EXTENDED ROLE OF SCIENTIFIC ADVICE AS A CONSEQUENCE OF THE NEW MEDICINES LEGISLATION IN THE EU INCLUDING A COMPARISON TO THE SITUATION IN THE USA

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Ellen Güttler
aus
Sachsenkam

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Betreuer und 1. Referent: Dr. Ekkehard Baader

Zweite Referentin: Dr. Petra Bettauer

List of Abbreviations

ASGT	American Society of Gene Therapy
BfArM	The German Federal Institute for Drugs and Medical Devices (i.e. Bundesinstitut für Arzneimittel und Medizinprodukte)
BLA	Biologic License Application
BRMAC	Biological Response Modifiers Advisory Committee
BWP	Biotechnology Working Party
CBER	Centre of Biologics Evaluation and Research
CDER	Centre of Drug Evaluation and Research
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
cGLP	current Good Laboratory Practice
CMA	Continuous Marketing Application
CMC	Chemistry, Manufacturing and Control
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedures (for human medicines)
CMS	Concerned Member State
CHMP/CPMP	Committee for Medicinal Products for Human Use /the former 'Committee for Proprietary Medicinal Products'
COMP	Committee for Orphan Medicinal Products
CR	Commission Regulation
CTA	Clinical Trial Application
CTD	Common Technical Document
DCP	Decentralised Procedure
EEC/EC	European Economic Community/ European Community
EMEA/EMA	European Agency for the Evaluation of Medicinal Products/ alternatively: European Medicines Agency
EOP2/EOP2a	End-of-Phase 2/ End-of-Phase 2a
EPAR	European Public Assessment Report
EU	European Union
EWP	Efficacy Working Party
FDA	Food and Drug Administration of the US Department of Health and Human Services
FDAMA	Food and Drug Administration Modernisation Act
FD&C Act	Federal Food, Drug and Cosmetic Act
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GT	Gene Transfer/Therapy
HA	Health Authority

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
MA/MAA	Marketing Authorisation / Marketing Authorisation Application
mAB	monoclonal Antibody
MP	Medicinal Product
MRFG	Mutual Recognition Facilitation Group
MS	Member State
NDA	New Drug Application
NME	New Molecular Entity
NML	New Medicines Legislation (referring to the new codified pharmaceutical legislation in the EU, effective since QIV 2005)
NIH	National Institute of Health (USA)
OTCD	Ornithine Transcarboxylase Deficiency
PA	Protocol Assistance
PDUFA	Prescription Drug User Fee Act
PEI	Paul-Ehrlich-Institute, Germany
PSA	Parallel Scientific Advice
PVP	Pharmacovigilance Plan
QWP	Quality Working Party
RAC	Recombinant DNA Advisory Committee
rDNA	recombinant Desoxyribonucleic Acid
RMS	Reference Member State
SA	Scientific Advice
SAE	Serious Adverse Event
SAG	Scientific Advisory Group
SAWG	Scientific Advice Working Group (precursor of:)
SAWP	Scientific Advice Working Party
SME	Micro, Small and Medium sized Enterprises
SPA	Special Protocol Assessment
SS	Safety Specification
SWP	Safety Working Party
TdP	Torsade de Pointes
TOC	Table of Contents
USA/US	United States of America /United States
WHO	World Health Organisation
X-SCID	X-linked Severe Combined Immunodeficiency

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1. Introduction

Health Authorities in general are willing to provide advice to companies in terms of regulatory science. As an example, the European Agency for the Evaluation of Medicinal Products (EMEA) considers it as one of its tasks to "…advise companies on the conduct of various tests and trials necessary to demonstrate the safety, quality and efficacy of medicinal products…" [18),12),46)] with the goal to evaluate at an early stage, when necessary, whether a Marketing Authorisation (MA) can be granted. This offer is, although almost always not legally binding, of great advantage for companies, because the authorities are capable to provide a wide spread expertise. Hence, by obtaining scientific advice (SA) a company receives precious input for the product development plan and learns whether the proposed regulatory strategy as a context for a possible solution of a certain scientific question is accepted by the agency. Depending on the agency, the scientific part of the objective is much more in the focus than the regulatory part. Early communication between the companies and the agencies will be established to see whether a certain issue will justify a meeting with the Health Authority (HA) for clarification by using scientific advice.

The meaning of scientific advice has rapidly increased since this initiative exists. Upon the New Medicines Legislation (NML), the EMEA for instance extended its task list [46)] and, due to an opening up to the public and the transparency initiative, the scientific advice procedure now should also involve groups outside the regulatory environment, such as public health institutions or patient organisations [37),46)].
Looking at the United States (US), the role of SA has been standardised and established in the legislative earlier than in the European Union (EU). Especially the Prescription Drug User Fee Act (PDUFA) enhances the meaning of SA during the process of preparation of a New Drug Application (NDA) and lays down the right of companies to obtain it [43)].

1.1 Scope of the Thesis

The scope of this thesis is to demonstrate the role of SA for drug development and subsequent Marketing Authorisation procedures, especially in the EU and US markets: The impact of the new NML and the resulting changes in SA activities should be shown. The most important procedures and types of SA should be described. The main focus of description is laid on the EU, because the role of SA increased after the NML implementation [37)]. In the discussion a comparison to the situation in the US will be provided.

The forms of scientific advice provided in terms of politics, fundamental research, and economy are not within the scope of this thesis, as this is dedicated to Regulatory affairs.

2. Overall scope of Scientific Advice

2.1 Phases of drug development

It may be useful for a company to apply for SA at certain stages of the development of a new drug. The following stages are the critical ones, causing the need for SA in many cases:

a) The stage prior to the start of the clinical development phase I (e.g. pre-IND meeting in USA and Japan): Mainly clarification is needed here if the pharmacological and toxicological data are sufficient in terms of safety and efficacy to start the clinical phase I.
b) The stage at the end of phase II, where the safety, rationale and the study design of the phase III of clinical development are discussed.
c) The pre submission of application-stage (e.g. EMEA): questions regarding the presentation of the data for the application can be clarified.
d) Postmarketing/maintenance: for some kind of variations, especially line extensions to gain approval for new indications, SA may be very helpful to clarify early whether the clinical data are sufficient, or whether bridging studies are needed, or whether, for some reasons, a full stand alone application might be necessary. Pharmacovigilance issues could be a cause for SA requests postmarketing [15)].

However, the development plan for a certain new active substance is the determining factor for a successful approval of the new medicinal product (MP) later on. Therefore, SA should be obtained at any time when there is a general decision to be made having a great impact on the successful development, approval or launch. The timing is important: SA should always be chosen when there are sufficient data available to present a certain concept, it should not be requested too early [51)].

2.2 Lack of guidance or interpretation of guidance

A meeting at an Authority is needed when no pharmacopoeia monographs, accessible guidelines and guidance documents provide sufficient clarification for a specific question [18)]. This could occur in the development of an orphan drug or of a new product (e.g. a new combination of active substances) where scientific advice can be gathered to clarify points which are usually not to be considered (e.g. clinical trial issues because of a very small patient population).

2.3 Special and typical topics for Scientific Advice requests

Individual studies can raise special questions: How should a company e.g. manage the fact that certain clinical trials provide perfect results but have been conducted in a non-Good Clinical Practice (GCP) environment whereas the Marketing Authorisation Application (MAA) should be submitted in the EU. It should be clarified with the appropriate agency which bridging studies will be inevitable to follow the GCP requirements as closely as possible, and which observations might be negligible because of the quality of the existing data.

On the other hand, there are lots of typical topics: Table 1 shows a list of general and typical topics focused on in SA[15].

