The Centralised Procedure from the Micro, Small and Medium-sized Enterprise's Perspective and Specific Obstacles of SMEs

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List of Abbreviations

ATMP	Advanced Therapy Medicinal Product
CHMP	Committee for Human Medicinal Products
COMP	Committee for Orphan Medicinal Products
CP	Centralised Procedure
CTD	Common Technical Document
eCTD	Electronic Common Technical Document
CVMP	Committee for Veterinary Medicinal Products
EC	European Commission
EEA	European Economic Area
EIB	European Investment Bank
EIF	European Investment Fund
EMEA	European Medicines Agency
ESTRI	Electronic Standards for the Transfer of Regulatory Information
EU	European Union
EVWEB	EudraVigilance Web Application
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Human Medicinal Products
ITF	Innovation Task Force
MA	Marketing Authorisation
NRG	(Invented) Name Review Group
OECD	Organisation for Economic Co-operation and Development
R&D	Research and Development
RMP	Risk Management Plan
SAWP	Scientific Advice Working Party
SAWP-V	Scientific Advice Working Party – Veterinary
SBA	Small Business Act”
SME	Micro, Small and Medium-sized Enterprises
SmPC	Summary of Product Characteristics
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation

1. Introduction

The European Commission (EC), as well as each Member State of the European Economic Area (EEA), continues a policy that focuses on the improvement of economic development, employment, and standard of living without prejudice of the financial stability. In order to achieve these targets they pursue different emphases: amongst others, the promotion of micro, small and medium-sized enterprises (SMEs). The grounds of the support of SMEs are well summarized by Günter Verheugen, Member of the European Commission Responsible for Enterprise and Industry[1]:

> *'Micro, small and medium-sized enterprises (SMEs) are the engine of the European economy. They are an essential source of jobs, create entrepreneurial spirit and innovation in the EU and are thus crucial for fostering competitiveness and employment.'*

In 2004 there were about 23 million SMEs in the whole European Union (EU) representing 99% of all enterprises. They employed about 75 million man and form the backbone of industrial development regarding advances in science and technology till this day.

Besides, SMEs are also engaged in the development of pharmaceutical innovations and new medicinal products. Innovative or new medicinal products may have a high economic value by decreasing costs of the health system (e.g. by reducing the hospital stay), the pension scheme (amongst others by avoiding early retirement), and the public health care (reducing the care needed). Furthermore, innovative drug products increase the living standard by reducing morbidity, as well as mortality, and the production value by reducing the time of inability to work[2].

The promotion of SMEs encompasses common support programmes or administrative assistances, as well as industry sector oriented incentives, e.g. fee reductions or waivers for SMEs engaged in the pharmaceutical sector. However, as a prerequisite, companies may only benefit and apply for such support programmes and incentives in case SME status has previously been assigned by competent authorities.

The SME status is assigned on basis of the Commission Recommendation 2003/361/EC[5] in consideration of predefined measurements and relationships between companies and business partners. The SME status is granted by an application procedure. Both, the SME status and the application procedure are described in the respective chapter.

The European Medicines Agency (EMEA) represents the competent authority to assign SME status to pharmaceutical SMEs. Up to and including the end of 2007 various companies submitted a SME declaration to the EMEA[3]. The SME status was assigned in 246 cases while 53 applications are under review. 40 enterprises have withdrawn their application or have not renewed their SME status. Most of them develop therapeutic products; only a small proportion develops diagnostic/imaging and preventive medicines, including vaccines. Amongst the products involved, the innovations and new medicinal products encompass therapeutic innovations (e.g. new target diseases, new mechanisms of action, new compound types, new treatment modalities), technical innovations (e.g. new delivery methods/formulations, new manufacturing techniques, nanotechnology), and scientific innovations (e.g. new research and development methods/tools, pharmacogenomics, biomarkers). These products can also be distinguished with regard to their biological or chemical origin. The biological products include recombinant DNA derived products (e.g. cytokines, monoclonals, transgene-derived, fusion proteins), cell-based products (e.g. autologous, allogeneic, xenogeneic, stem cells), classical biological products (e.g. blood-derived, vaccine, enzymes, living organisms), nucleic acid-based compounds (e.g. gene therapy, DNA vaccines), as well as tissue engineering. The chemical compounds include new chemical entities, new formulations or delivery methods, oligopeptides, as well as generics. Regarding the therapeutic areas the products may also be classified mainly as anti-neoplastic and/or immunomodulating agents, alimentary tract and metabolism agents, central nervous system agents, and general anti-infectives for systemic use.

The economic and social importance of pharmaceutical SMEs is well known. Despite of that, there are several issues which have a negative impact on the development and marketing of new medicinal products. In most cases the financial situation is not secured and may be assessed as critical, respectively. But this is not the only obstacle. Further ones are also known and presented below, as well as options to overcome these issues.

As a basic requirement a medicinal product is only permitted to be placed on the EEA market when a Marketing Authorisation (MA) has been granted by the competent authorities. A MA may be issued either by each Member State for its own territory or by the EC in cooperation with the EMEA for the entire Community within a Centralised Procedure (CP). Pharmaceutical SMEs are frequently engaged in the development of innovative medicinal products for which the CP is mandatory. Therefore, only the CP is taken into account. In this context this presentation highlights topics with significance for SMEs, hurdles, and incentives which may be applied for before, during and after the CP in order to improve the situation of SMEs, as well as to support appropriate product development.

2. European SME Definition

Generally, the term SME is used for differentiation of micro, small, and medium-sized enterprises from larger enterprises; the nature of these enterprises is dissimilar particularly with regard to qualitative attributes like ownership, responsibility for business success, funding or resources, and autonomy of decision. In contrast, the determination of their SME status is principally based on measurements like staff headcount, turnover, and sometimes also by balance-sheet total. The measurements for these determinations may deviate across the European countries.

In 1996 the EC adopted the first Commission Recommendation 96/280/EC[4] regarding a general SME definition. The definition has been applied for across the Community. Moreover, all Member States, as well as the European Investment Bank (EIB) and the European Investment Fund (EIF) were also asked to use the definition as widely as possible. A common and generally accepted definition and the implementation of such a definition over the whole EU and its Member States is essential because SMEs benefit from Community and/or national Research & Development (R&D) support programmes, from regional funds, from financial support by venture capital companies, or loans by the EIB and the EIF. Unequal treatment and competition distortions may occur in case that different definitions are applied for. The first Commission Recommendation was replaced by Commission Recommendation 2003/361/EC[5], which was adopted in May 2003 and which came into force at the beginning of 2005. Commission Recommendation 2003/361/EC[5] is only applicable to legal persons, self-employed persons, family business and partnerships, or associations in case they are regularly engaged in an economic activity. The EC SME definition distinguishes

three classes of SMEs, micro, small and medium-sized enterprises, based on three quantitative measurements and one qualitative attribute, namely staff headcount, turnover, balance sheet total (each on an annual basis), and business relationship to other companies.

Enterprises get no SME status and lose the SME status, respectively, if the requirements are not fulfilled on two consecutive accounting periods. The same applies for larger enterprises which fulfil the requirements on two consecutive accounting periods; they may apply for SME status. The bases of calculation of measurements are the last approved accounting periods. In case that the thresholds can not be calculated from the last approved accounting periods because corresponding enterprises are newly-established enterprises the thresholds shall be derived from a reliable estimation.

2.1 Quantitative Measurements: Staff headcount, Turnover, Balance sheet total

Apart from the (qualitative) attribute 'relationship to other companies' the previously defined SMEs criteria as well as the current ones are presented in Table 1. It shall be emphasised that Member States, EIB and EIF may fix lower thresholds or may make use of only one criterion, e.g. the staff headcount, for the implementation of support programmes due to administrative simplification.

The staff headcount is expressed in annual work units including owner-managers, partners, full-time, part-time, and seasonal employees without apprentices and students and employees on maternity or parental leave periods. The turnover measurement is determined by calculating the income minus rebates and value added taxes or other indirect taxes.

Table 1 Previous SMEs definition criteria and current ones

	till end of 2004	**as from beginning of 2005**
Micro enterprise	staff headcount: < 10 turnover: not defined balance sheet total: not defined < 25% are controlled by “other” public bodies	staff headcount: < 10 turnover: < 2 Mio balance sheet total: < 2 Mio < 25% are controlled by “other” public bodies
Small enterprise	staff headcount: < 50 turnover: < 7 Mio balance sheet total: < 5 Mio < 25% are controlled by “other” public bodies	staff headcount: < 50 turnover: < 10 Mio balance sheet total: < 10 Mio < 25% are controlled by “other” public bodies
Medium enterprise	staff headcount: < 250 turnover: < 40 Mio balance sheet total: < 27 Mio < 25% are controlled by “other” public bodies	staff headcount: < 250 turnover: < 50 Mio balance sheet total: < 43 Mio < 25% are controlled by “other” public bodies

Comparing the two Commission Recommendations, the different staff headcounts were maintained whereas the thresholds for company turnover and balance sheet total were defined for the first time (micro enterprises) and are considerable increased, respectively.

The adjustment of turnover and balance sheet total was necessary in order to take into account the economic development since 1996. The adaptation of the financial ceilings enabled enterprises to invest in their own company and allows larger enterprises to invest in SMEs without losing the SME status. Both lead to a stronger growth of the SMEs concerned and a faster development of new medicinal products.

In order to receive SME status compliance with staff headcount, as well as with one financial threshold, the turnover or balance sheet total threshold, is mandatory.

