provide information on the EU regulatory environment for medicines. The newsletter is disseminated to registered SMEs and interested parties. The distribution list has expanded over the years and now includes qualified persons for pharmacovigilance from SME companies, representatives from academia and other interested parties from the EU Network.

The SME Office also makes specific announcements on topics that have a direct impact on SMEs.

2.3. Support to innovation

Most newly authorised medicinal products are marketed by large and intermediate-sized companies. When the products are traced back through development, it has been shown that SMEs and academia play an important role in the sourcing of pharmaceutical innovation[5]. Hence, the SME regulation included significant financial incentives for companies to engage with regulators during the development programme and discuss the evidence requested to support a product approval.

2.3.1. Advanced therapies medicinal products

The regulation on advanced therapies medicinal products (ATMPs) introduced specific incentives for developers of ATMPs, which are often SMEs.

To support the development of this class of products, a procedure that enables early review of quality and non-clinical data of ATMPs, the certification procedure for ATMPs, is available exclusively to SMEs.

[5] H.Lincker et al, "Where do new medicines originate from in the EU"?", Nature Drug Discovery, February 2014, vol 13, pp. 92-93

ATMP certification allows a developer to confirm the extent to which the available data comply with the standards that apply for evaluating a dossier, and aims to identify issues early on, so that these can be addressed prior to filing. To date, the uptake has been limited to 6 certification procedures.

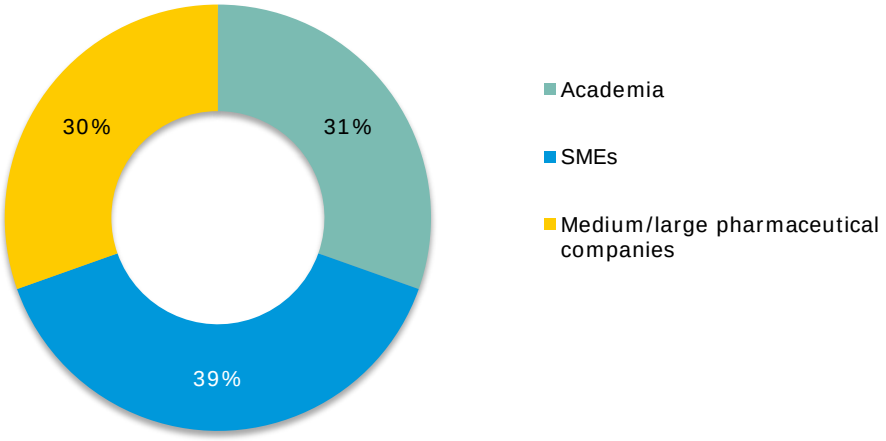
Sponsors requiring clarification as to whether their product is classified as an ATMP can also receive confirmation prior to submitting any application to the Agency. This procedure has increased regulatory certainty for the development of ATMPs.

2.3.2. Innovation Task Force

The Agency's Innovation Task Force (ITF) provides a platform for early dialogue with applicants to proactively discuss scientific, legal and regulatory aspects of emerging therapies, novel technologies and borderline products. The Innovation Task Force is a multidisciplinary group that works in co-operation with working parties of the Agency, and provides a forum to facilitate informal exchange of information and provide guidance early in the development. ITF is open to medicinal products for human and veterinary use.

This early dialogue is of particular value for smaller structures and it is interesting to note that, in 2015, 39% of the requests for ITF briefing meetings were coming from SMEs and 31% from academia.

ITF briefing meetings by type of requester (2015)