Tab. 1) General and typical topics focused on in SA (modified according to [15])

General and typical topics focused on in SA	
QUALITY	- Design of stability programme - Manufacturing issues - Comparability
BIOTECHNOLOGY	- TSE - Viral safety - Change of formulation - Biosimilars
PRECLINICAL	- Carcinogenicity (waivers/models) - Reproductive toxicity - Bridging program (e.g new indication) - Compatibility of strategy/ legal requirements and guidelines (incl. justifications of deviations as appr.) - Paediatric requests
CLINICAL/BIOMETRY	**Primary endpoints** - Choice/Acceptability/relevance - Surrogate parameters - Composite endpoints - Oncology endpoints **Secondary endpoints** **Methodology/Design** - Inferiority, Equivalence-Delta - Superiority - Blinded or open trials - Analysis **Methodology** - Interim analysis - 'Early' applications - MA under exceptional circumstances - Number of studies at the time of MA **Control** - Placebo/comparator - Dose and study regimen - Concomitant medication /treatment **Trial duration** **Population** - Inclusion/Exclusion criteria **Safety exposure** - Long term safety data - Specific safety concern - Immunotoxicity - Cardiotoxicity (e.g. QT prolongation, TdP) **Paediatric development**

3. The role of Scientific Advice in the EU

3.1 Local Health Authorities

The different national authorities in the EU also provide SA which is comparable with the SA provided by the EMEA when considering a marketing authorisation (see). It is not possible here to explain the different types of meetings that will be offered by the different Health Authorities. Therefore the meetings offered by the BfArM, the German Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich-Institute (PEI), shall serve as an example:

3.1.1 Scientific Advice at the BfArM/ PEI

Scientific and regulatory advice regarding safety, quality and efficacy can be requested at any stage of the development of a medicinal product before and after registration by a pharmaceutical company is obtained, in case that, as with the EMEA, existing guidance does not apply or is not exact enough for the solution of a certain problem [50)]. Hence it could facilitate to choose a country as a Concerned Member State (CMS) or Reference Member State (RMS) in a Mutual Recognition Procedure (MRP) or Decentralised Procedure (DCP). A future project of the BfArM/PEI will be the portfolio meetings, in which the BfArM invites applicants to report about their product pipelines [51)]. The purpose of this new feature, which is not yet possible within the scope of SA at the EMEA, is to establish the SA as an entrance portal for applicants and to accompany the development process from an early stage. This should allow for a dialogue with the applicant as early as possible and to find agreement upon a certain development plan. As in the portfolio meetings not only one MP is introduced at the agency, but the whole pipeline, the agency can, if the offer is accepted by the pharmaceutical industry, internally compare pipelines from different pharmaceutical companies and can therefore deal with three advantages: a) to learn from SA procedures on similar products from different companies and distribute under consideration of confidentiality the general outcome and experience within SA procedures coming in later on and can somehow streamline incoming requests on similar products from a procedural view and b) to identify the need of general guidance to be set up as early as possible and c) to receive an overview on the upcoming workload in terms of applications to be expected in the national setting, including MR and DCP procedures and when, and for which therapeutic areas. The main purpose is to contribute to a more effective development of MPs and to an acceleration in the approval processes on a national basis [15),50),51)], but the local SA is also of advantage when a centralised procedure is planned. (see section 3.1.2)

3.1.2 Meetings at the BfArM/ PEI to prepare submissions to the EMEA

Meetings at the BfArM/ PEI can be helpful in the pre-submission status of orphan drugs or can serve as a preparation to decide who will be the possible rapporteur or co-rapporteur in a planned centralised procedure. This result of SA at local HAs is still valid, due to the fact that although it is not mentioned explicitely anymore in the new legislation that the suggestions of Rapporteurship by the applicant have to be taken into account by the Committee for Medicinal Products for Human Use (CHMP) when selecting the Rapporteur for a certain centralised procedure, the CHMP's view is to further try to follow the applicants recommendations. To obtain several SAs from different national Authorities

could facilitate the adoption of a common view at European level especially on efficacy and safety issues. The centre of excellence offered here, for instance expertise for indications such as oncology and gastroenterology at the German Authority or the knowledge in respiratory at the HA of Ireland and United Kingdom can be gained. These consecutive procedures will support companies in refining their questions for a possible future SA procedure at the EMEA: SA from a national HA can serve as a rehearsal with one agency to be prepared to apply at another one, in order to clarify the contents of the briefing document and streamline the list of questions from one SA procedure to the next, so that a possible SA at the EMEA is applied for in an absolute mature stage of scientific approach to the questions. This also allows for sound design of different suggestions of the company on how to deal with a certain issue needing clarification via SA, so that the Scientific Advice Working Party (SAWP) mainly needs to choose a proposed option (considering that an application format in which the EMEA would be asked to design an own solution would not be accepted), as well as to obtain a 'preview' on the topic from EMEA experts or CHMP members who are also involved in the national SA work. It is of paramount importance for a company to have a clear regulatory strategy before meetings for SA are scheduled. The selection of the agency for a meeting will mainly depend on this strategy.

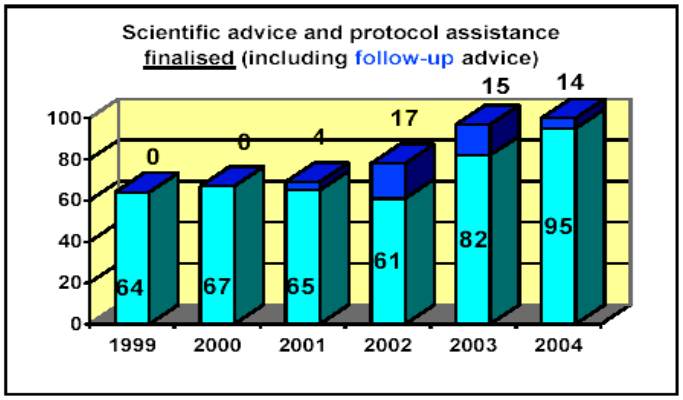
3.2 The meaning of SA provided by the EMEA in the light of CHMP - figures

Since the creation of the EMEA in 1995, the SA framework has evolved and SA workload increased significantly [37)]. The new Regulation (EC) No. 726/2004 established the SAWP as a standing working party of the CHMP with the sole remit of providing SA (see section 3.3.1). The SAWP currently faces a continuous increase in the number of procedures and meetings with applicants [37)].

3.2.1 Numbers and timelines of SA/PA procedures reviewed

A steep increase in the number of procedures was observed since 2001, nearly doubling in 4 years [37)]. In 2003, there have been a total of 97 SA and Protocol Assistance (PA) procedures given by the CHMP and in 2004, there has been a slight increase to a total of 109 finalised procedures (see figure 1) [41),48)].