The staff headcount, as well as the turnover threshold is calculated by defined formulas. This procedure highly assures that only amounts without measurement distortions by variables or deviations which may occur across Member States are taken into account. The balance sheet total has to be assessed with attention because this measurement may be variously affected, e.g. by reserves. However, the corresponding impacts are reduced due to the fact that the threshold has to be met on two consecutive years; therefore, the impact should be not very eminent. In addition, the recommendation defines that the limit of one financial threshold can be exceeded without loosing the SME status. Applying this procedure, the economic activities of enterprises in varying industry sectors are incorporated in the definition. The exemption considers that not all SMEs are equal and that there are differences in business strategies and in industry sectors with varied impacts on the predefined thresholds, e.g. the turnover values of trade and distribution enterprises are commonly higher than in the processing industry, whereas the balance sheet total may be smaller in comparison to the processing industry and vice versa. This course of action secures equal treatment of companies in varying industry sectors. Besides, with the definition of various thresholds the recommendation bears in mind that there are SME classes which need different assistance or support in accordance to their enterprise size, e.g. the definition of specific financial thresholds for micro sized enterprises thus enables authorities to promote these companies with special measures.

2.2 Qualitative Attribute: Company Relationships

In order to differentiate the varying company relationships, enterprises are defined as autonomous enterprises, partner enterprises or linked enterprises. Enterprises can be regarded as autonomous enterprises if they are absolutely independent from other enterprises or in case they hold less than 25% of the capital or voting rights in one or more other unlinked companies and vice versa. Besides, the definition allows a funding by public investment corporations, institutional investors including regional development funds, venture capital companies and business angels (investment of less than 1.25 million Euros) without jeopardising the SME status. The same applies for local autonomous authorities with a budget of less than 10 million Euros and not more than 5.000 citizens, universities, and non-profit research centres. The funding of these investors must not exceed 50% in case they are unlinked. Enterprises can apply for SME status if the measurements of staff headcount, turnover, and balance sheet total meet the limits, as mentioned in section 2.1.

A partner enterprise is defined as an enterprise which holds 25% - 50% of the capital or the voting rights of another enterprise and/or vice versa. Partner enterprises can apply for SME status if the measurements of staff headcount, turnover, and balance sheet total subject to the corresponding proportion of percentage of shares or voting rights meet the above mentioned limits. If there are several partner enterprises the same calculation has to be done for each one; the measurement sums have to correspond with the above mentioned limits, too.

A linked enterprise is defined as an enterprise which holds the majority of voting rights of another company, or has the right to appoint or remove the majority of administrative, management or supervisory body of another company, or has the right to exercise a dominant influence over another company in accordance to a contract between these enterprises or to a provision in the memorandum or articles of association, or an enterprise which is shareholder in or member of another company, controls alone pursuant to an agreement with other shareholders in or members of that enterprise, a majority of shareholders´ or members´ voting rights in another one. In the context of linked enterprises the engagement of natural persons in different enterprises shall also be noticed in case that the corresponding enterprises are engaged in the same relevant market or in adjacent markets. Linked enterprises can apply for SME status if the combined measurements of staff headcount, turnover, and balance sheet total subject to the corresponding proportion of percentage of shares or voting rights meet the limits as stated in section 2.1.

An exemption from the above described circumstances represents the investment of “other” public bodies. If 25% or more of the capital or the voting rights are directly or indirectly controlled by one or several public bodies a company can not be regarded as a SME.

The attribute 'company relationship' is an important characteristic in order to establish a clearer picture of an enterprise’s economic situation and to assess interactions between enterprises, respectively, as well as to make sure that the SME status is assigned only to enterprises with SME characteristics. Consequently, the Commission Recommendation contains characterizations and threshold calculations regarding autonomous, partner, and linked enterprises in accordance to the different degree of integration. In addition, in order to support SMEs, the Commission Recommendation enables improved access to capital and R&D without loosing the ranking as an autonomous enterprise and the SME status, respectively. The Recommendation allows the funding by different organizations like public investment corporations, institutional investors including regional development funds, venture capital companies and business angels, as well as by local autonomous authorities, universities, and non-profit research centres of up to 50% in case they are unlinked and that these investors are not involved in the management of the supported enterprises.

The interest of certain investors is commonly somewhat different. The engagement of universities and non-profit research centres allows SMEs to benefit from the financial engagement and the R&D findings, whereas universities and non-profit research centres may transfer their knowledge into practice. The engagement of business angels is explicitly emphasised because apart from their financial engagement they are also able to advise SMEs with regard to management assistance and performance monitoring. “Other” public bodies must not directly or indirectly control 25% or more of the capital or the voting rights of enterprises due to the fact that public bodies may give such enterprises a competitive advantage, particularly with regard to funding in comparison to enterprises which have to finance themselves by private equity capital. In addition, it likely is difficult to determine the corresponding measurements for such public bodies and furthermore, the legal certainty increases.

2.3 SME declaration

In order to obtain their SME status pharmaceutical enterprises have to send a SME declaration[6] to the EMEA. The declaration contains, if completed, general information about the enterprise concerned, the status quo with regard to the enterprise type, as well as common details about partner or linked enterprises, and particulars about the corresponding thresholds. After receipt of the signed sworn declaration together with the annual accounts for the last two consequential years, the proof of establishment and data about the company's ownership structure, the EMEA may issue an EMEA-SME number and assign the SME status. Not until receipt of their SME status enterprises may benefit from incentives mentioned amongst others in Commission Regulation (EC) 2049/2005[7]. As a matter of course, the EMEA has the right to ask for further information or to perform audits to ensure that the SME criteria are met. The SME status is assigned for two years. In order to maintain the SME status, enterprises have to submit a completed and updated annual declaration or at the latest three months in advance of the end of the two years period together with the latest approved accounts.

3. Centralised Procedure

In accordance with Regulation 726/2004[8] a single marketing authorisation, valid across the whole Community, can be issued in the context of a CP. Pursuant to Article 3 the CP is mandatory for medicinal products developed by means of biotechnological processes, as well as for designated orphan medicinal products. The same applies for medicinal products for human use containing new active substances for which the therapeutic indication is the treatment of acquired immune deficiency syndrome (AIDS), cancer, neurodegenerative disorder, diabetes, auto-immune diseases, other immune dysfunctions and viral diseases. Furthermore, the CP is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers and from end of 2008 for advanced therapy medicinal products (ATMPs) as defined in Article 2 of Regulation (EC) No 1394/2007[9], except they are prepared on a non-routine basis. In addition, there are transition periods to transfer already approved national ATMP marketing authorisations in Community marketing authorisations: four years for gene or cell therapy medicinal products and five years for tissue engineering products.

The CP may also be applicable for medicinal products with new active substances where the substance was not authorised in the Community before, for significant therapeutic, scientific or technical innovations, as well as for medicinal products due to public interest, e.g. generics authorised via national procedures, Mutual Recognition Procedure or Decentralised Procedure in order to secure fast access to patent free medicinal products across the Member States, as well as pandemic medicinal products. It is optional for generic applications of medicinal products authorised via the CP and for immunological veterinary medicinal products.

It is also possible to make use of the CP for non-prescription medicinal products[10]; for example, new combinations of already known substances approved in non-CPs are considered as new active substances. In addition, non-prescription medicinal products which do not have non-prescription status all over the EU may also be eligible for the CP: in this case a generic application of an originator medicinal product authorised for self-medication in one or two Member States has to be filed to the EMEA. Subsequently, after marketing authorisation is granted, the prescription status may be adapted in accordance to Article 71 and 72 of Directive 2001/83/EC[11]. Another option to receive marketing authorisations for non-prescription medicinal products is to file a hybrid application including relevant data on switch and hybrid aspects (e.g. new strength) in case the originator product is not authorised in self-medication. Until now, nine applications for non-prescription medicinal products were submitted from which seven were accepted and two were rejected.

A Community marketing authorisation can only be obtained if a complete marketing authorisation application is submitted to the EMEA. Within the EMEA the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP) are responsible for the scientific evaluation of the corresponding application dossiers. Apart from this approach the Committee for Orphan Medicinal Products (COMP) is responsible for assessment of the designation as an orphan drug, whereas the marketing authorisation application itself is assessed in cooperation between the CHMP and the COMP.

3.1 Dossier requirements

In accordance to the application procedure each Community marketing authorisation application for innovations and new veterinary medicinal products has to include all needs

mentioned in Article 12 (3) of, and Annex I to Directive 2001/82/EC[12], whereas application dossiers for human medicinal products have to comply with the requirements detailed in Article 8 (3) of, and Annex 1 to Directive 2001/83/EC[11]. The data encompass administrative information, as well as data regarding quality, safety and efficacy of the medicinal products. In addition, they should be presented in accordance with the Notice to Applicants[13] and EU-Common Technical Document (CTD) format, respectively. Guidance is available at VICH/ICH level and EU level, particularly in the European Pharmacopoeia and in "The Rules Governing Medicinal Products in the European Union". These rules contain administrative and scientific guidance, guidelines of good manufacturing practices, pharmacovigilance guidelines, as well as clinical guidelines for human medicinal products and the legal framework for the establishment of maximum residue limits for veterinary medicinal products. Moreover, further finalised and draft guidelines are also available on the EMEA websites. The guidance provides information to facilitate the interpretation and implementation of Community pharmaceutical legislation. They are also intended to assist applicants for further interpretation of the detailed requirements for the demonstration of quality, safety and efficacy.

Dossier requirements increased over the past years due to improved scientific information and greater experience with regard to the implementation of new medicinal products. Apart from administrative dossier requirements there are also specific dossier requests in accordance to the medicinal product concerned and the indication proposed. In order to shorten the time to market and to increase planning reliability, applicants need exact and comprehensive information about the respective dossier requirements and the corresponding guidance as soon as possible. In most cases the information is available, but available only from different sources, so that the inclusion for product development is hindered. Furthermore, applicants already have to provide for various information during the development process of medicinal products, even if only concept papers or draft guidelines are published (for example, Annex I of Directive 2001/83/EC[11] will be amended in order to include specificities of ATMPs[14]). Thus, despite the commonly broad discussions regarding the content and interpretation of such concept papers and draft guidelines, there is still an uncertainty if product development is consistent with the expectations of the competent authority. Applicants also have to adapt their course of action in accordance to changing legislative or regulatory requirements, e.g. as of 26 July 2008 there will be an obligation to submit study results conducted in accordance to a paediatric investigation plan, to submit a waiver or a deferral. All in all, while collecting and

presenting data to the necessary extent is very complex an (as much as possible) exact fulfilment of dossier requirements is very important because an incompliance may lead to a delay during the application procedures, to withdrawal or even refusal of marketing authorisation applications. Considering this, the applicant may consult the appropriate scientific advice working parties and Committees, respectively, for scientific advice in case that there are still outstanding issues.