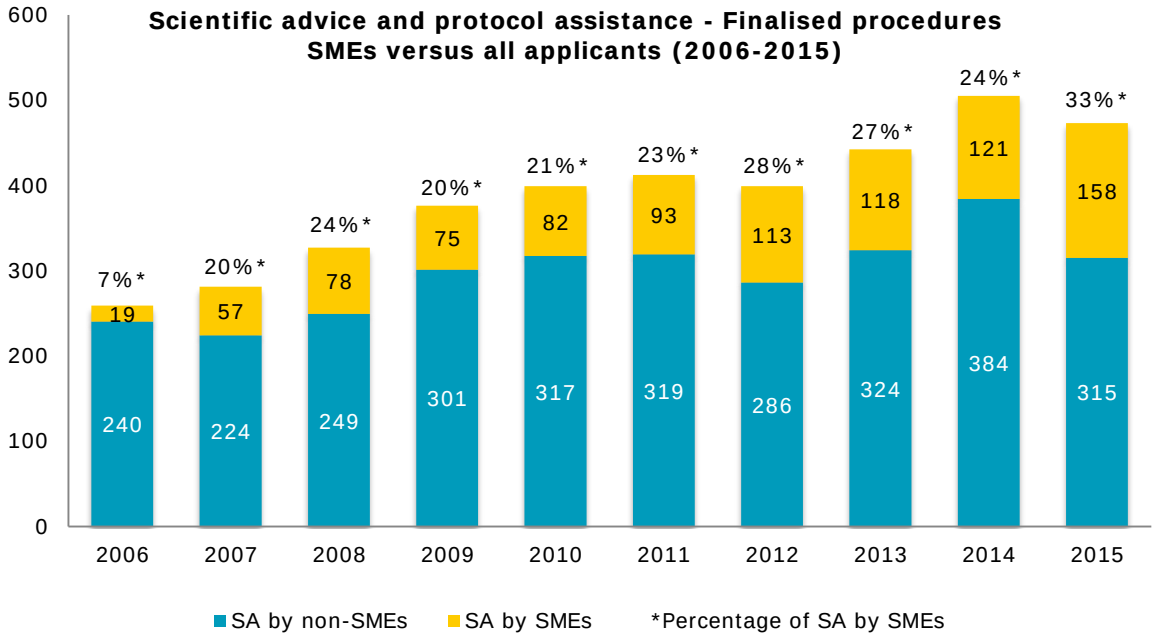


2.3.3. Scientific advice and protocol assistance

Scientific advice and protocol assistance during the development of a medicinal product has been a mainstay for initiating scientific and regulatory dialogue in the development of medicinal products over the past 10 years. It has played a major role in the support to pharmaceutical innovation by SMEs.

The proportion of requests for scientific advice and protocol assistance from SMEs has increased over the years. In 2015, the number of scientific advice and protocol assistance procedures finalised for human medicines developed by SMEs stood at 158, which represents 33% of all procedures and a 30% increase compared to 2014.

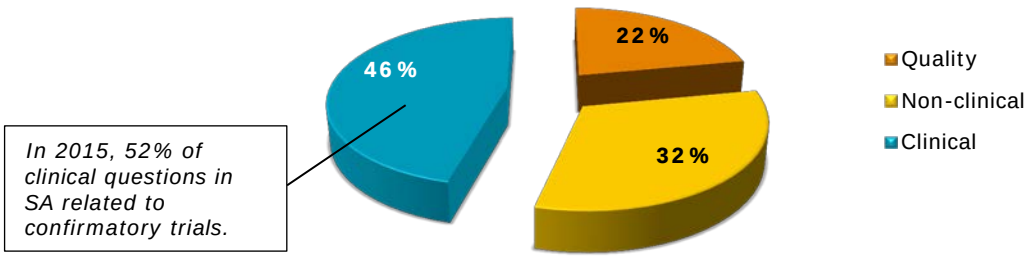
Scientific advice and protocol assistance accounts for the largest proportion of the financial incentives allocated to SMEs by the Agency.



The proportion of requests received by SMEs is even more important when considering protocol assistance. In 2015, the number of protocol assistance for orphan drugs developed by SMEs represented 44% of all protocol assistance procedures.

Scientific advice for human medicines may be requested on all aspects of development: clinical, non-clinical and/or quality aspects. Over the last 5 years (2011-2015), 46% of the issues discussed in scientific advice and protocol assistance procedures for human medicinal products developed by SMEs were on clinical aspects of the product development.

Scope of scientific advice - human products - SMEs (2011-2015)



Quality and clinical aspects of development programmes of human medicinal products continue to be a problematic area for SMEs. An analysis of major objections for marketing authorisation dossiers submitted by SMEs to the EMA between 2011 and 2013 showed that approximately 46% of major objections were on the quality documentation, 47% on the clinical safety and efficacy documentation and 7% on the non-clinical development[6].

[6] Constantinos Ziogas, 'A regulator's insights for SMEs in the biologics and advanced therapies sector', Regulatory Rapporteur, February 2016, vol 13, pp. 23-25

Initiating dialogue early with regulators as part of a scientific advice procedure, repeating it at major milestones of the development program and complying with the advice received is important to increase the positive outcomes of regulatory submissions[7]. Addressing pharmaceutical development should be a key aspect of advice being sought by SMEs.