Fig. 1) Scientific advice and protocol assistance finalised (including follow-up advice)



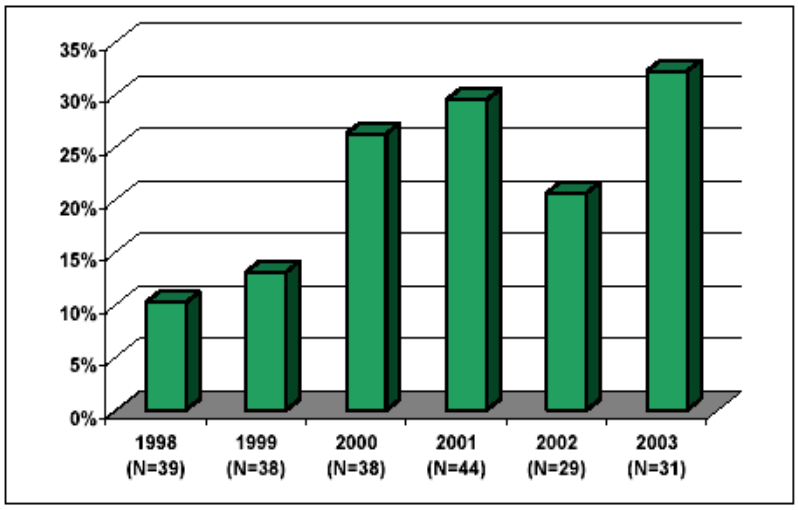
Timelines for the SA/PA procedures improved in 2003 thanks to the introduction of meetings for two working days for the SAWP, two weeks before the CHMP meetings. The mean time between start of

procedure and adoption of advice letter was 76 days, compared to 87 days in 2002 [41]. In 2004, the mean duration of the procedure was 86 days. Including validation time the overall procedure took about 100 days [48].

3.2.2 Impact of SA on MAAs

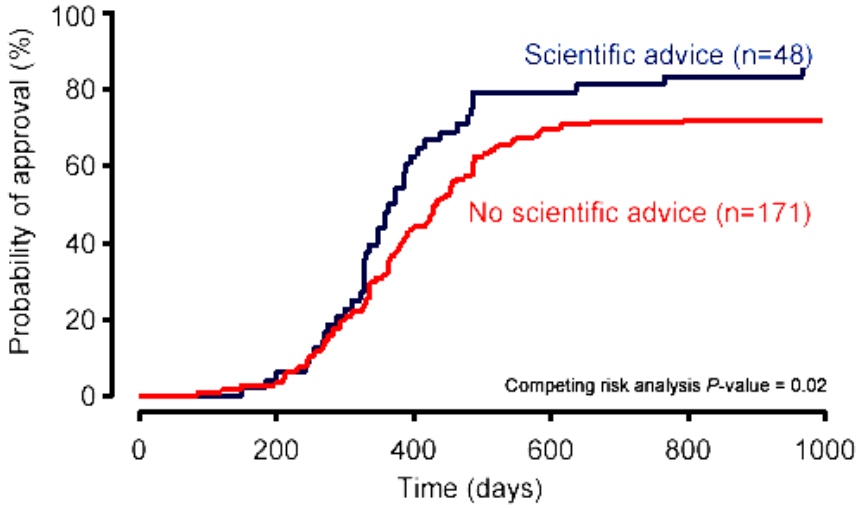
The proportion of MAAs preceded by SA is growing, but is still not more than 30 per cent, e.g. for applications submitted in 2003 (see figure 2) [48].

Fig. 2) Proportion of MAAs preceded by SA – by start year [48]



There is a significant association between prior SA and success of MAAs. Figure 3 shows a success rate of 85% (41/48) for 48 MAAs with SA given since 1998 versus 72% (123/171) success rate for those without SA (see figure 3).

Fig. 3) Impact of Scientific Advice (n=48) on the outcome of MAAs since 1998 [48]



These figures show that the role of SA/PA increased since its commencing, and that a clear impact can be seen on success rates of MAA in terms of approvals depending on SA prior to submission, given that the contents of the advice letter have been implemented. Especially the reduced incidence of major objection on the choice of endpoint in pivotal trials was statistically significantly associated with prior SA obtained and implemented. Although SA is associated with higher success rates, the data overall do not seem to indicate that SA speeds up the approval process. However, a trend seems to exist for shorter clock-stop time over the last few years.
This reflects how useful this tool is for stakeholders, namely the EMEA and the pharmaceutical industry, and that a tendency to enhance its meaning by widening its tasks is a logical consequence. However, the SA must be followed, otherwise the positive impact can not be found. It is important to mention that all figures available her derive from the time before the NML came into force (end of October 2005 for Directive 2001/83/EC as amended and 20. November 2005 for Regulation (EC) No 726/2004, also referred to as 'new regulation' in the following sections).
This means, that if such a tendency of an extended need of SA (and this is only measured exemplatory for the SA in context of MAAs submitted in the centralised procedure) could be seen already before the NML, a further increase of this tendency should be expected after the NML due to its new challenging requirements (see sections 3.3 and 3.4).

3.3 Legal basis and scope of SA/PA in the EU

SA may be requested for all medicinal products for use in human beings, as defined in Directive 2001/83/EC as amended, irrespective of medicinal product's eligibility for the centralised procedure or not [18)]. According to article 57-1(n) of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004, one of the tasks of the EMEA as the "Agency, acting particularly through its committees" is " advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products" [18),37)].

The SA provided by the agencies, usually on a company's request, consists of information regarding the implementation of certain regulatory guidance and requirements for a special scientific issue with a medicinal product under development, if the guidelines accessible by the company are not clearly applicable to a certain objective and need interpretation [18)].
It is the responsibility of the CHMP to give SA to industry by answering to specific questions relating to e.g. the manufacturing of the product, the preclinical safety and clinical development based on the documentation provided by the company in the light of the current specific knowledge. In this respect it is neither the role of the CHMP to substitute the industry's responsibility in their product development, nor can SA be legally binding on the EMEA with regard to any future MAA [18)].
SA is focussed on scientific issues, while regulatory aspects should be clarified in an SA presubmission meeting or in a presubmission meeting for a MAA in the centralised procedure.
However, SA received from the EMEA is applicable throughout the EU, it may be useful for procedures under the scope of mutual recognition such as DCP and MRP as well and it does not preclude consultations with national competent authorities. Therefore communication between the companies and the agencies will be established to see whether a certain issue will justify a meeting with the HA for clarification by using scientific advice [39)].

After having received the designation of an Orphan drug status, a company is also entitled to request SA according to article 6 of the Regulation 141/2000, the protocol assistance (PA) [17)]. PA applies as long as it is provided within the scope of a planned submission of an MAA for an orphan medicinal product. The range of questions, the focus on scientific issues and the non binding character is similar to SA requests, however, especially in the discussion of orphan drugs the questions should be expressed within the designated orphan indications. There are three main types of specific questions anticipated: Two are related to the criteria for Marketing Authorisation:

a) Requests concerning development of medicinal products for rare conditions in terms of pharmaceutical, pre-clinical and clinical development and b) Requests concerning study design to demonstrate clinical superiority over an orphan comparator [17),45)].

The third type is related to the criteria for designation of orphan drug status and deals with the significant benefit criterion [45),8)]. Once the initially assumed significant benefit which is a 'clinically relevant advantage or a major contribution to patient care' has been demonstrated at the time of MA application, the chance for obtaining the MA is increased [18),17)]. PA is provided without obtaining fees.

As far as the extended role of SA and PA following the implementation of the new regulation is concerned, it is described in the regulation's preamble no. 25 that "the field of activity of the Scientific Committees should be enlarged and their operating methods and composition modernised. Scientific advice for future applicants seeking marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular, micro, small and medium-sized enterprises (SME) should be put in place…" [37)].
Moreover, not only companies but also health care professionals and even patient organisations shall play a more active role in the scientific advice process, according to article 78 (2), where it reads "The committees…shall in general establish contacts, on an advisory basis, with parties concerned with the use of medicinal products, in particular patient organisations and health care professionals' associations…..relevant to the indication of the medicinal product concerned " [37),46)].