3.2 Dossier development and procedural assistance

3.2.1 Scientific Advice and Protocol Assistance

The legal basis for scientific advice is given by the EMEA in Article 57 (1) n of Regulation (EC) 726/2004[8]. Protocol assistance for designated orphan medicinal products is based on Article 6 of Regulation (EC) No 141/2000[15]. In accordance to these articles the Scientific Advice Working Parties (SAWP/SAWP-V) as standing working parties with the only task of providing scientific advice or protocol assistance have been established. Scientific advice, as well as protocol assistance, depends on the cooperation of the scientific advice administrator, the SAWP/SAWP-V, additional experts, other Working Parties, the COMP, the Paediatric Committee, the CHMP, and the CVMP. Both requests may only be submitted in case of insufficient information in form of EU guidelines, Pharmacopoeia monographs or draft documents, and should contain only prospective questions and issues relating to quality, non-clinical, and clinical aspects, as well as questions regarding to the establishment of Maximum Residue Limits for veterinary products. Pharmacovigilance and risk management plans may also be subjects for scientific advice. Furthermore, scientific advice may be requested in case of uncertainties relating to EU guidelines interpretation or where companies choose to deviate in their development plan from guidance documents. Advice requests regarding paediatric developments, the design of trials, marketing authorisation applications under exceptional circumstances, conditional marketing authorisations, emerging and new therapies, and broader and more general advice for specific types of medicinal products or treatments are also eligible subjects. Besides, protocol assistance is also applicable if issues regarding the designation criteria significant benefit, similarity and clinical superiority arise. Follow-ups are also possible and are not restricted to the topics of the initial request, but have to fall within the same therapeutic indication and initial area/areas (commonly 40 days procedure)[16].

Advice applications should be submitted to the EMEA in accordance to the fixed submission dates. The application itself consists of a cover letter, which includes amongst others information and details about the applicant, the product concerned, the active substance, and data with regard to the type of request. In addition, the request contains the crucial briefing document including the questions, the proposed responses, on overview about the development stage and already received findings, background information, bibliographical data, overviews about previous scientific advices, as well as contract agreements with consultants or contract research organisations.

The advice procedure is started when the EMEA Secretariat receives the letter of intent at the latest 2 months in advance to the start of the procedure on whose basis the SAWP appoints two coordinators. A pre-submission meeting may take place before the final request is submitted. SMEs are strongly recommended to make use of pre-submission meetings because it is an opportunity to receive already feedback from the coordinators, e.g. on the list of questions, to identify further issues which should be included in the request or to receive advice, and also to obtain further information concerning the procedure itself. After receipt of the application and validation by the EMEA Secretariat the scientific advice is prepared by both coordinators independently from each other. Their reports are forwarded to the SAWP/SAWP-V for discussion and adoption of a common position. At this stage the SAWP/ SAWP-V decides if the procedure is closed within 40 days or if further discussion is crucial. In the latter case the procedure is closed after 70 days; the joint report and the highlighted controversial issues are forwarded for comments to the SAWP/SAWP-V, to the relevant working parties and maybe to additional experts, whereas the company gets the highlighted controversial issues which are considered during the discussion meeting. During the discussion meeting, comments and new information are presented to the SAWP/SAWP-V and included in the revised joint report of the coordinators. In accordance to the 40 days procedure the joint report and the draft advice letter are adopted by the SAWP/SAWP-V, passed to the CHMP/COMP/CVMP for formal adoption, and send to the company. After receipt of the final advice letter the company may ask for a clarification on parts that are not clear enough.

3.2.2 Pre-submission meetings

Additional to scientific advice and protocol assistance pre-submission meetings also support applicants. They take place in advance of application submissions, for example for scientific advice, marketing authorisation or orphan drug designation, and are intended to support

applicants with regard to procedural, regulatory and legal issues. SMEs are generally encouraged to make use of such pre-submission meetings due to their restricted experience on the conduct of CPs.

Pre-submission meetings for marketing authorisation applications can be applied by the usage of a specific request form which simultaneously serves as a manual[17]. The manual focuses on the most important topics and contains links to corresponding question and answer documents. In accordance to scientific advice and protocol assistance, the request should be accompanied by background information as information about the development programme, product information, or the draft MA application form, as well as topic specific information. The timeline for the submission of the request form together with the draft SmPC and background information has to be met. In other cases, e.g. scientific advice, pre-submission meetings may be requested while sending a letter of intent including a request for a pre-submission meeting to the EMEA. Once a meeting date is agreed in accordance to the fixed submission dates and the date arranged between applicant and EMEA, respectively, companies have to send the relevant background information and the draft request. Pre-submission meetings are based on the cooperation of a core team, namely Product Team Leader and Product Team Members, which are responsible for the handling of all procedural aspects of the application. For veterinary medicinal products a Product Manager is nominated by the EMEA in order to handle all procedural aspects and to keep the applicant informed about all issues regarding the application. Depending on the issues concerned further participants from the EMEA may also participate in pre-submission meetings. At the end of procedures applicants are responsible to draw up meeting minutes which should be agreed between the EMEA and the applicants.

3.2.3 ITF consultation

Apart from scientific advice and protocol assistance applicants may also get in touch with the Innovation Task Force (ITF) in order to receive scientific, legal or regulatory advice. The ITF may be regarded as an informal scientific discussion platform. The ITF duties include briefing meetings which enable an early dialogue between applicants and the authority, as well as regulatory advice on the eligibility to make use of certain procedures. Typical products for ITF activities encompass emerging therapies and technologies, as well as borderline therapeutics for which no scientific, legal and regulatory experience is available. Requests

should be submitted in accordance to the fixed submission dates. Request form and background information are sufficient for a consultation and advice request, respectively. Briefing meetings commonly take place 2 months after receipt of the request form. At the end of these meetings applicants are responsible to draw up meeting minutes which should be agreed between EMEA participants and applicants. In case of regulatory advice the applicant is informed in writing about the outcome.

3.2.4 Comparison of different procedural assistances

Scientific advice, protocol assistance, and consultations with the ITF are crucial elements in the development of medicinal products, particularly for new unknown products for which no or only insufficient guidance is available. The procedures enable the applicant to get in touch with the authority, to exchange ideas between the stakeholders, to share the development strategy with the authority and to make sure that the development of the medicinal product is consistent with existing or draft guidelines, as well as to develop faster safe and effective medicinal products and to provide an overview on potential incentives. Altogether, the probability of positive outcomes of application procedures is strongly increased in case of participation and usage of these options. Nevertheless and apart from the submission strategy which is usually the determinant for the choice of procedure, national scientific advice may be also suitable in certain circumstances, for example if at national level expertise is available. Additionally, the national procedure is cheaper than the centralized one. However, if essential scientific advice is necessary or an ultimate decision is asked for, the centralized scientific advice is the procedure of choice particularly for innovative or unusual products and regarding conditional fee exceptions.

Pre-submission meetings are intended to support SMEs to submit applications in conformity with legal and regulatory requirements. They enable applicants to anticipate and discuss issues with the EMEA which may already be addressed in the documentation accompanying the application. Thus, this proceeding facilitates timely evaluation and termination of procedures, respectively. Pre-submission meetings also enable SMEs, often being unfamiliar with the CP, to get in touch with the EMEA. In whole the same considerations for scientific advice, protocol assistance, and consultations with the ITF should also be valid for pre-submission meetings.

3.3 Pre-authorisation Inspections (GMP, GCP and GLP)

Directive 2003/94/EC[18] for human medicinal products and Directive 91/412/EEC[19] concerning veterinary medicinal products contain principles and guidelines regarding Good Manufacturing Practices (GMP). Further guidance is available in Volume 4 of the rules Governing Medicinal Products in the EU. GMP ensures that the manufacturing of medicinal products complies with appropriate quality standards. GMP inspections are performed in case of product or process related issues which are arisen during the assessment process.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials. It includes protection rights and provides assurance of safety and efficacy of new developed compounds. Details are enclosed in the Clinical Trial Directive 2001/20/EC[20], in the GCP Directive 2005/28/EC[21], and in Volume 10 of the rules Governing Medicinal Products in the EU. Regarding veterinary medicinal products VICH Topic GL 9 is applicable, which provides guidance on the design and conduct of all clinical studies of veterinary products in the target species. Generally, GCP inspections are conducted as routine inspection from case by case.

Good Laboratory Practice (GLP) is a quality management system for the process and the conditions under which laboratory studies during non-clinical trials are planned, performed, recorded, monitored and archived. Details are expressed in Directive 2004/9/EC[22] and 2004/10/EC[23]. GLP inspections are only conducted if retrospect specific issues related to the application assessment are necessary.

In accordance to Article 57 (1)(i) of the Regulation (EC) 726/2004[8] the EMEA is responsible for pre-authorisation inspections regarding GMP, GCP and GLP in the context of marketing authorisation applications within the CP, whereas the inspections are performed by national competent authorities. Pre-authorisation inspections are conducted within the 210 days period for scientific evaluation of application dossiers. It is emphasised that all sites concerned should be ready for inspection from the time of submission of the application. Currently, for certain medicinal products, particularly medicinal products for which the CP is mandatory, some applicants have not all information about specific GMP and GCP requests or changes within definite guidelines, so that it is difficult for them to prepare the documentation appropriately. However, inspections are usually conducted parallel with the clock-stop period. At the end of such an inspection the applicant receives an inspection report for comment on

major objections or in order to submit an improvement plan. Finally, findings and comments are integrated in the scientific evaluation of the application by the EMEA.