For products eligible to the centralised procedure, scientific advice can also be sought on the justification for applying for a conditional marketing authorisation for human medicinal products or for a marketing authorisation under exceptional circumstances. In 2015, 13% of scientific advice procedures for human medicinal products included topics relating to conditional marketing authorisation and 4% included questions relating to marketing authorisation under exceptional circumstances. It is anticipated that these figures will increase in light of the Priority Medicines Scheme[8] (PRIME).

For orphan designated medicines, the scope of protocol assistance often related to the demonstration of significant benefit, a key aspect of the evaluation of marketing authorisations for orphan designated products.

The scope of scientific advice is now being expanded to post-authorisation safety and efficacy studies for medicines. This will help to improve the design of studies meant to collect further information on a medicine once it is on the market.

It is encouraging to note that an increasing number of SMEs utilise a broader range of scientific advice such as biomarker qualification and parallel scientific advice with health-technology-assessment (HTA) bodies. The aim of parallel scientific advice with HTA bodies is to allow medicine developers to receive advice from regulators and HTA bodies, early in the development of a medicine, on evidence that both parties will need to determine a medicine's benefit-risk balance and value. In 2015, 8 biomarker qualifications (36% of all qualifications) and 5 parallel scientific advice with HTA bodies (17% of all procedures) were finalised for SMEs.

2.4. Human medicinal products authorisations

From December 2005 to December 2015, 119 marketing authorisation applications (MAAs) for human medicinal products have been submitted by SMEs. Of those, 60 have received positive outcomes and 42 have resulted in negative outcomes (10 negative opinions and 32 withdrawals).

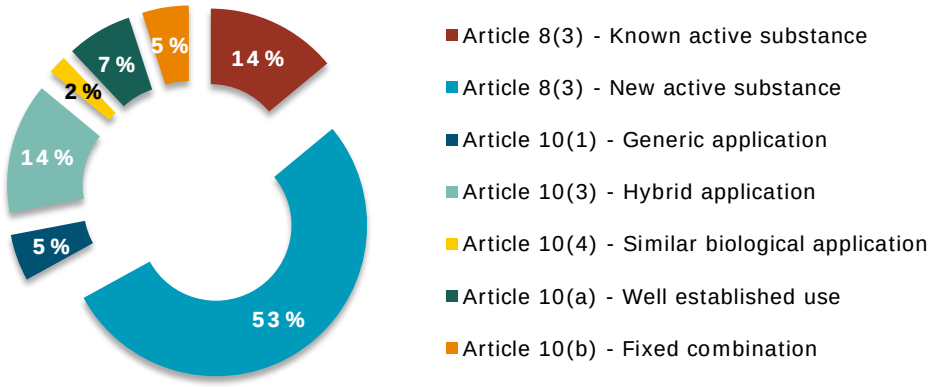
Key indicators of SME dossiers for human medicinal products over the past 10 years are:

- 42% of the products that have received a positive opinion are orphan medicinal products.
- 3% are advanced therapy medicinal products.
- 55% of SME applicants that received a positive opinion applied for scientific advice prior to filing a MAA. This has likely contributed to the improvement in regulatory compliance, which has been demonstrated to be associated with more favourable dossier's outcomes.
- 13% of the products received a conditional marketing authorisation and 7% of the products were authorised under exceptional circumstances.
- The majority of products that received a positive opinion by the CHMP was authorised on the basis of article 8(3) of Directive 2001/83/EC and contained a new active substance. It confirms that the marketing authorisations incentives introduced by the SME Regulation supported innovation and the development of new medicines by SMEs.

[7] Regnstrom J. et al., Eur J Clin Pharmacol. 2010 Jan; 66(1):39-48. doi: 10.1007/s00228-009-0756-y. Epub 2009 Nov 20 ; Hofer MP et al., Nat Rev Drug Discov. 2015 May; 14(5):302-3. doi: 10.1038/nrd4621. Epub 2015 Apr 17