3.3.1 The SAWP and Experts network

In accordance with Council Regulation (EEC) 2309/93 the group responsible for advising applicants started its activities as a CPMP consultation group (1996), and was re-established as a formal Committee for Proprietary Medicinal Products (CPMP) Working Group (the Scientific Advice Working Group, SAWG) in 2003. It was formed as a Multidisciplinary Expert Group, based on complementary scientific competences not on a national representation. With the introduction of Regulation (EC) No 141/2000, the activities of the group extended to providing PA for orphan drugs. In order to deal with the increasing number of applications and improve dialogue with industry, the meetings were separated from CPMP meetings and extended, at last to 3 full days. New procedures for SA/PA were also put in place, the last changes will become effective in July 2006 [37)].
Article 56 (3) of the new regulation provides that "The Executive Director, in close consultation with the Committee for Medicinal Products for Human Use (CHMP)….., shall set up the administrative structures and procedures allowing the development of advice for undertakings, …., particularly regarding the development of new therapies. Each committee shall establish a standing working party…." [34),46)].

Hence, as of May 2004, the Scientific Advice Working Party (SAWP), replacing the SAWG, was established by the CHMP (the former CPMP), with the sole remit of providing Scientific advice. The current composition of the SAWP includes wide ranging expertise such as pharmaceutical development, preclinical safety, pharmacokinetics, statistics and therapeutic fields for which there are frequent requests and those defined in the Annex of the new regulation (see section 3.4.2.2) [37)]. The multidisciplinary SAWP group comprises 1 Chair, 25 members, among which 1 Vice-Chairperson and 3 members of the Committee for Orphan Medicinal Products (COMP). The members are appointed by the CHMP (COMP) for three years. SAWP members are COMP-, CHMP-members or EMEA experts. In the nomination, the fair representation of expertise in the different developmental phases named above should be ensured. The Chairperson and the Vice-Chairperson are elected by the CHMP, both for three years, renewable. The role of the SAWP, in order to optimise research and development, reduce uncertainties in regulatory outcomes and accelerate time for approval of a MAA, consists of the following three parts:
Firstly, it consists of the tasks connected directly to SA procedures:

- Coordination of the provision of SA/PA and forwarding of an integrated view as regards quality, preclinical, clinical safety and efficacy, relating to the development of medicinal products and orphan medicinal products, to the CHMP and COMP for adoption within a defined timeframe and format. Focus is laid on products intended for the new mandatory centralised procedure. This scope also includes follow-up advice.
- The SAWP provides SA/PA on prospective questions raised by applicants on the development of their products. Attention should be paid to development and methodology issues of products intended for small populations.
- In addition to its own expertise, involvement of appropriate expertise (from internal or external experts, Working Parties or ad hoc groups) in SA and PA should take place when necessary. Specialised expertise may be consulted in the provision of PA due to the fact that the scientific knowledge may not be represented appropriately for rare diseases.
- The SAWP may develop interactions with interested parties, in particular patient's organisations and other regulatory agencies. The following two aspects are falling under the scope of interactions with other agencies: a) Provision of SA for products intended for marketing outside the Community, in context of the co-operation with the World Health Organisation (WHO) and b) provision of opportunities to applicants to discuss with other regulatory agencies, in particular with the Food and Drug Administration (FDA), their global development programmes. The latter should follow a request from the applicant to arrange such parallel scientific advice procedure [34)].

Secondly, advice should be given within the scope of certain new areas coming into the focus of the SAWP following to the NML:

- Provision of Advice about the justification on whether a specific medicinal product being developed for a specific therapeutic indication falls under the scope of the conditional marketing authorisation for a medicinal product, and, for products being justified, provision of advice on the acceptability of the development programme for conditional marketing authorisations.
- SA on paediatric developments (except Paediatric Investigational Plans as defined in the Regulation on medicines for children when implemented)

- Provision of advice about the justification for applying for a marketing authorisation under exceptional circumstances, and, for products being justified, provision of advice on the acceptability of the development programme within this scope.
- Provision of advice on the design of trials to assess safety and efficacy in a new indication to bring significant benefit compared to existing therapies and also for a well – established substance.
- Provision of SA to SMEs, taking into account their specific needs

Thirdly, the SAWP role consists of the tasks being a consequence of the SA procedures performed as a whole in order to streamline and harmonise expertise and provide general guidance as a reaction on the current 'hot topics' being brought up by the progress in scientific development:

- The SAWP ensures consistency between SA/PA given to sponsors and available EU guidance documents as appropriate
- Mobilise appropriate and specific expertise, especially for new and emergent therapies such as gene therapy and associated cell therapies etc. and for questions related to pharmacogenetics/ pharmacogenomics
- Cooperation with other EMEA Committees, Working parties, Scientific advisory groups and the EMEA scientific secretariat, not only for a certain SA procedure, but especially when questions raised seem to have touched issues requiring general clarification, in particular to create a guideline/points to consider document in a specific therapeutic area, to publish standard Q&A documents and to organise workshops and think-tank meetings on specific and rapidly evolving topics.

It should be mentioned that the SAWP is not responsible for regulatory assistance [34)].

When it comes to this third task regarding development of guidance documents, SA procedures are the first step to discover the need of guidance in a certain scientific field. Therefore the SAWP as the party earliest involved in the trends in the development of new guidance documents and standards for regulatory science, is working closely together with a network of internal experts and external academic experts outside the agencies. The internal experts are mainly organised in the different Working Parties, which are, just as the SAWP itself, established by the EMEA to fulfil specific tasks, such as the Efficacy Working Party (EWP) which is providing recommendations to the CHMP on all matters relating to the clinical part of drug development. One of the EWPs task is to prepare, review and update guidelines in specific therapeutic areas and on methodology and interpretation of clinical trials [51)]. Another example is the Biotechnology Working Party (BWP) which is composed of experts setting up the guidelines for the challenging biotechnology field with its ethical and procedural specialties on a broad scientific expertise. The cooperation between the parties is a permeable system. The external experts are mainly taking part in the Scientific Advisory Groups (SAGs). These are established by the CHMP to provide advice in connection with the evaluation of specific types of medicinal products or treatments, mainly in terms of therapeutic areas. They consist of European experts selected according to the particular expertise required on the basis of nominations form the CHMP or the EMEA [51)]. A list of experts which are nominated by the different MS authorities to assist in EMEA procedures has been published on the EMEA website.

For instance, there are the SAG on Cardiovascular Issues and the SAG Advisory Group on Anti-infectives as well as the SAGs on diseases of the Central Nervous System (CNS) or on Diabetes/Endocrinology. They are to be consulted for the development of guidance documents [51)].

As the network described above is established to develop guidance from the scientific issues the EMEA becomes aware of, there is also a network used for each scientific advice procedure itself, which is created by the CHMP (COMP), SAWP, the coordinators, the working parties and the SAGs to be involved and single external experts as appropriate.
The SAWP may consult relevant Working Parties or Scientific Advisory Groups in relation to the evaluation of preclinical and /or clinical questions including safety, for a specific product within agreed timelines. The SAWP is delegating, according to the relevant SOPs, the task of evaluating pertinent quality related issues to the BWP or to the Quality Working Party (QWP). The communication between these participating groups is kept up by forwarding the applicant's request and the co-ordinator's draft report(s) to the relevant working party or the SAG. All participating groups report to the SAWP which remains responsible for the consolidated advice forwarded for adoption to the CHMP/COMP [34)].
The new SA procedure foresees several opportunities to exchange expertise from other scientific EMEA groups involved and to appoint single external experts as appropriate (see section 3.4.1 and Annex 1) [37)]. The SAWP may involve additional expertise (including patients representatives) in SA/PA procedures for all aspects to ensure the highest level of scientific knowledge in particular at discussion meetings. For each procedure a specific team is built up from the groups involved, supported by assistance from their teams in the national agencies in the MS.