3.4 Submission of the application and timetable for the CP

In the following table the timetable and the activities are summarized. The table gives an overview about the milestones and the CP process. Essential information for SMEs is further elucidated.

Table 2: CP timetable

Timetable	Action
	First advice by ITF, for example regarding the Orphan drug designation
	SME designation
- 36 to – 12 months	Scientific advice – pipeline information
- 18 to – 12 months	Request eligibility for CP, Request name review
- 7 months	Applicant should inform the EMEA about the intention to submit an application
	The applicant should take into account a pre-submission meeting. The corresponding letter of intend and the request should include amongst others - draft SmPC - justification of eligibility for evaluation through the CP - the legal basis of the application - statement regarding Article 14 (7) conditional marketing authorisation - statement regarding Article 14 (8) exceptional circumstances - statement regarding Article 14 (9)/39 (8) of Regulation (EC) No 726/2004[8] accelerated assessment - scientific advice received in the past - statement if orphan drug designation is granted - proposed classification for the supply of the medicinal product - proposed Invented Name for the medicinal product

	- details of proposed manufacturing and batch release arrangements - whether the quality dossier presents enhanced product and process understanding (Design Space concept and Process Analytical Technology) - any request for total or partial fee exemptions - an indication of any regulatory issues or difficulties already identified which may require clarification or detailed consideration
	Rapporteur and Co-Rapporteur are appointed by the CHMP; furthermore a Product Team for human medicinal products and a Product Manager for veterinary medicinal products are nominated by the EMEA in order to handle all procedural aspects and to keep the applicant informed about all issues regarding the application
- 4 months	Applicant should inform EMEA and the EC in case that multiple applications are submitted including an explanation for such a proceeding
	Request for accelerated assessment can be submitted at any time prior to the submission of a marketing authorisation application.
Day 0	Each marketing authorisation application has to be submitted electronically as non-eCTD or eCTD to the EMEA, Rapporteur and Co-Rapporteur in accordance to the fixed submission dates and the date arranged between applicant and EMEA, respectively. Start and finish dates of the procedures as well as other interim dates are also fixed and may be used as an orientation guide. The submission include amongst others - application form - product information (SmPC, PIL, Labelling) - English mock-ups of the outer and inner packaging - readability test - environmental risk assessment - pharmacovigilance system - a risk management plan, where appropriate

	- modules 2 - 5
	Rapporteur meeting
Within 10 working days	Validation by the EMEA - In case that additional data or information is required the applicant has to send the information simultaneously to the EMEA, Rapporteur and Co-Rapporteur. Validation of the procedure is terminated – starting of the procedure; simultaneously, the EMEA informs the applicant about further CHMP members who should additionally be supplied with the application documentation. Additionally a specific core number is assigned.
Day 1	Start of the procedure
Day 80 (85 Vet)	Receipt of the assessment report(s) from Rapporteur and Co-Rapporteur(s) by CHMP/CVMP members and EMEA.
Day 100	Rapporteur, Co-Rapporteur, other CHMP/CVMP members and EMEA receive comments from members of the CHMP/CVMP.
Day 115	Receipt of draft list of questions (including the CHMP/CVMP recommendation and scientific discussion) from Rapporteur and Co-Rapporteur.
Day 120	CHMP/CVMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA – Clock stop. The applicant should ensure that the questions are responded within the time frame agreed with the CHMP/CVMP; at the latest after 6 months for human medicinal products and 6 months for veterinary medicinal products which may be extended upon justified request. Alternatively, the application should be withdrawn.
Day 121	Submission of the applicant's responses, including revised SmPC, labelling and package leaflet texts in English. Restart of the clock.
Day 150 (160 Vet)	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP/CVMP members and the EMEA.
Day 170	Deadline for comments from CHMP/CVMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP/CVMP

	Members.
Day 180	CHMP discussion and decision on the need for adoption of a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped (normally 1 month + max. 2 months additionally in exceptional circumstances) to allow the applicant to prepare the oral explanation. Clock stop.
Day 181	Restart of the clock and oral explanation (if needed).
Day 210	Adoption of CHMP/CVMP Opinion + CHMP/CVMP Assessment Report (and timetable for the provision of product information translations)
+ 120 Days	Possible appeal/Re-examination procedure

3.4.1 Statement regarding Article 14 (7) - Conditional Marketing Authorisation (human medicinal products only)

The rules for granting conditional marketing authorisations are laid down in article 14 (7) of Regulation (EC) 726/2004[8] and Commission Regulation (EC) 507/2006[24], respectively. Conditional marketing authorisations are commonly based on pre-clinical and pharmaceutical data, whereas comprehensive clinical data referring to safety and efficacy of medicinal products is missing. In order to ensure that the missing data is supplied certain post approval commitments have to be made. In addition, each conditional marketing authorisation is approved under stringent conditions to guarantee that no unfavourable medicinal product is available on the market, e.g. the restrictive medicinal product character is published. Besides, each conditional marketing authorisation is valid only for one year on a renewable basis; the renewal together with an interim report about the already performed obligations have to be submitted 6 months prior to the expiry date of the marketing authorisation. In case that the missing data is provided, a conditional marketing authorisation can become a "normal" marketing authorisation. However, conditional marketing authorisations are only approvable for medicinal products for the treatment, diagnose or prevention of serious diseases and for emergency situations, as well as for orphan drugs. As a prerequisite, diverse conditions have to be fulfilled: the risk of missing data must not overweight the expected benefits; the missing data can be submitted by the applicant at a later date; unmet medical needs are fulfilled; and in addition, the risk-benefit assessment has to be positive. Due to the great public interest

conditional marketing authorisations applications are also eligible for an accelerated assessment procedure. Requests should be submitted together with appropriate statement, justification, and further data. Appropriate requests are assessed in the context of the overall assessment of CP applications.

3.4.2 Statement regarding Article 14 (8) of Regulation (EC) 726/2004 - Marketing Authorisation under Exceptional Circumstances (human medicinal products only)[25]

Marketing authorisations under exceptional circumstances may be granted in case that no sufficient data on the efficacy and safety of medicinal products can be provided by the applicant due to the rarity of indications concerned, on grounds of the present level of awareness, or for the reason that it would be unethical to collect such information. Each marketing authorisation under exceptional circumstances is also approved under stringent conditions, particularly regarding that the product character comes into public, the safety, and the risk management. These marketing authorisations are reviewed annually to re-assess the risk-benefit balance. Nevertheless, the fulfilment of any requirements focused on the provision of information on the safe and effective use of the medicinal product will usually not lead to the completion of a full dossier. Therefore, marketing authorisations under exceptional circumstances are valid for five years and may be renewed subsequently for an unlimited period. Requests should be submitted together with an appropriate statement and justification. Appropriate requests are assessed in the context of the overall assessment of CP applications.

3.4.3 Statement regarding Article 14 (9)/ 39 (8) of Regulation (EC) No 726/2004 - Accelerated Assessment Procedure (human and veterinary medicinal products)

During the application phase of medicinal products certain incentives may be given to applicants to facilitate or to fasten the marketing authorization. These incentives include, amongst others, an accelerated assessment procedure (150 days instead of 210 days) in cases a medicinal product is intended to meet major public or animal health needs, particularly with regard to therapeutic innovations. Requests should be submitted either electronically or in the context of a letter of intend/pre-submission request together with an appropriate justification[26, 27]. Requests are assessed in advance of CP application evaluation.

Table 3 Standard timetable for the accelerated assessment procedure

Timetable/days	Action
-120	Notification of intent to submit a request for accelerated procedure
-30 to -10	Submission of request
-20 to 0	CHMP plenary meeting preceding the start of the procedure Circulation of EMEA/Rapporteur report CHMP opinion on the request Validation
1	Start of the procedure
60	Receipt of the assessment report(s) from Rapporteur and Co-Rapporteur(s) by CHMP/CVMP members and EMEA
80	Rapporteur, Co-Rapporteur, other CHMP/CVMP members, and EMEA receive comments from members of the CHMP/CVMP
90	Opinion or need for clarification/Oral explanation
115	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP/CVMP members and the EMEA.
120	Possible oral explanation (and/or opinion)
150	Finalisation and opinion or switch to normal timetable if major public health interest no longer exist

The above mentioned procedures may be very interesting for applicants, particularly SMEs, who are strongly engaged in the development of new and promising medicinal products which commonly fulfil the above mentioned criteria.

3.4.4 Orphan drug designation

Orphan Drugs are those drugs used for diagnosis, prevention or treatment of rare diseases. The EU defines a rare disorder as one with a prevalence of 5 : 10,000 Europeans. There are approximately 6,000 orphan diseases, out of which 80% are genetic. The remainder are caused by infections, allergic and autoimmune disorders or poisonings, or have unknown causes. Despite variable aetiology, rare diseases share similar traits; they are usually chronically debilitating, degenerative and often life-threatening. Due to their relatively low prevalence, rare diseases have been neglected by the most stakeholders. As a result, knowledge and awareness of the vast majority of rare diseases is still limited or totally absent.

Besides, even when recognized, many rare diseases cannot be treated, simply because no medicinal products or therapies exist.