[8] PRIME scheme

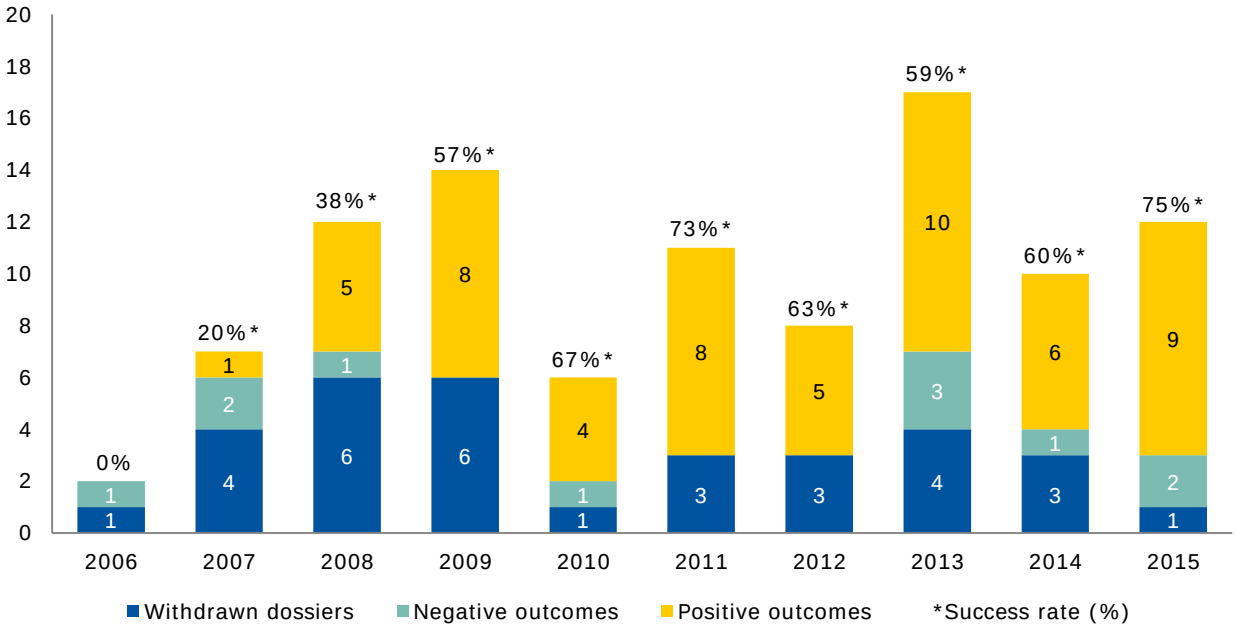
Legal basis for submission of marketing authorisation applications - successful applications - SMEs (2006-2015)



- Almost all marketing authorisation applications submitted by SMEs over the last 10 years have followed the standard timetable of the centralised procedure (opinion within 210 days, less any clock stops). Only 3% of the applications benefited from a shortened review via the accelerated assessment procedure (opinion within 150 days). It is anticipated that the number of accelerated assessment procedures will increase following the launch of the PRIME initiative.

Over the last 9 years, the success rate of SMEs in the marketing authorisation process for human medicinal products improved: the 3-yearly success rates were respectively 68% and 65% for the periods 2010-2012 and 2013-2015, compared to a figure of 38% during 2007-2009. The highest success rate of 75% was reached in 2015; the figure however still lags behind the average for all applicants (91% in 2015).

SME applicants - MAA outcome by year for human medicines (2006-2015)



An analysis carried out by the SME Office showed that SMEs play an important role in pharmaceutical innovation, especially in the field of orphan medicines. The impact of licensing activity between

developers on the profile of applicants was examined[9]. Nearly half (48%) of SMEs which develop a product from the start retain it through to the stage of marketing authorisation representing 13% of marketing authorisation holders. The other half of products (52%) are out-licensed to large or intermediate-sized companies or the SME merges with or is acquired by a larger company, during the course of product development.

Support to SMEs in the post-opinion phase

Medicinal products that have received a positive opinion have benefited from the SME translation service provided by the Agency. The translation of the product information of a medicinal product represents a considerable financial and administrative burden to SMEs willing to enter the EU market. The relevance of this incentive has been highlighted repeatedly in SME surveys.

The SME initiative introduced incentives for post-authorisation procedures in 2014. Fee incentives apply for post-authorisation procedures for centrally authorised products (such as variations) and pharmacovigilance activities (e.g. periodic safety updates reports, literature monitoring) irrespective of the authorisation route of the product.

2.5. Veterinary products

Over the last 10 years, 20 marketing authorisation applications for veterinary medicines developed by SMEs have been assessed by CVMP. Of those, 16 have received positive outcomes and 4 have resulted in negative outcomes (1 negative opinion and 3 withdrawals).