3.4 New and extended role of SA according to Regulation (EC) No 726/2004 (referring to Directive (EC) 2001/83 as amended)

The new Regulation outlines the principles for modernising the operating methods of the committees and provides for more general in depth scientific advice with the aim of improving advice given to applicants. The legislation gives this task to the EMEA Executive director to be 'achieved in close consultation' with the CHMP. For this purpose, a consultation phase was initiated involving CHMP and SAWP members. As a result, this consultation lead to the identification of areas where developments are expected in order to fulfil the stakeholders needs to ensure public health and see who needs scientific advice. This is mainly the pharmaceutical industry. However, since better SA means better, more efficient and faster development of safe and effective medicines, SA is beneficial to patients and healthcare professionals as well. Apart from changes in the procedures (see), another key aspect includes more interaction, communication and transparency with stakeholders, through extension of scope and increased use of follow up procedures, publication of standard question and answers documents for frequently asked questions, and other new measures from the SAWP such as incentives to SMEs, additional specific expertise and new competences (see). The new SA framework also envisages more collaboration with academia, learned societies and patients' organisations [37)].

3.4.1 New framework of SA/PA requests and procedures

Usually the scientific advice takes place on a company's request in writing. Before the draft and hence the final submission of this request is made, a letter of intent to submit an SA or PA request is forwarded to the EMEA secretariat and it will be either an SA presubmission meeting requested and arranged or not. Depending on this presubmission meeting, the planning phase will follow the longer or the shorter schedule. The structure and content of the request should be as follows: it should consist

of a cover letter with all relevant information to company, description of the medicinal product, the indication, the type of request and area of advice. Here the justification for the request should be provided as well as the detailed table of contents (TOC). Attached should be a briefing document including the questions, ordered sequentially to address specific issues. Each question should be followed by a company's position including a justification. In the annex of the request all relevant background information and documentation should be provided (a detailed description is made in annex 1) [13),2)].

A scientific advice administrator will be appointed by the EMEA to be in charge of validation and processing of the request, who will be the contact person for the company for any discussion concerning the validation of the request and for any questions related to the planned or ongoing procedure. He is in charge of managing the scientific advice or protocol assistance procedure.

The SA/PA provided to companies is the result of collegial work by the coordinators, the experts, the different Working Parties, the SAWP, the COMP (for questions within the scope of PA) and the CHMP. The answer is prepared by the coordinators and then submitted to the relevant Working Parties for comments and to the SAWP for discussion and adoption of a common position, before being forwarded to the CHMP or COMP for formal adoption and hence provided to the company as the finalised SA letter [18)].

From a procedural point of view, the whole measure starting with the letter of intent and resulting in the finalisation of the SA letter consists of three phases: The planning phase with or without presubmission meeting, the evaluation phase (30 days), and the 'core' SA procedure itself lasting from the discussion of the first reports of the coordinators until the adoption of the final advice letter. There are two general scenarios possible for the timetable of the core procedure, depending on the SAWP decision, whether a discussion meeting with the applicant is needed or not. The simplified procedure applies when no discussion meeting should take place (40 days, often chosen for follow-up SA procedures), the standard procedure (70 days) including a discussion meeting is the most frequent scenario. The extended procedure of 100 days may be chosen in exceptional cases until July 2006[18),39)]. A detailed overview of the procedure timetable is given in Annex 1.

The current procedure for SA has been revised, and will be changed as adopted in April 2005 by the CHMP and outlined in the pertinent guidance document [37)], finalised April 2006 and becoming effective in July 2006 in order to follow the challenges of the new Regulation (see section 3.4.2).

One of the key aspects of the new procedure is the systematic and early involvement of coordinators and their assessors/experts in the presubmission phase in all types of advice. This can be seen comparing the old procedure to the new proposed framework directly from the timepoint of coordinator appointment. In the ongoing procedure the coordinators will be appointed on procedure day 0. This is the timepoint when the SAWP has adopted the validated request, so that at this time it is absolutely clear that there will be an SA/PA procedure initiated. The new procedure nominates the coordinators at the timepoint when the letter of intent is provided by the company. This is in the earliest possible state of the presubmission phase, about 2 months before day 0 or SAWP adoption.

SA presubmission meetings will be an opportunity for applicants to introduce and receive feedback from coordinators on the proposed development programme for the medicinal product concerned on the list of issues and identify additional issues to be included in the request. These meetings remain optional, but hey are strongly recommended, especially for first time users of SA, for PA, for SMEs, for broad and more general SA on specific types of medicinal products and therapies. More detailed

information regarding the procedure can be obtained, and regulatory questions can be asked which are outside the scope of scientific advice. This shows the relevance of the early coordinator involvement: Firstly, this measure enables companies and coordinators to establish contact to each other as early as possible to facilitate the proceeding application. Secondly, it allows to streamline the procedure to reach a finalisation within 40 or maximally 70 day (versus the 100 days procedure formerly more frequently used) [37].

Another key aspect of the new framework is the implementation of additional expertise: The establishment of earlier formal contacts to SAWP and EMEA Working parties and Groups, including greater involvement of SAGs and external experts already during the presubmission phase will create input networks and maximise the use of available expertise.

The next example of the changed procedure reflecting the extended role and effectiveness enhancement of the SA procedure is the recently introduced concept of peer review:
In order to extend clarity and ensure consistency in the provision of scientific advice, this new framework will consolidate the involvement of CHMP by formalising the peer review before final adoption of the SA letter. The practicalities of the peer review are still to be defined in upcoming guidance documents, however this will clearly involve reviewers from SAWP, CHMP and COMP, in addition to the EMEA secretariat, whose responsibility is to ensure the quality-assurance throughout the procedure. In every phase of the SA procedure, the presubmission phase, the evaluation phase, and the 'core' procedure, a peer review step or a related step is planned such as EMEA review of evidence quality assurance, resulting from the review of scientific memory as derived from previous SA or MAA procedures or existing European Public Assessment Reports (EPARs). The option for requesting a parallel or joint SA meeting together with the EMEA and the FDA is included in the new EMEA SA procedure and should be applied for well in advance of the planning phase so that it can be agreed timely by the SAWP [37] (see section 4.).

3.4.1.1 Follow-up procedures

In the former framework, a follow-up request to an initial request of an SA/procedure could only be provided in order to reconsider the advice already given in the light of new information available or in cases of changes or amendments to the development programme for which SA or PA was initially given. The definition of a follow-up request has now been reconsidered and allows more flexibility to applicants. A follow-up request is now defined as any subsequent request falling within the same therapeutic indication and areas as the initial request. Area in this context means quality, preclinical or clinical development, including pharmacovigilance aspects.
By widening the definition, the applicants are now able to seek a follow-up request on new issues which were not initially included in the first advice (as long as it remains within the defined indication or area). When submitting a follow-up request, applicants should still make reference to the previous first CHMP advice issued, and the questions included should still remain prospective. To ensure continuity, one of the 2 coordinators involved in the initial request will be proposed for reviewing the follow up request. This opened definition is an incentive to encourage applicants to seek SA/PA as many times as necessary throughout their development programme, to ensure continuity in the support

by the CHMP during the development of their MP and to reduce uncertainties of the MA process outcome [18),37)].