The designation is based on the criteria laid down in Regulation EC 141/2000[15]. Designation applications have to be submitted prior to submission of marketing authorisation applications in order to benefit from certain incentives. Applicants should notify the EMEA of their intention to submit an application at least two months prior to the planned submission date. Besides, applicants are encouraged to request protocol assistance and a pre-submission meeting prior to filing such an application[28]. The application should contain, amongst other things, the application form, a justification that the criteria laid down in Article 3 (1) are met, a description of the development stage, and an explanation of the proposed therapeutic indications[29]. Furthermore, preliminary preclinical and/or clinical data is generally required. If more than one indication is applied for the same product, separate applications should be submitted for each orphan indication. Deadlines for submission are published on the web-site of the EMEA. After receipt of the application the EMEA verifies the validity of the application, and once the validation process is completed, a time-table for the evaluation is adopted. A copy of the application is forwarded to all COMP members. Subsequently, the Committee gives its opinion within maximal 90 days. If a negative outcome seems to be probable the sponsor may be invited for an oral explanation prior to adoption of the opinion. In this case the coordinators prepare a document highlighting the points of disagreements and request for clarification. In case the Committee holds that the application does not satisfy the criteria set out in Article 3(1), the Agency informs forthwith the applicant. Within 90 days after receipt of the opinion, the applicant may submit detailed grounds for appeal. On this basis the Committee decides whether its opinion should be revised. The EMEA forwards the final opinion of the Committee to the Commission, which adopts a decision. The decision is notified to the applicant and communicated to the Agency and to the competent authorities of the Member States. In case of a positive decision, the designated medicinal product is entered in the Community Register of Orphan Medicinal Products and the assessment report is published on the EMEA web-site[30].

Under normal market conditions pharmaceutical companies are only slightly interested in developing and marketing medicinal products intended for only a small number of patients suffering from rare diseases. They are to a much greater extent interested in developing drugs for common disorders affecting millions of patients rather than treating a small number of

patients with a broad extension. It is therefore necessary to stimulate the research, development and marketing of medicinal products by the pharmaceutical industry. The orphan drug designation is the prerequisite to receive such incentives.

3.4.5 Proposed Invented Name for the medicinal product

In accordance to Article 6 of Regulation (EC) No 726/2004[8] and Article 1 (20) of Directive 2001/83/EC[11] medicinal products authorised via the CP are generally allowed to bear only one invented name, or a common name or scientific name accompanied by a trademark or the MAH. However, invented names are frequently used for new medicinal products. In advance of the request applicants have to ensure that invented names are reviewed in accordance to the relevant legislation and guidance. Besides, in order to make sure appropriate naming, applicants have to inform the EMEA about the designated names of medicinal products in advance of the application procedure. The "name request" should contain the request form including the proposed invented name(s), the proposed SmPC and maybe further background information. The Invented Name Review Group (NRG) as a subgroup of the CHMP or the CVMP, respectively, reviews the designated name(s)[31, 32] in cooperation with the competent national authorities, the EC and the WHO in order to identify potential safety risks or public health concerns presented by the invented name. After evaluation of any comment the proposed invented name(s) may be accepted, refused or companies are asked for further clarifications. In contrast to the CVMP decision making process NRG recommendations have to be primarily presented to the CHMP for adoption. Subsequently, applicants are informed about the outcome of the consultation. In case that a proposed invented name is not eligible, a new invented name, as well as a common name or scientific name accompanied by a trademark or the name of the MAH may be used.

All in all, this proceeding ensures that marketing authorisations may be granted without delay related to invented name issues.

3.4.6 Environmental risk assessment

Generally, when using medicinal products, parts of it may be introduced into the environment. For this reason, their potential impact on the environment has to be investigated before a MA is granted[33]. Following the appropriate guidelines, the environmental risk assessment is a

step-wise, phased procedure. In phase I the environmental concentration of the active substance in the surface water is taken into account. If the active substance concentration in the surface water exceeds a predefined action limit or if other performed investigations reveal a possible environmental risk a phase II analysis has to be conducted. In this case indicator species are used for the evaluation of the potential environmental impact. Besides, for assessing the environmental risk, also market data, pharmacological activities, toxicology of the active substance, as well as related substances have to be provided.

Apart from the main focus on the release of the active substance to the environment the disposal of unused medicinal products, as well as proper labelling are also appropriate targets of the environmental risk assessment. In case that no risk is inherent in the medicinal product, a brief justification for the absence of the environmental risk evaluation may be sufficient.

3.4.7 Pharmacovigilance system

The approval of marketing authorisations for new medicinal products is based on the evaluation of the risk-benefit analysis of the medicinal products at that time. However, in most cases the entire information of all available data is not overarching, so that competent authorities make provisions in order to identify, validate, quantify and evaluate adverse reactions associated with the use of the medicinal products and thus to prevent harm to patients. In accordance to Regulation (EC) No 726/2004[8], Directive 2001/83/EC[11], Directive 2001/20/EC[20], Directive 2001/82/EC[12] and Volume 9a/9b[34, 35] of the Rules Governing Medicinal Products in the EU pharmaceutical companies have specific obligations with regard to pharmacovigilance. Applicants or MAH should have permanently and continuously an appropriately qualified person responsible for pharmacovigilance at their disposal, as well as a pharmacovigilance system for the collection and notification of any adverse reaction during the development and following the marketing authorisation of medicinal products. In order to obtain an overview about the system details pharmaceutical companies have to describe the pharmacovigilance activities in a pharmacovigilance file which has to be provided to the competent authorities in the context of new marketing authorisation applications or extension applications.

Commonly, a pharmacovigilance system covers all aspects of routine pharmacovigilance activities and is mainly related to the system in use.

3.4.8 Risk Management Plan

In accordance to Article 8(3) (ia) of Directive 2001/83/EC[11] the applicant is supplementary obliged to submit a risk management plan in certain cases and for certain product types, respectively[36]. In contrast to the pharmacovigilance system, a risk management plan provides for product specific issues. The plan contains product specific safety information that is derived from the development period. In addition, based on afore mentioned information, the risk management plan contains information about the identification, the characterisation, and the prevention of risks. The plan also contains information about appropriate risk minimising activities which should be taken into account in case of identified or potential significant risks, or if certain particulars are not available, e.g. information about drug-drug interactions, usage problems (e.g., dose, storage, or delivery), medication errors, abuse and diversion, and use in high-risk patients or circumstances.

All in all, the main target of a risk management system is to ensure that the balance strikes in favour of the advantages of medicinal products by a risk reduction approach. Alternatively, in case the applicant is not obliged to submit an EU-RMP, the applicant or the MAH should get in touch with the competent authority in order to ensure that a brief justification for the absence of an EU-RMP is sufficient.

3.4.9 Re-examination procedure

The re-examination procedure is, amongst others, applicable to CHMP/CVMP opinions in the context of new marketing authorisations[37]. After receipt of an unfavourable opinion from the CHMP/CVMP the applicant may apply for a re-examination of this opinion. Within 15 days after opinion receipt the applicant has to inform the EMEA in written about the request. Subsequently, within 60 days after receipt of the opinion the applicant has to pass on the details for the request to the EMEA. After receipt of the applicant’s request, the CHMP/CVMP appoints a Rapporteur and maybe a Co-Rapporteur, both different from those appointed for the initial opinion. After approximately 30 days, the first assessment report is prepared by Rapporteur and Co-Rapporteur and submitted to the CHMP/CVMP. The CHMP/CVMP members may comment the assessment report and afterwards the joint assessment report is completed by the assessors. At the latest on day 60 a hearing with the applicant may be held and in addition, the CHMP/CVMP adopts its final opinion.

The re-examination procedure enables applicants to verify if the first decision of the Committee corresponds to the relevant legislation and current scientific opinion, respectively. But it is emphasised that the re-examination procedure is based on the data available when the first decision was taken by the corresponding Committee. Applicants are well advised to provide for this circumstance and in case of doubt to prepare for a new marketing authorisation application inclusive new data.

Table 4 Decision-making process after a standard CP

Timetable	Action
Day 210 + 15	EMEA sends the final opinion to the Commission including the translation of the product information performed by the EMEA
Day 225 + 15	Commission prepares a draft Decision
Day 240 + 22	Standing Committee consultation
Day 262 + 15	Commission to issue the final Decision
Day 277	End of procedure

With regard to Norway, Iceland and Liechtenstein the legally binding act of the EC has first to be transposed into corresponding legally binding acts in these states.

After the final decision is granted the EMEA publishes the CHMP/CVMP opinion (European Public Assessment Report) on the web-sites of the EMEA.

3.4.10 e-Submission

In accordance with Regulation (EC) No 726/2004[8], Directive 2001/83/EC[11], Directive 2001/82/EC[12] and Volume 9a/9b[34, 35] of the Rules Governing Medicinal Products in the EU applicants and marketing authorisation holder are engaged to report suspected serious adverse reactions to the EMEA. The electronic exchange and management are supported by EudraVigilance, the data processing network and management system which is managed and operated by the EMEA. Nevertheless, a pharmacovigilance system, as well as an ESTRI gateway is required for the compilation, storage, management and electronic transmission.

Apart from the electronic exchange of suspected serious adverse reactions the electronic submission of application dossiers and post-marketing activities in accordance with the Notice to Applicants, Volume 2B - Electronic Common Technical Document (eCTD) has also to be taken into account. The EMEA notified plans to implement the electronic-only submission in eCTD format for the CP[38]. The EMEA accepts electronic-only submissions from 1st July 2008, strongly recommend electronic-only submission in eCTD or non-eCTD (e.g. documentation is presented in a folder structure and as word-files) format from 1st January 2009, and strongly recommend electronic-only submissions in eCTD format from 1st July 2009. Regarding SMEs there is only limited support available by the EMEA[39].

