

Second EMEA workshop for SMEs: Focus on quality

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Reviewed by

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This is a review of the second European Medicines Agency (EMA) Workshop for SMEs (micro, small and medium-sized enterprises), which was held at the EMA in London on February 8, 2008. During the workshop there was a session in which parallel tracks were presented, one for chemical products, the other for biological products. This review does not include all of the material presented and in particular does not include that presented in the biological track. Details of the full programme, including copies of slides presented, can be found at <http://www.ema.europa.eu/SME/SMEworkshops.htm>

Update from the SME Office

The first topic covered was an update from the SME Office, presented by **Melanie Carr** who heads the EMA's SME Office (an article on the SME provisions by Mrs Carr was published in *Regulatory Rapporteur* in May 2006). The operations of and basis for the SME Office were summarised and the following statistics were highlighted. At the end of 2007, a total of 246 companies had been assigned SME status. These companies are from 21 countries in the European Economic Area. The top three countries account for over a half of all SMEs (UK 25 per cent, Germany 18 per cent, and France 17 per cent). The majority of SMEs are engaged in the development of human medicinal products, nine in veterinary, eight in both human and veterinary, and there are 19 consultants. There were approximately 40 per cent more requests for SME status in 2007 than in 2006, with a fairly even spread of the company sizes (91 medium, 79 small, 76 micro). Over half of SMEs (65 per cent) are considered by the EMA to be developing innovative products. These are defined by innovation: therapeutic (eg, new target diseases, new mechanisms of action), technical (eg, new delivery method, novel formulation) and scientific (eg, new research and development methods or tools, new biomarkers). An analysis of the product types shows that 58 per cent are chemical (mostly new chemical entities) and 37 per cent are biological (mostly recombinant deoxyribonucleic acid).

Up to February 2008, the SME Office has processed fee reductions totalling €4.2 million for Scientific Advice and €2.6 million in deferred fees for marketing authorisation applications (MAAs) and inspections. Free translation assistance had been provided to two SMEs and the translations were considered to be of a good quality as well as timely.

Twenty-three SMEs have submitted MAAs (20 human and three veterinary). Thirteen of the applications for human medicinal products were for products with orphan medicinal product status. Of the 20

human applications, 13 were undergoing assessment, three were withdrawn, three had a negative outcome and one product received an accelerated assessment with positive outcome.

An analysis of applications was presented that demonstrated the importance of adhering to advice and of seeking follow-up advice if necessary.

Scientific advice on quality aspects for biologicals

Prof Jean-Hugues Trouvin (Chairman of the Biologics Working Party [BWP]) provided an overview of the mandate, composition and functions of the BWP and highlighted the role that the BWP plays in the assessment process during the Centralised Procedure. Following assessment of an application by the Rapporteur and Co-Rapporteur, the BWP harmonises, clarifies and consolidates the issues and initiates discussions at the Committee for Medicinal Products for Human Use (CHMP).

The role of the Scientific Advice Procedure was discussed, in particular when it should and should not be used, as summarised in Table 1.

Table 1: Appropriate and inappropriate use of scientific advice

Appropriate use of scientific advice

To provide advice and recommendation on difficult technical issues or where the guidelines can be interpreted in a number of ways. It should also be used to address issues not covered by available guidelines.

Inappropriate use of scientific advice

To obtain a pre-evaluation of the dossier to determine the extent to which it would be considered complete.

For bargaining with the CHMP or scientific groups with a view to seeking the waiving of tests or to reduce the development plan.

As a means of obtaining consultancy to obtain further input or suggestions with respect to the development of a product (this is the duty of the company).

To seek approval or assessment of the suitability of a product for use in clinical trials, as this is the responsibility of the national competent authorities.

Prof Trouvin commented that the quality of the scientific advice given is directly related to the relevance and quality of the questions posed by the company, as well as the quality of the documents provided supporting the company's position.

Common Technical Document-Quality (CTD-Q)

George Wade (EMEA) provided a summary of the components of the quality section of the CTD (otherwise known as CTD-Q). He stressed the importance of understanding that the CTD is purely a format and template for the dossier and does not define the data requirements for the content. This appears to have been confused by some companies.