3.4.2 What are the major topics in which the new and extended role of SA becomes real?

According to the new Regulation, the SAWP may deal with or give special emphasis to the following new aspects:

3.4.2.1 SA to be broader and more formalised-the 'regulatory/scientific memory concept':

Broader and more general advice for types of medicinal products or even treatments should be provided in collaboration with the relevant working parties. This is aiming on a concept to collect all information given like in a library or thesaurus, and this will be reached by the systematic EMEA quality check, as described above. The maximal involvement of more experts, even external ones, is another contribution to reach this goal. This will enhance the emphasis on emerging therapies and new therapies. In this context the consultation of patient organisations and health care professionals within the SA procedure will be supportive. Systematically collected SA documentation should be used as a source to develop guidance and guidelines, but not only in context with MAAs, but also for treatment concepts e.g. in terms of changes to state-of-the-art therapies or disease management programmes [37)].

3.4.2.2 Emphasis on products intended for the new mandatory centralised procedures

According to the Annex of the new regulation in combination with article 3, the concept of the Part A and Part B products formerly used to define the conditions for the MAA of a new medicinal product in terms of being approved mandatory or facultative via the centralised procedure before the NML has been changed [12)].

Since November 2005, when the new regulation came into force completely, the following indications have been introduced defining new medicinal products in these therapeutic areas to be only authorised via the centralised procedure in the EU:
Acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes and, as of 20 May 2008, auto-immune diseases and other immune dysfunctions and viral diseases. Hence, medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000 are completing the list [37),46)]. As outlined in the last part of this annex, after 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal modifying these list of indications for new active substances and the Council shall take a decision on that proposal by qualified majority [46)].

But not only these indications will provide a wide field for future scientific advice: Because of the rapid development of new and better manufacturing methods and the deeper knowledge in the clinical experience, biotechnology medicinal products will also be a great source for SA requests. These are defined by their manufacturing or the genetic engineering principle of their function, as described in the annex in the following way:

Medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma and monoclonal antibody methods [46)].

Any medicinal product in the composition of which there is a proteinaceous constituent obtained by means of recombinant DNA technology, falls under the scope of this point of the Annex to the Regulation, irrespective of whether or not the constituent is an active substance of the medicinal product. This list of biotechnological medicinal products and indications has to be under close observation of the EMEA to be adapted as appropriate. In order to gain more experience and expertise with these products and these indications, scientific advice will probably be more often requested by companies and with the systematic collection of the SA procedure documentation at the EMEA, will be an early source to obtain tendencies in scientific development but also in the clinical experience of those medicinal products allowing for constant collection of information regarding possible amendments of the Annex, rather than the MAA procedures themselves.

In the following two sections two examples on MP groups which belong to biotechnological medicinal products are described to outline the extended and enhanced role of Scientific advice in this emerging area.

3.4.2.2.1 GT-products: An example for the role of SA for innovative MPs in emerging therapies

Medicinal products developed by means of one of the biotechnological processes as outlined in the annex (see above) are also the candidates used in the setting of gene therapy being mandatory for the centralised procedure. Moreover, gene therapy can be an appropriate treatment in some of the mandatory indications, such as neurodegenerative disorders, e.g. for Chorea Huntington, special oncologic diseases (Philadelphia chromosome, linked to leukaemia) or certain immune dysfunctions. Moreover this therapeutic concept is linked closely to many possible orphan drugs. Since gene transfer (GT) products contain genetic and other materials of biological origin, many of the quality considerations for recombinant (rDNA) products and other medicinal products manufactured by modern biotechnological methods will apply to manufacture of gene transfer products. The presentation of the MA application dossier for GT products must of course fulfil the same administrative and scientific requirements as for any other medicinal product as laid down in the legislation, however, special additional requirements are necessary as outlined in the part II of the annex I of Directive 2001/83/EC as amended.
These include requirements relating to establishments, in which GT medicinal products are manufactured (current Good Manufacturing Practice, Good Laboratory Practice - cGMP, cGLP), and considerations of environmental impact of the use of gene transfer products on the deliberate release of genetically modified microorganisms. The Agency will take any effort to avoid adverse effects on humans health of the environment, which might arise from the deliberate release of placing on the market of any kind of genetically modified organisms (e.g. genetically modified viruses acting as gene transfer vectors). The environmental impact of the use of GT products has implications for the

authorisation and conduct of clinical trials as they may present viral safety and other biosafety issues related to intrinsic safety properties and also the safe handling in relation to environments and the wider human population [40)]. Hence, the occurrence of immunogenicity is to be considered, influenced by the properties of the active substance and finished product, as virtually all biotechnology derived therapeutic proteins being the result of this therapeutic concept elicit some level of antibody response. In so far, immunogenicity is a clear safety issue also to be assessed and clarified for GT products, providing a wide field for SA issues. This topic is further described in section 3.4.2.2.2 [26)].

As for any new technology, a flexible approach for the control of these products is being adopted so that recommendations can be modified in the light of experience gained from production and use, and from further developments, also by SA/PA. Whilst the recommendations given in guidance documents regarding GT products provide a general approach, individual products may present specific quality control and safety concerns, for example as in the case of DNA vaccines intended for prophylactic use in a large number of healthy individuals. The production and control of each product will be considered on a case-by-case or product specific basis reflecting the intended clinical use of the product. As regulatory experience with this treatment is still growing, in order to address product specific issues and more generally scientific issues not covered by or deviating from existing guidance, the CHMP is providing SA in this area on quality, nonclinical and clinical aspects of GT-development programmes [40)].

According to data published in 2003, out of more than 300 SA procedures provided on development, four sponsors developing GT products have used this procedure at that time. Only very few candidate products have had a development plan oriented towards regulatory procedures ultimately leading to the EU wide issuance of an MA. The same publication states that, “sixteen percent of GT clinical trials are conducted in EU and 80% in USA; more than 87% of worldwide GT clinical trials are in an early development”. This reflects, as a snapshot for 2003, on the one hand the ongoing efforts in research and on the other hand the status of early development in the clinical development of GT. Until end of 2002, three GT medicinal products have been designated as orphan medicinal products and for one of them a PA process has been initiated. SA/PA has been provided for GT products intended for the treatment of oncology conditions, immunological disorders and infectious diseases (1, see section 5.3.3.1). Since then, the CHMP has already mobilised important scientific resources in order to meet the regulatory challenges of this still rapidly evolving field. State-of-the-art scientific advice has been provided on a case-by-case basis, and an *ad hoc* expert group on GT has been established and extended on the basis of multidisciplinary competences (e.g. involving the Safety Working Party SWP, the BWP, SAWP etc.) to provide, as also for other therapeutic fields, additional recommendations resulting in guidance to reflect the progress in experience.
It is expected that in the future more requests of scientific advise will be lodged by sponsors, taking into account the potential opened up by the ongoing exploration of the human genome, the refinement of vector designs and types and especially as a consequence of further experience gained within the progress of GT research from the early clinical phases into phase III-trials [40)]. However, this field is still under close observation and vivid discussion in terms of risk management of biosafety issues.
Therefore it is described here as an example for future developmental areas, whose proceedings are as much a relevant and inevitable challenge as the method is under controversy discussion (see section 5.3.3.1).