SMEs who have no pharmacovigilance system, as well as an ESTRI gateway at their disposal, are allowed to perform the electronic reporting, as well as the medicinal product report generation and administration, by EVWEB, an internet-based reporting tool of the EudraVigilance Database Management System. As a prerequisite, MAHs only have to register with the EMEA and attend a training course in order to enable the correct use of EVWEB. This means that no additional costs for infrastructure or software arise and the financial charge is minimised simply because SMEs have only to invest in the instruction of their staff. Electronic dossier submissions facilitate the handling of procedures for both competent authorities and industry, for example by automation and standardisation of administrative tasks, reducing of handling of paper, reducing in management and archiving, as well as with regard to navigation and life-cycle management. In addition, the dossier compilation in accordance to CTD and the corresponding electronic version eCTD, respectively, also facilitates the dossier preparation by the applicant and the assessment by the competent authorities. This means that the time for submission and assessment, as well as the time to market is decreased, whereas the return of invest due to an earlier commercialisation and lower costs for submission increase. On the other hand companies are forced to invest in necessary IT-infrastructure, staff and training or to commission service providers and consultancy companies with the electronic submission. The latter alternative may be not so personnel intensive and expensive, but in consideration of the man-power and financial situation of the majority of SMEs a remarkable burden.

4. Obstacles, Support and Incentives

4.1 Financial strengths of SMEs

The development of innovative active substances or medicinal products is often characterised by long lasting development periods, by high risk for failure and often high costs of up to one billion Euros for one medicinal product. The same applies – in a smaller range – for the improvement of already existing products. Pharmaceutical SMEs are in addition strained by fees for the approval of medicinal products, as well as by pre- and post-marketing activities. They are often not very creditworthy due to a limited business performance and/or insufficient business information or have no adequate securities required for collateral based bank lending. In order to overcome these financial gaps SMEs rely on topic public funding programmes, financial instruments of the EIF, venture capital or risk financing, as well as sectoral specific support and fee exemptions, respectively.

Pharmaceutical SMEs may benefit from the Seventh Framework Programme for research and development (FP7) and partially from the Entrepreneurship and Innovation Programme. FP7 bundles all topic and research-related EU initiatives, whereas the Entrepreneurship and Innovation Programme, amongst others, supports investments in technological development and innovation and in addition improves access to finance for SMEs through venture capital investment and loan guarantee instruments. At national level support programmes are often designed in accordance to the country specific company structure and fields of activity, e.g. the German Federal Ministry of Education and Research supports SMEs in the context of their “KMU-innovativ” initiative. This initiative supports, for example, biotechnology companies which are strongly represented on the German market. Another programme is the “Scientific Research for the People“ project, which supports, inter alia, the cooperation between industry and science in order to develop new areas of innovation. Financial instruments of the EIF provide risk capital for SMEs, loan guarantees to encourage banks to make more debt finance available to SMEs, for example by micro-credits and mezzanine capital, and furthermore help to reinforce the capacity of financial intermediaries to invest in and lend to SMEs. Despite these endeavours SMEs continue to suffer from funding issues because banks persist to lend only against collateral and are commonly risk-averse. At national level the financial strength of SMEs might also be improved due to an attractive law, e.g. taxation law harmonised with SMEs requirements. In accordance with the SME definition

funding of SMEs is facilitated due to the access of different investors of up to 50% of the capital or voting rights of SMEs without interference of the SME status.

Furthermore, the financial strength of pharmaceutical SMEs is improved due to assistance from the EMEA and the EC. Fee exemptions are established for the CP pursuant to Council Regulation 726/2004[8], particularly Article 70.2 thereof, and in accordance with Commission Regulation (EC) No 2049/2005[7] laying down rules regarding the payment of fees to, and the receipt of administrative assistance from the EMEA. The regulation envisages

- 90% fee reduction for pre- and post-authorisation inspections
- 90% fee reduction for scientific advice
- a conditional fee exemption; the fee payable for a marketing authorisation application is due only in case that after a scientific advice given by the EMEA a marketing authorisation is granted.
- 90% fee reduction for scientific services
- 90% fee reduction for the establishment of maximum residue limits for veterinary medicinal products in order to support the establishment of such limits
- 100% fee reduction for administrative services (excluding parallel distribution)
- SMEs may request fee deferrals to the end of the procedures for fees which are payable for marketing authorisation applications or related inspections in order to avoid economic weakening during the assessment of a marketing authorisation application
- common administrative assistance and assistance in terms of translation arrangements are also provided in order to facilitate the handling of the CP for SMEs, as well as to reduce the translation costs for the product information

Apart from the above mentioned incentives, pre-submission meetings, as well as ITF consultations are generally free of charge. Additionally, there are specific incentives for ATMPs and orphan drugs. The ATMP development by SMEs is supported by a 90% fee reduction for scientific advice. The scientific evaluation whether a product falls within the definition of an ATMP is free of charge. There are also fee exemptions for ATMPs regarding the marketing authorisation application fees and common incentives for post-authorisation activities within the first year after approval; the fees are reduced by 50% in case of public health interest. Protocol assistance and follow up procedures, as well as pre-authorisation inspections for designated orphan drugs are free of charge. In addition, 50% application fee

reduction and 50% fee reduction for post-authorisation activities, including annual fees in the first year after granting of a marketing authorisation, are envisaged. The financial strength is also enhanced by a market exclusivity period of 10 years after granting a marketing authorisation. The ten years' market exclusiveness is prolonged up to twelve years in case that appropriate paediatric data is presented. Fee reductions may also be granted by the EMEA Executive Director in cooperation with the relevant scientific committee in exceptional circumstances and for imperative reasons of public health. There is also a CVMP programme regarding free scientific advice for the research and development of veterinary medicinal products for minor species and for rare indications in animals. Finally, the SME Regulation also provides for the establishment of national measures. An overview about the available national measures is published in Annex I of the User Guide for SMEs[40]. Fee exemptions should be expressed in the letter of intend/pre-submission meeting.

The financial situation of pharmaceutical SMEs might also be improved if payment for patent applications is deferred, reduced or waived, as well as if patents and other company specific rights or intellectual values, e.g. granted marketing authorisations, marketing authorisations applications, dossiers or preclinical and clinical data are taken into account in case of loan requests or investment decisions.

4.2 Networking, Cluster and Partnership

SMEs require access to external information, knowledge, know-how, technology and possibly facilities in order to strengthen their own capacity for innovation. This can be traced back on their limited access to human and financial recourses, as well as to the rapid changing of general conditions and regulations. In addition, the requirements for the development and marketing of innovations are not only limited to the innovations, but also pertain to special fields, e.g. drug regulatory affairs.

Apart from licensing of preliminary work the interdisciplinary working, networking and cooperations with partners and institutions, as well as the building of clusters are possible methods of resoluting the lack of resources, information and know-how. The SME definition already takes the above mentioned issues into account. On the one hand the cooperation between different companies is eased because the SME definition contains ceilings and instructions for the calculation of thresholds to determine the proportion up to which

companies may invest in another one without jeopardising the SME status. On the other hand, in order to facilitate the knowledge transfer from the science base to industry and practical experience of knowledge vice versa, the collaboration of SMEs with universities and non-profit research centres are encouraged. Universities and non-profit research centres may even hold up to 50% of the capital stock of SMEs. Moreover, there are also support programmes to facilitate the cooperation between universities and non-profit research centres with SMEs. A corresponding national German research programme is the "Research Bonus Programm"[41]. The aim of this programme is to activate additional potential for cooperation with industry, particularly with SMEs. Further national projects are the German "Pharma-Initiative für Deutschland"[42], as well as competence networks already implemented in different areas, e.g. cancer, neuroscience, healthy aging and orphan drugs. One of the key roles of the former initiative is a joint implementation strategy of different development lines by syndicates. The German Federal Ministry of Education and Research together with agencies from Belgian, Finland, France, Italy, The Netherlands, Austria and Spain also support biotechnology SMEs in the context of their ERA-Net Eurotransbio programme. The goal of this initiative is to establish cross-border partnerships between SMEs, to improve and accelerate technology transfer, as well as to strengthen European efforts to achieve sustainable industrial development. Besides, the EC launches the web portal of the Enterprise Europe Network whose focus is, amongst others, the promotion of cooperations and cluster formation between enterprises, universities and research centres. Another approach is the Innovative Medicines Initiative[43] as a public-private partnership between the European Community and the pharmaceutical industry. IMI intends to implement collaboration within the pharmaceutical sector in order to develop effective and safety medicinal products. In addition, the SME office acts as an one-stop-shop for pharmaceutical SMEs and as an information exchange platform, e.g. for SMEs which participate in workshops. Furthermore, information exchange and networking are also supported by special organisations and institutions like EuropaBio for the biotechnology-based industry and national clusters like "BioRegionen" in Germany. Clusters are systems in which the income on public and private investments increase due to the spatial or cultural proximity and which make the exchange of implicit knowledge easier. Clusters also result from closer cooperation between enterprises and Member states.

4.3 Access to international markets

Internationalisation is one of many possibilities to increase competitiveness of SMEs. Typical hurdles for SMEs to participate in international markets encompass, amongst others, shortage of working capital to finance exports, limited information to analyse markets, inability to contact potential customers, obtaining reliable foreign representation, and inadequate quantity of and/or untrained personnel for internationalisation. However, the hurdles are not uniform and constant but change in relation to company size and company experience regarding internationalisation.

In order to overcome these hurdles the EC launches the web page of the Enterprise Europe Network[44] whose focus is the internationalisation of SMEs. Further information is available on the web-page of the European portal for SMEs – Going international[45]. In addition, there are support programmes to encourage the internationalisation and trade with countries in Asia, Latin America, Africa, The Caribbean and Japan. Pharmaceutical specific programmes are not available.

4.4 Intellectual Property Rights

Intellectual Property Rights can be described as rights or privileges which are assigned to the owner in order to exclude third parties to make use of it. For pharmaceutical SMEs patents are of all Intellectual Property Rights the most important ones. They are granted by national or regional patent offices. Related information can be found on web-pages both of the patent offices and of the World Intellectual Property Organization, as well as on the web-pages of the IPR-Helpdesk[46] which possesses a special SME gateway. Nevertheless, obstacles and hurdles coming in question concern insufficient knowledge about property rights and the corresponding property right systems, patent application, high costs, and lack of legal and technical support during the development of successful strategies for the use of IPRs as part of the business strategy. The latter point is a company specific issue and therefore may be resolved only in cooperation with a patent consultant or attorney.