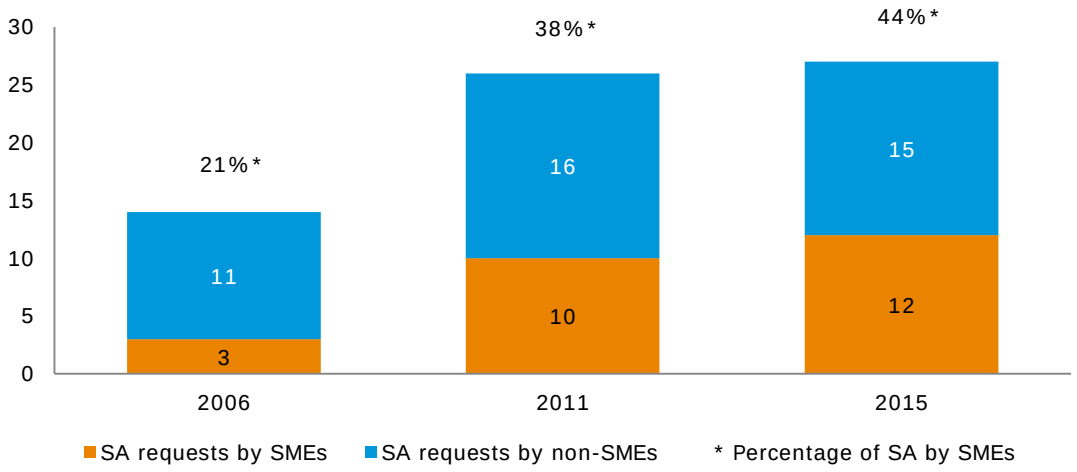
Key indicators of SME dossiers over the last 10 years for veterinary products are:

- 25% of the products that have received a positive opinion are MUMS (Minor use/Minor species) products.
- 19% of the products are vaccines.
- The success rate of SMEs in the marketing authorisation process for veterinary medicinal products is 80% in average over the last 10 years. The majority of products that received a positive opinion by the CVMP are generics (56%) authorised on the basis of article 13(1) of Directive 2001/82/EC.
- All marketing authorisation applications submitted by SMEs for veterinary products over the last 10 years have followed the standard timetable of the centralised procedure. None of them benefited from a shortened review via the accelerated assessment procedure.
- 38% of SME applicants that received a positive opinion applied for scientific advice prior to filing a marketing authorisation application.

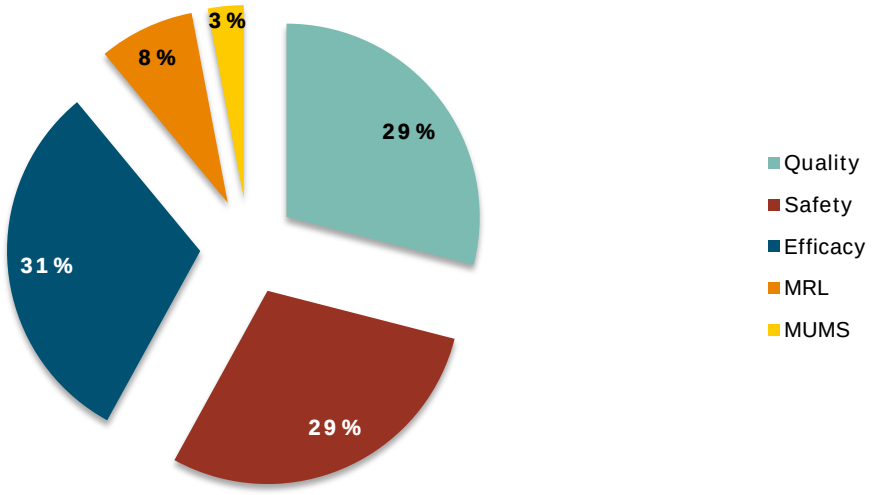
The number of scientific advice for veterinary medicines has increased over the last 10 years. Back in 2006, 14 requests for scientific advice were submitted and of those, 3 came from SME applicants, which represented 21% of all requests. In 2015, 27 requests for scientific advice were submitted and of those, 12 came from SME applicants, which represented 44% of all requests.