3.4.2.2.2 Biosimilars: Another example for the role of SA for biotechnology derived MPs

In January 2006, the CHMP provided its first positive opinion on an application for authorisation of a 'biosimilar' MP, which have to be approved via the centralised procedure [32),39)]. In principle, the concept of similar biological medicinal product is applicable to any biological medicinal product. However, the success of such a development approach will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.
Difficulties could occur because there is a spectrum of molecular complexity among the various products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell therapy etc.).
Moreover, parameters such as the three-dimensional structure or posttranslational modifications such as the glycosylation profile, can be significantly altered by changes considered to be 'minor' in the manufacturing process. Hence it could be expected that there may be subtle differences between biosimilar products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Thus, the safety/ efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects.
Therefore the following considerations apply, containing possible SA topics:

- The standard generic approach consisting in the demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies, which is 'essential similarity' (according to the 'generic definition' in article 10, Directive 2001/83/EC) is normally applied to chemically derived medicinal products [16)]. Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically inappropriate for these products [29)].
- Comparability exercises to demonstrate biosimilarity are more likely to be applied to highly purified products, such as some biotechnology-derived mps, which can be thoroughly characterised. On the other hand, the biosimilar approach is more difficult to apply to other types of biological medicinal products which by their nature are more difficult to characterise, such as biological substances arising from extraction from biological sources or those for which little clinical and regulatory experience has been gained (e.g. gene and cell therapy products).
- Whether a medicinal product would be acceptable using the biosimilar approach depends on the state of the art of analytical procedure, the manufacturing process employed, as well as clinical and regulatory experiences.
- The requirements to demonstrate safety and efficacy are essentially product-class specific. Therefore, the non-clinical/ clinical data package is determined on a case-by-case basis, for situations where product class specific guidance has not been defined.
- Pharmacovigilance issues

Clinical considerations

The need for clinical efficacy and safety data should be approached as if data from confirmatory and comparative efficacy /safety studies were needed. Important issues to be taken into account when designing and justifying the clinical program for a biosimilar product include clinical experience gained with the reference product if relevant with respect to e.g.

- Whether a dynamic marker has been accepted as a surrogate marker for clinical studies
- The relationship between dose/exposure and the surrogate marker

- Drug/receptors interaction
- Disease specific mechanisms of action
- Target organs for activity
- Pharmacokinetic properties (including biological barriers of relevance)

In clinical trials sometimes surrogate markers are used instead of a definite clinical endpoint.
A dynamic marker is a surrogate marker for efficacy, if therapy-induced changes in that marker to a large extent can explain changes in clinical outcome.
Surrogate markers are usually more sensitive to changes in activity and can be assessed earlier than clinical endpoints and therefore, may be more useful when comparability has to be shown with clinical data. However, as the goal of comparative exercise is showing the equivalence of the product, usually data are needed concerning the quantitative relationship between the surrogate and the clinical endpoint to enable defining and justifying the equivalence margin in terms of efficacy.
There might be situations when the requirements with respect to formal validation are less stringent. Examples include the absolute neutrophil count and granulocyte colony stimulating factor (GCSF) or early viral load reduction in chronic hepatitis C and alpha interferons. In cases where formal validation of the surrogate marker is missing, a comprehensive justification is expected taking into account the above mentioned issues and regulatory scientific advice might be necessary.

Immunogenicity

The issue of immunogenicity must always be considered when a claim of comparability is made, especially when repeated administration is proposed. Immunological studies are expected if physico-chemical characterisation is not sufficient due to the complexity of the molecule and an impact on immunogenicity cannot be excluded with reasonable certainty. Pre authorisation studies are required for a claim of comparability to another product.
The factors triggering immune reactions against biotechnology derived proteins are often not fully understood in individual cases. However, the occurrence of immunogenicity is influenced by the properties of the active substance and finished product. Further possible origins of immunogenicity are for example post translational differences, that may occur between various expression systems although the genes themselves are identical. Extraction and purification processes of the therapeutic protein as well as product and process related impurities may affect immunogenicity. Furthermore, host factor including genotype and concomitant diseases associated with immune dysregulation, previous exposure to other therapeutic proteins that might cause cross reactivity, could also play a part. Repeated administration of an antigen may increase the likelihood of an immune response. In assessing possible risk factors for immunogenicity previous experience with the product or other products of the same class should also be taken into account.

In view of the unpredictability of the onset and incidence of immunogenictiy post marketing monitoring of antibodies at predetermined intervals will be required. Special consideration should be given to those products where there is a risk that the immune response could affect the endogenous protein that has unique biological function. Safety considerations in terms of pharmacovigilance planning and risk management programs (see section 3.4.2.4) should be made, especially if signals detected before the authorisation show that the risk of serious but rare immune mediated response is considered to be high [26)]. The individual study plans may contain many possible requests for SA.

In the authors view, this section and section 3.4.2.2.1 both show, how single independent SA requests and procedures initiate general guidance.
For instance, all the existing European guidelines on biosimilarity result from similar types of issues and questions raised such as described above by different sponsors following comparable product developments and requesting SA procedures independently. Upon realising in overviews that repeatedly SA procedures had been provided on similar issues, the SAWP, CHMP and experts network concluded the need for the creation of points to consider and finally of guidelines. Only these groups are in the position to realise such tendencies, as the sponsors act independently and follow strict confidentiality rules against their competitors.

3.4.2.3 MPs in the 'optional scope' of the centralised procedure (DCP, CMD(h), and referrals)

According to article 3 of the Regulation (EC) No 726/2004 there are further medicinal products defined which could be, but do not need to be necessarily approved via the centralised procedure under certain circumstances, because they are new in the EU. In case the decision is made not to apply for a certain MP meeting the definition for a potential centralised procedure, the article 28 of the Directive 2001/83/EC as amended defines, that these products have to be mandatory approved via the new DCP, when there are plans for a marketing in more than one EU country [16)]. This procedure initially came into force since October 2005, so that the experience for an MA procedure via the decentralised procedure is still very low. In general, this new procedure could lead to an earlier market approval than the 'classic MRP', as the step of a single national MA approval before the MR phase takes place is not needed. However, during this procedure there are several steps which could lead to a referral (according to articles 29 ff of Directive 2001/83/EC) [16),14)]. In this case, the Coordination group is, according to article 27 of the directive, responsible for the clarification of the referral [16),21)].
The new DCP is in so far much more a candidate for a referral than the former MRP, that the first EU authorisation will not be granted before all Member States (MS) involved have accepted the SPC and the AR provided by the RMS, although countries which have accepted the SPC could market the MP without expecting the end of the referral procedure, however, if there is no agreement on Assessment Report or Summary of Product Characteristics, this would lead to a single national authorisation only in the RMS [14)]. This would create an unfortunate situation in the countries which have started the launch before the end of the decentralised procedure. Therefore all stakeholders in such a procedure are very keen on finding a solution for a positive outcome. This means a lot of additional work for the Coordination group (CMD(h), the former Mutual Recognition Facilitation Group MRFG) as it is up to them to clarify the referral rather than handing it over to the EMEA.
The extended role of SA in this context becomes quite clear: Scientific advice provided by the EMEA in the presubmission phase of the MAA in the decentralised procedure can be a perfect tool to avoid possible referrals later on. It will help the Coordination group and the applicant to see very early the EMEAs view on a certain scientific issue, which can occur in the context of each topic listed in table 1, and this is important to know, because the EMEA will be the last instance for a decision of any referral. And it will prevent the EMEA from having to deal with too many referrals in the context of DCP, which is normally not on the EMEA task list as an authorisation procedure and therefore the number of referrals per given time frame can not be planned in advance. SA might be a tool to decide whichever procedure might to be applied better in general for an MP within the scope of article 3, the centralised or the DCP [51)].

SA obtained from local authorities of the planned member states could be a good tool to find the RMS and to find very early obstacles in certain countries in terms of treatment conventions or habits or scientific positions in cases where different but equally valued scientific approaches are existing in the academic field. The use of antibiotics versus resistance profiles is a good example.
The same arguments apply also for referrals emerging in context of MR Procedures, Variations and general questions of community interest [16),39)].