The Quality Overall Summary (QOS) is designed to be a textual summary of the quality data and is not required to be critical (as the Expert Reports had been). There is no requirement for tabulated summaries of the quality data. Key parameters for the active substance and the medicinal product that impact the safety and efficacy profile should be emphasised in the QOS. Relevant tables and figures may be used at the applicant's discretion.

A comment was made regarding the fact that the EMEA prefers to avoid the use of the term "drug", especially in publishing European Public Assessment Reports. Thus the term "active substance" should be used instead of "drug substance" and the term "medicinal product" should be used rather than "drug product".

The Quality Working Party (QWP) is reviewing how the quality part of an application is assessed. It has been noted that even if there are numerous quality questions (as many as 200 in one case) a dossier can still be deemed to be suitable for approval. It is felt that many questions are frequently posed on a "nice to know" basis and to "complete the dossier". The QWP is considering a more risk-based assessment, comparable to the risk-benefit approach taken when assessing clinical data.

Recent experience in quality assessment

Dr Cornelia Nopitsch-Mai (The Federal Institute for Drugs and Medical Devices [BfArM], Germany) gave a summary of the general requirements for the quality section of the dossier, highlighting a number of deficiencies that have been noted. For the active substance, information was often lacking with respect to the starting materials, the route of synthesis and the impurity profile. There needs to be discussion of how the impurity profile of the active substance may carry over to the medicinal product. There are often insufficient data on the absence of reagents and solvents from the final active substance, and these are not adequately controlled by the specifications. Impurity limits are often found to not be in line with the European Pharmacopoeia.

For the medicinal product, test methods are frequently not adequately validated, and impurities are inadequately controlled, with no limits for unspecified or total impurities. Mass balance data are often found to be missing from stability studies. In-use stability data are commonly absent. Where a product is used for infusion, compatibility data are sometimes not shown with other infusion solutions. At times, stability data are found to be missing for the product stored in the container that is intended for the market.

The regulation of advanced therapies

Nicolas Rossignol (European Commission) provided an overview of the regulatory framework for advanced therapies (gene therapy, cell therapy and tissue engineering) medicinal products and the incentives available to SMEs. This includes a provision for certification of quality and non-clinical data, enabling SMEs to obtain a certified opinion with respect to the suitability of their data to support the continued development of their product. It should be noted, however, that the opinions represented by the certificates are not legally binding. They are intended to provide an indication that the work done by the SME meets a certain standard of competence. This scheme is expected to be rolled out by early 2009.

The EMEA Innovation Task Force

Dr Constantinos Ziogas (EMEA) described the role of the EMEA's Innovation Task Force (ITF). The aim of the ITF is to proactively handle issues associated with emerging science, especially the impact on the regulatory framework (as neatly summarised in the EMEA's article in the March 2008 issue of *Regulatory Rapporteur*). The ITF is an EMEA multidisciplinary group from scientific, regulatory and legal groups. Within the ITF there are specialist groups for cell therapy products, gene therapy products, nanomedicines, genomics and borderline combination products. The ITF's main tasks are to provide an informal "soft landing" for sponsors by means of briefing meetings, and to provide regulatory advice on the eligibility of innovative and borderline products to EMEA procedures by classifying the product or technology in relation to regulatory frameworks, especially where these may span regulatory boundaries. An example of a borderline product given was phages. The ITF interacts with resources from the EMEA's scientific committees (eg, CHMP and the Committee for Orphan Medicinal Products) and working parties (eg, Cell Products Working Party, Gene Therapy Working Party, BWP) as well as individual experts from the EU. The ITF provides an important opportunity for dialogue with the EMEA in the run up to the implementation of the Advanced Therapies Regulation.

A number of significant incentives have been provided to promote innovation and the development of new medicinal products by SMEs. These include administrative and procedural assistance, fee exemptions for certain administrative services, fee reductions, deferral of fees for applications for marketing authorisations or inspections, conditional fee exemptions and translations of product information. Details of these incentives and further information for SMEs can be found on the SME Office's web pages: <http://www.emea.europa.eu/SME/SMEoverview.htm>. The SME Office is dedicated to providing SMEs with practical guidance and this workshop, together with the one held a year earlier are an excellent demonstration of this.