In all Contracting States of the European Patent Convention patent application is already facilitated because patent applications may be submitted to the European Patent Office. The European Patent Office in its capacity as regional patent office may grant a European patent which represent no consistent right across all Contracting States. The European Patent

"disintegrate" in a group of independent national patents mentioned in the patent application which may be centrally revoked or narrowed due to an opposition-, limitation- or revocation procedure. Because there is no common patent system companies have also to take into account national requirements like annual fees and the requirement to translate patents into national languages. This latter is a time consuming and expensive procedure and particularly for SMEs a great burden. From 1st May 2008 the situation is eased with the London Agreement coming into force. The agreement indicates that European patents have no longer to be translated either widely abstain from or entirely into national languages in case they are formulated in one of the official languages German, English or French of the European Patent office and in addition, the patent filing language is an official language or has been indicated as another official language in the Contracting State(s). This procedure reduces the application costs noticeably.

Another point for consideration is the inconsistent implementation of legislation, legal systems, as well as dispute resolution systems across the Contracting States. Until now, in case of patent infringement and in order to dispose of litigation, action has to be taken in each country concerned. But the costs of such litigations may be exorbitant particularly for SMEs and may be very risky due to different judgments across countries.

4.5 Bureaucracy and administrative burden

SMEs are affected by both EU and national legislation of the Member States. Although the specific policy in favour of SMEs (taking into account the "Think Small First" principle) has already been implemented, there are a lot of administrative burden, overregulation and bureaucracy with a great negative impact on SMEs.

On the whole, the issues concern also pharmaceutical SMEs. Furthermore, they are supplementary strained by European legislation in order to receive, to maintain and to monitor Community marketing authorisations. On the other side, the marketing authorisation application is facilitated because there are no national requirements and particularities which have to be taken into account because the EMEA is the only contact point and responsible for all pre- and post-marketing activities.

5. Conclusion

As mentioned, SMEs possess a high economic and social meaning. Nevertheless, the majority of SMEs have to overcome specific obstacles and hurdles which have a negative impact on their growth, as well as on the development of new medicinal products and innovations. In order to overcome these obstacles Member States and the EC foster SMEs with specific programmes and incentives. But across Europe it is essential that all efforts to overcome these obstacles are based on a common legally binding SME definition because diversity in implementation may have a negative impact on consistency and effectiveness of the supporting measures and may lead to competition distortions within the Community. The determination of SME status is based on the determination of staff headcount, turnover and balance sheet total, as well as on the determination of the relationships between companies. The first three measurements provide hard facts which cannot be individually interpreted and therefore indicate appropriate criteria for the determination of the SME status. The latter one takes into account that there may be different relationships between companies which have an enormous impact on the human or financial recourses of a company. However, in some cases predefined measurements discriminate enterprises, e.g. companies exceeding the staff headcount limit still matching the overall SME character, because the measurements are arbitrary ceilings. Besides, the SME definition does not sufficiently provide for post marketing authorisation requirements of pharmaceutical SMEs. Enterprises which pursue research and development of new medicinal products are dependent on a larger number of employees. The current limit for staff headcount is sufficient for the development but not for the manufacturing and marketing of medicinal products. On the other hand, the main target of the SME initiative is the promotion of innovations and the development of new products so that in most cases post-authorisation activities like manufacturing in commercial scale size and marketing of medicinal products are out of interest. However, in case of potential prospective post authorisation incentives, pharmaceutical SMEs should be enabled to benefit from such incentives even when – for example due to marketing activities – the staff headcount increases considerably. Alternatively, the EMEA should be provided with a scope at its disposal and assign SME status with sense of proportion in accordance with the SME economics.

Altogether, the definition is suited to foster SMEs into consideration to the different SME subcategories and with regard to their relationship to other companies and organisations. Nevertheless, the definition should be a dynamic policy in order to allow for the economic

development in the Community or the appearance of further obstacles in the future. Alternatively, the Recommendation should be updated regularly.

The administrative handling of a SME declaration is accelerated and simplified for both the EMEA and enterprises by the usage of the model self-assessment declaration. The declaration substitute former declarations with possible different contents and on the other hand may be used as a user manual for the enterprises which shall fill in the declaration. In addition, autonomous enterprises, which represent the majority of SMEs, have to complete only the first page. Therefore, the model declaration used by the EMEA reduces the administrative burdens for SMEs and support enterprise to ask for SME status.

The CP is intended for innovations and new medicinal products which fall within the scope of public interest. In contrast, non-prescription medicinal products which commonly do not fall within the above mentioned scope are also eligible for the CP. This proceeding will lead to further discussions with all stakeholders because guidance developed for the CP does not cover the needs of non-prescription medicinal products and in addition does not provide for the different legal status of corresponding non-prescription medicinal products across the Member States. Therefore, there is legal gap until the necessary adjustments are made.
The CP as such includes unfavourable aspects for SMEs. In most cases SMEs are unfamiliar with the proceeding, the regulatory environment or have limited experience in interacting with the EMEA. Although SMEs are already supported, e.g. by pre-submission meetings in order to receive procedural, regulatory, and legal advice from the EMEA, they are obliged to deal with these new and sometimes additional regulatory and procedural requirements on the basis of limited recourses. Besides, the multiplicity of dossier requirements, the various information sources and in some cases the uncertainties with regard to the interpretation of guidance or even the lack of information may hinder and defer the product development. The EC and the EMEA, respectively, already provide for these circumstances. SMEs are supported by partial or total fee reductions for scientific advice, protocol assistance, ITF consultation, and pre-submission meetings. In order to overcome the aforementioned obstacles SMEs should apply for requests at early stages and throughout the development process in respect of a development plan in order to ensure that appropriate tests, trials and investigations are conducted. This proceeding may avoid objections and delay during application procedures. However, the conformity with the principles of GMP, GCP and GLP is mandatory. Generally, GMP, GCP and GLP principles are in force for all medicinal

products. Nevertheless, at present there are no guidance documents for GMP and GCP requirements for certain medicinal products for which the CP is mandatory, particularly for ATMPs. Several guidelines are under preparation but until now they are not published for consultation. In addition, there are uncertainties regarding the harmonisation in terms of data requirements for ATMPs in combination with GCP and with regard to changes of Annex 2 of the EU rules on GMP. The proposed changes include also a new part of Annex 2 on specific biological products types, amongst others, animal immunosera, recombinant products, gene therapy, monoclonal antibodies and tissue-engineered products. The guidance documents should ensure that the requirements are properly implemented and, moreover, they should assist companies to comply with the corresponding provisions. Altogether, SMEs are well advised to get in touch with the advisory committees to ensure complaints with the corresponding requirements. The same applies for procedures in accordance with Article 14 (7), Article 14 (8) and Article 14(9)/39(8) of Regulation (EC) No 726/2004[8]. The different procedures enable applicants to gain faster or general access to the Community market for essential medicinal products. In order to discuss the different requirements with the authority and to ensure compliance with the corresponding needs, SMEs should seek advice as early as possible.

Another point for consideration is the orphan drug designation. The EU orphan drug designation was designed to encourage the development of products that demonstrate promise for the diagnosis, prevention and/or treatment of rare diseases. The evaluation process has a fixed duration and cannot be lengthened to accommodate for the lack of data or other omissions so that the applicant should ensure that all requirements are fulfilled. The easiest way is seeking protocol assistance and to propose a request for a pre-submission meeting. It is emphasized that SMEs should always seize the chance of orphan drug designation because the incentives granted may lower the costs to market. In addition, the risk of competition is reduced in the first 10 years of sales and the time to market may be reduced in case of an accelerated assessment, as well as when a marketing authorisation under exceptional circumstances or a conditional marketing authorisation is granted.

SMEs are frequently engaged in the development of new pharmaceutical products with a potential inherent risk for the environment, individuals or even for a patient group as a whole. Therefore, it is mandatory that these applicants have to provide an environmental risk assessment, a description of the pharmacovigilance system, and a risk management plan. The pharmacovigilance system may represent a problem for SMEs because they might not have the financial resources to purchase, outsource or operate an appropriate system. However,

SMEs may use the EVWEB tool, e.g. for the reporting and the transfer of ADRs, which enabled them to resolve these issues without engaging excessive human or financial recourse. Regarding the environmental risk assessment and the risk management plan these circumstances should already be taken into account during the development and the pre-authorisation period, respectively, in order to identify, to characterise and to investigate the inherent risks. Unfortunately, the evaluation and the judgment are not always obvious so that the competent authority should be contacted by the applicant. In both cases scientific advice is available by appropriate working groups. It is highly recommended to make use of such an advice request in order to receive advice on probable precautionary and safety measures with respect to the use and disposal of a medicinal product, as well as on the need for development or content of an EU-RMP. The advice procedures should take place at the latest during the pre-submission meeting.

As mentioned medicinal products authorised via the CP are allowed to use only one name across all Member States. In most cases the name of a medicinal product is an invented name. In order to exclude infringement of intellectual property rights, confusion in printing, handwriting or speech, and to avoid misleading connotations several checks have to be done by the applicant. It is likely that SMEs have not the adequate human or financial resources to perform these checks in a preselection process across the Member States. Therefore, SMEs may use the common name or scientific name accompanied by a trademark or the applicant's name so that this issue may be resolved without further burden on SMEs. But due to justice it would be helpful if the EMEA provides SMEs with a selection of appropriate invented names which may be used for the corresponding medicinal products.