[9] H.Lincker et al, “Where do new medicines originate from in the EU”?”, Nature Drug Discovery, February 2014, vol 13, pp. 92-93

Requests for scientific advice for veterinary products – SMEs versus all applicants (2006/2011/2015)



Scope of scientific advice - veterinary products - SMEs (2015)



Amongst the companies registered with the EMA which are active in the veterinary field, 29% of them declared that they develop MUMS products.

A policy aimed at stimulating applications for MUMS/limited markets was introduced in September 2009. The policy is intended to assist applicants with the submission of applications for products for limited markets and to stimulate the development of new veterinary medicines for minor species and for rare diseases in major species.

Over the last 7 years (2009-2015), 152 requests for classification under the MUMS policy were received, with 60 originating from SMEs (39%).

3. Engagement with stakeholders

Since its inception, the SME Office has engaged with SMEs Stakeholders in the implementation of the SME initiative.

Surveys[10] were conducted to elicit direct feedback from SMEs and stakeholders on their level of satisfaction with the support provided by the SME Office and on the challenges they faced.

Roundtable meetings with representatives of SME organisations were also organised to discuss the results of the surveys, to share experience, to listen to SMEs' expectations and to enable exchange of views on achievements, challenges and opportunities for SMEs.

To mark the 10th anniversary of the implementation of the SME Regulation, the Agency held a meeting with representatives of stakeholder organisations on 27 November 2015[11]. The aim of the meeting was to provide an overview of the achievements of the SME initiative 10 years after it was enacted, to present the SME survey conducted in 2015 by the Agency and to engage in a dialogue on future initiatives to support SMEs and innovation in the pharmaceutical sector.

In this meeting, the importance and relevance of the SME initiative over the last 10 years was acknowledged by all parties[12].

A high level of satisfaction was received in particular on the fee incentives, on the regulatory support provided by the SME Office and on the translation assistance provided by the Agency. Initiatives to increase awareness on the regulatory framework, such as the SME user guide, the SME newsletter and the organisation of dedicated workshops and training events, were also mentioned as being particularly useful.

The feedback was representative of the results of the SME survey[13] conducted in 2015 that showed that the incentives of the SME programme have been considered as being very relevant or relevant for the large majority of registered SMEs which have benefited from the scheme.

During the roundtable meeting, areas for further development of the SME initiative were discussed such as the mandate of the network of EU innovation support structures in the National Competent Authorities, the need to increase regulatory dialogue with authorities and to increase the involvement of SMEs in the legislative process. The need to enhance awareness of the SME incentives for companies active in the veterinary field and the importance of looking at aspects of market access for medicinal products were also underlined. In general terms, recruitment of qualified staff, education and training were also noted as being potential future challenges.

4. Conclusion

The achievements detailed in this report, the positive feedback received in the 2015 survey and the stakeholders' roundtable meeting show that the SME Regulation has been successful in meeting its objective, which is to support pharmaceutical innovation in small and medium-sized enterprises.

The number of SMEs registered with the Agency has increased dramatically over the last 10 years. The uptake of regulatory and scientific advice by SMEs and the provision of financial incentives throughout the product development are significant. It is encouraging to see that, in 2015, the success rate of SMEs in the marketing authorisation process was at its highest level in 10 years.

[10] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000063.jsp
[11] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/11/event_detail_001242.jsp&mid=WC0b01ac058004d5c3
[12] Report on the European Medicines Agency roundtable meeting with stakeholders - 10th anniversary of the SME initiative
[13] EMA/242286/2016

Encouraging small enterprises to open up a regulatory dialogue on multidisciplinary disciplines early in the development process will remain a priority for the SME Office.

Other initiatives from the Agency to support innovation by SMEs are being put in place and include the Priority Medicines Scheme (PRIME) and the development of a framework for interaction with academia.

Access to the market is emerging as an important challenge faced by SMEs. The collaboration between EMA and the European Network for Health Technology Assessment (EUnetHTA), in particular in the area of coordinated advice and early dialogue involving regulators and HTAs, represents a major opportunity for SMEs.

The Agency is committed to continuing to support SMEs in the pharmaceutical sector. An action plan setting out the Agency's activities to tackle effectively challenges of SMEs will be elaborated taking into account the SMEs stakeholders' feedback and the EU Medicines Agencies Network Strategy to 2020.

Contacts for further information

E-mail queries: sme@ema.europa.eu

Constantinos Ziogas, MD: Tel +44 (0)20 3660 8463