Apart from the already mentioned aspects it would be desirable that the EMEA also provides a web-tool for the compilation, management and submission of electronic applications or renders the possibility of renting storage and publishing software in order to reduce costs for SMEs. If own systems are preferred, local workshops for staff training, a guide for the assessment of vendors, and an assessment of available tools, as well as a confirmation that these systems comply with regulatory requirements may be helpful. In case that SMEs which already implemented eCTD structures agreed on to introduce other SMEs in this complex area an early bird incentive should be taken into account for these SMEs. In addition, a common fee reduction for SMEs to compensate the additional costs for eCTD applications may be useful, too.

Pharmaceutical SMEs suffer from a multitude of obstacles which have an impact on the development of innovative medicinal products. The magnitude of obstacles differs in respect of company size and available resources.

EU or national support programmes are one alternative to overcome funding gaps which are in most cases topic programmes and linked to specific objectives. Nevertheless, the preparedness of SMEs to participate in these programmes declines even though these programmes improve the financial situation in long-term. The reluctance of SMEs to participate in such support programmes is due to high administrative requirements and the long period between project proposal, project start and first payment. Further barriers are the requirement to participate only as a consortium and the lack of awareness of these programmes. The latter issue may be resolved if there would be SME contact points in each Member State in order to inform SMEs about the support programmes. The contact points may also assist SMEs with regard to issues regarding the financial instruments. The funding by financial instruments should be extended, particularly for start ups, by special guarantee schemes, mezzanine capital or EU funds in order to support micro-credit schemes at national level. Apart from the already mentioned support programmes and financial instruments the access to venture capital and other types of financing should be improved. The first step was already done when the updated SME definition came into force which allows and facilitates the engagement of funding institution and other organisations. But at national level there are not so many venture capital funds, business angels or other organisations which are prepared to invest in young innovative SMEs, particularly in the start up stage, due to the low return on investment and the high risk for failure. Therefore, a pan-European venture capital market with increased liquidity and a broader investor base should be established.

Commission Regulation (EC) 2049/2005[7] lays down rules regarding the payment of fees and the receipt of administrative assistance from the EMEA. The CP fee exemptions and administrative assistance mainly affect major financial and administrative hurdles involved in pre-marketing procedures and are generally applicable to both human and veterinary medicinal products. Altogether, the fees policy takes sufficiently into account the financial situation of SMEs prior to and during a marketing authorisation application and attempts to resolve or at least to mitigate the main financial and administrative hurdles. On the other hand, the financial situation of SMEs after the approval of a MA is not taken into account. No efforts have been undertaken to reduce the financial burden on SMEs during the maintenance of MAs; the annual fees and the fees for variations deemed to be very high. Thus, to enable SMEs to market the approved new medicinal products the fees for maintenance should be

reduced particularly in the first years after approval when turnover and business development are insufficient. Besides, there are also further fee exemptions and incentives which are granted in order to increase development of specified medicinal products, e.g. ATMPs, orphan drugs, and veterinary medicinal products for minor species and for rare indications, on grounds of public and animal health interest. As mentioned, these fee exemptions after granting a marketing authorisation are very interesting for SMEs when turnover and business development is insufficient. However, in case of orphan drugs the financial allocation by the Community decreases whereas simultaneously marketing authorisations and designations as orphan drugs increase. There is concern that fee exemptions and incentives may be strongly limited in the future. In terms of quantification of company specific rights and intellectual values SMEs are already supported due to the assignment of orphan drug designations and in the future by Certificates for Quality and Non-Clinical Data of ATMPs[47]. Both the designations and the certificates can be used as quality confirmations of presented data for loan requests or investment decisions, because the applicant receives – together with the mentioned confirmations – also an evaluation report detailing the reasons for the conclusion and, where appropriate, a list of remaining questions or outstanding issues. These confirmations facilitate the decision making process of investors and also enable SMEs to sell their data for an appropriate price already during the development stage in case they are unable to develop products up to readiness for marketing.

Generally, immaterial assets are important values of SMEs. Better methods for balancing of these assets enable third parties to calculate the company value more exactly and thereby improve the chances of SMEs in obtaining the required venture capital or loans; but until now there is no portal or European contact point.

Regarding patent applications in the Contracting States of the European Patent Convention the financial burden on SMEs is already improved due to the London Agreement came into force which aimed to reduce the translation time and effort for patents.

Internationalisation is a key fact for growth and competitiveness of pharmaceutical SMEs; usually, internationally active SMEs are growing faster in comparison to domestic ones. Development and expansion can be increased by access to relevant information as already performed via web-portals. The importance of knowledge transfer, the cooperation between SMEs, universities and research centres, as well as the support of clusters are sufficiently taken into account by national and Community assistance and programmes. These efforts should be maintained or even broadened. Apart from the above mentioned considerations the

access of pharmaceutical SMEs to the European market is already secured because marketing authorisations granted by the Commission are valid for the entire Community. The marketing may be conducted from a national company site but there are also national peculiarities which have to be taken into account. For this reason, national contact points comparable with the SME office which are in the position to inform SMEs about the peculiarities, as well as about possible cooperation partner in order to cover the whole post-marketing activities should be available.

In order to improve innovation it is necessary to implement an efficient property right system. Regarding SMEs the costs for patent application and maintenance have to be affordable because SMEs have to economise with their financial resources. Therefore, the London Agreement should be a milestone on the way to the Community patent[48]. The Community patent as a unit right across all Contracting States facilitates the handling of patent applications by the European Patent Office as a one-stop-shop and therefore decreases time till granting of a patent across all countries concerned, as well as increase law certainty. Moreover, in case that agreement is reached that patents are allowed to be formulated in one of the official European Patent Office languages patent costs strongly decrease because translation costs as one of the most cost drivers are not to apply. If such a procedure is not enforceable, fee reductions or other administrative assistance, e.g. translation assistance, should be taken into account. Besides, due to the lower burden on the patent authorities the quality of patent assessment and thus the quality of patents may increase. This is also a very important fact because SMEs are strained by patents without presenting novelty or by patents with broadly based claims; commonly SMEs have not the resources to apply for withdrawal of patents and are thus hindered in the development of innovations and new medicinal products. In order to avoid unequal treatment and distortions a harmonised legislation, without local peculiarities and the same legal system should be established across all Contracting States. However, defending the Intellectual Property Rights still remains a challenge for SMEs and represents a main obstacle for them. This issue may be decreased when alternative procedures such as mediation or arbitration are consulted in order to resolve disputes flexible and cost-effective.

Bureaucracy and administrative burden may be derived from legislation and regulatory systems which were developed to serve needs of larger companies, and from rampant regulatory requirements. In order to overcome these issues the involvement and the feedback

of SMEs in the legislative procedure, exemptions and mitigating measures intending to facilitate the implementation of legislation by SMEs, as well as simplification of the corresponding legislation for SMEs should be taken into account. First steps have already been done in the context of the action programme for reducing administrative burdens in the European Union and the "Think Small First" initiative. In comparison to other industry sectors the situation for pharmaceutical SMEs seems to be better because Commission Regulation (EC) 2049/2005 also provides for the establishment of a SME office within the EMEA. The SME office was established due to the lack of experience of the majority of SMEs with the CP. The tasks of the SME office encompass administrative and procedural assistance regarding the requirements of Regulation (EC) 726/2004[8], monitoring of applications and requests, as well as facilitating the communication between SMEs and the EMEA; the SME office acts as a one-stop-shop for pharmaceutical SMEs. Besides, in order to further support SMEs regarding medicinal product legislation the EMEA SME office informs SMEs about news and available information and guidelines. The website of the SME office also contains a vast array of additional product information that are of interest for SMEs.

The EC plans to face problems affecting SMEs in a Small Business Act for Europe in order to sensitise competent authorities, as well as the publicity for the problems of SMEs. Thereby, the SBA should provide a solid basis for a SME policy and for all other EU legislation procedures taking into account the "Think Small First" initiative. Regarding the envisage obstacles an industry sector specific approach should be preferred.

6. Summary

This article focuses on SMEs which perform centralised procedures to obtain European marketing authorisations for medicinal products.

Pharmaceutical SMEs suffer from a multitude of obstacles. In order to overcome these obstacles, the EC, as well as Member States, foster them in form of support programmes and administrative assistance. The SME status, as a prerequisite to benefit from such programmes and incentives, is based on the SME definition taking into account thresholds like staff headcount, turnover, and balance sheet total each on an annual basis, as well as qualitative standards like business relationships to other companies. All in all, the SME definition is well established and takes sufficiently into account the needs to foster pharmaceutical SMEs in consideration of existing SME subcategories and with regard to business relationships. The SME status application which has to be submitted to the EMEA is facilitated due to the use of the model declaration.

The CP is generally used for the marketing authorisation application of innovations and new human or veterinary medicinal products. In contrast, under certain conditions the CP may also be used for the marketing authorisation application of non-prescription products. But this proceeding is not fully sophisticated and will give rise to further discussions. However, the CP from the SMEs perspective is centred including topics, hurdles and incentives with significance for SMEs. Key aspects encompass, amongst others, dossier requirements, advice procedures, as well as specific procedures in accordance to Article 14 (7), Article 14 (8) and Article 14(9)/39(8) of Regulation (EC) No 726/2004[8], orphan drug designation, and e-submission.
Despite the difficulties and hurdles the CP enables SMEs to gain faster access to the single market and simultaneously to assure appropriate quality of the medicinal products due to the cooperation between the EMEA and national competent authorities.

Obstacles can be divided in financial, administrative and company-specific obstacles, as well as in specific hindrances for pharmaceutical SMEs. The impacts of the obstacles depend on the company size and available resources. In order to overcome these obstacles SMEs are supported by common support programmes at regional, national and Community level. In addition, pharmaceutical SMEs are also supported by specific financial incentives and fee

reductions, as well as by procedure-related administrative assistance granted by the EMEA. Not all problems could be solved. Nevertheless, the described incentives are sufficient to ensure smooth marketing authorisation application submissions.

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