3.4.2.4 Emphasis on safety aspects including pharmacovigilance plans and risk management programme (E2E)

Pharmacovigilance, in the WHO definition, is 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems'.
This definition shows already several possible connections to Scientific advice issues. Pharmacovigilance planning and risk management programs have become more relevant during drug development and postmarketing, at least with the implementation of the International Conference on Harmonisation (ICH) E2E guidance, effective in the EU since June 2005. The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. The knowledge related to the safety profile of the product can change over time through expanded use. During early postmarketing period the product might be used in settings different from clinical trials with their ideal patient populations, and a much larger population might be exposed in a relatively short timeframe. Therefore once a product is marketed, new information will be generated which can have an impact on the benefits or risks of the product. The monitoring and evaluation of this additional information should be a continuing process in close consultation with regulatory authorities. The benefit-risk-balance can be approved by reducing risks to patients through effective pharmacovigilance. Industry and regulators have identified the need for better and earlier planning of pharmocovigilance activities before a product is approved. This ICH guideline shall encourage harmonisation and consistency, to prevent duplication of effort, and could be of benefit to public health programs. According to the guideline, a method for summarising the important identified risks of a drug, the important potential risks, and the important missing information including the potentially at risk populations and situations where the product is likely to be used that have not been studied pre approval. This is called safety specification (SS).
The guideline proposes a structure for a pharmavcovigilance plan (PVP) and sets out principles of good practice and design and conduct of observational studies.
It is recommended that company pharmacovigilance experts get involved early in product development. Planning and dialogue with regulators should also start long before license application. SS and PVP should be documents that might be submitted at the time of license application or earlier (stand alone ore incorporated in the Common Technical Document - CTD).
A SS and PVP can also be developed for products already marketed (new indication or major new safety concern), and could be used as the basis for discussion of pharmacovigilance activities with regulators.
Four points are important, and deliver need for SA:

- Planning of pharmacovigilance activities throughout the product life cycle
- Science based approach to risk documentation
- Effective collaboration between regulators and industry

- Applicability of the PVP across the three ICH regions [38)]

For the two points mentioned first, SA could be of importance in this context in order to set up a Safety Specification for a certain medicinal product or also, if certain issues are known, for a whole class of substances. Drug-drug interactions will play a relevant role.
In general, the elements to be implemented in a certain SS could require SA. For example, in the context of the preclinical safety data, a question could be what kind of toxicity is of paramount interest or necessity, and what kind could be neglected. In the clinical part of the SS, the limitations of the existing human safety data base, or the populations not studied in the pre approval phase could create SA requests, e.g. in how far could it be relevant from a safety point of view to include data on sub-populations carrying known genetic polymorphisms, or on patients of different ethnic origins [38)].
Hence, epidemiology of the indication could lead to scientific discussions, e.g. the classification of relevance of co-morbidity. When it comes to the PVP, especially the action plan for safety issues could lead to SA requests, in terms of appropriate study designs, especially to create reliable long term safety data on the basis of sophisticated sample size considerations in order to include as little as possible patients. In general, all topics related to clinical questions as shown in table 1 are applicable in the context of SA requested for SS and PVP [15)].

The extension of the role of SA in association with safety aspects and risk management plans will mainly be based on the fact that the industry is not yet used to the framework of very early implementation of pharmacovigilance planning, i.e. already starting from the preclinical development phase and until today the experience on creating the documentation and plans the guidance requests still is very low. Many questions will also aim on sophisticated solutions in terms of avoiding of unnecessary data in order to be most effective in the PVP on the one hand, but also to gain the experience on limited costs on the other.

As far as communication effectiveness and applicability are concerned, harmonisation of pre approval pharmacovigilance requirements, e.g. within substance classes, and the creation of Q&A documents, points to consider and further guidance documents will be a new challenge for SA experts in this field.

3.4.2.5 SA request for products in the scope of conditional approval and MA under exceptional circumstances

An applicant may request advice on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in article 2 of Commission Regulation (CR) (EC) No. 507/2006 on conditional marketing authorisation for medicinal products for human use [10)]. These categories are: Firstly, MPs which aim at the treatment, prevention or the medical diagnosis of seriously debilitating or life-threatening diseases; secondly, MPs to be used in emergency situations, in response to public health threats duly recognised e.g. by the European Community; and thirdly, MPs designated as orphan drugs [10)].
For those medicinal products a conditional MA can be granted by the EMEA before all data are available when a positive benefit-risk balance is demonstrated, based on scientific data but with pending confirmation. Although the authorisation is valid for one year on a renewable basis, it is not intended to remain indefinitely. Once the pending studies are provided, it is turned into an normal

MA[35]. However, the MPs of the listed categories must fulfil the following special requirements to be eligible for a conditional MA, as laid down in Article 4 of the same Regulation.

- a) The risk/benefit balance of the MP is positive
- b) The applicant will most likely be able to provide the comprehensive clinical data in a short timeframe.
- c) Unmet medical needs will be fulfilled

Especially in the case of c), although the regulation provides a definition, scientific advice will most probably be sought for a justification whether a certain MP, once falling within the given categories, fulfills an unmet medical need.
Hence, as the planning of the clinical development plan in order to prepare an MAA always occurs at an early stage of development, its success will critically depend on whether a conditional MA is a possibility. Therefore it is necessary to provide a mechanism for the agency to give companies advice on whether an MP falls within the scope of conditional approval. Such advice is an additional service provided by the agency, which is a new feature as a consequence of NML [10].

An applicant may also request advice on acceptability of the development programme for future MAA under exceptional circumstances [28] according to Article 14 (8) of the new Regulation. Reference is also to be made to part II of Annex I of Directive 2001/83/EC, as amended. An MA under exceptional circumstances can be granted given that the applicant cannot provide comprehensive data as usual, the MA will be reviewed annually to reassess the risk-benefit balance, and any specific procedures, imposed as part of the MA, will be fulfilled. These measures are aiming at the collection of as many information as possible on the safe and effective use of the product in question, including an effective risk management planning, and will usually not lead to the completion of a full dossier, so that a normal MA could not be the outcome expected. This is the main difference to the conditional MA. The inability to provide comprehensive data may be caused by the following reasons: a) The planned indications are encountered too rarely to find a reasonable way to provide comprehensive evidence, and b) comprehensive information cannot be provided in the present state of scientific knowledge.
Inability to provide comprehensive data should be discussed very early during drug development. The applicant is encouraged to seek scientific advice on the limitations imposed by the rarity of the disease, or the limited possibilities to collect comprehensive information even partially in the present state of scientific knowledge. Advice may be also requested from the EMEA about justification for applying for an MA under exceptional circumstances [28]. Hence, some MPs could fall under the scope of both types of authorisation (e.g. orphans).

3.4.2.6 SA requests for MP, marketed exclusively outside EU in the context of WHO collaboration (acc. Article 58(2))

Article 58 (2) of the new regulation makes provision for SA by the EMEA on medicinal products intended to be marketed exclusively out side the European Community. SA can be requested during initial development, before an application for a CHMP scientific opinion or in the post-opinion phase.

The existing procedural guidance on SA will also be applicable for SA on possible future applications for a CHMP scientific opinion in the context of cooperation with WHO; these procedures are described in section 3.4.1 and in the Annex I.
The same fee applies; in exceptional cases, total or partial fee exemption may be granted by the EMEA Executive Director for MPs eligible for a CHMP scientific opinion on recommendation from CHMP. Any request should be sent to the EMEA with the appropriate justification as early as possible (at least 3 months prior to the anticipated date of submission of SA request) [27)].

3.4.2.7 Patient groups and health care professionals

Since the patient, formerly considered a passive recipient of healthcare and advice, has turned into a more empowered and proactive consumer of healthcare in our democratic information society, this change is commonly known as the Empowered Patient concept. Patients and consumers are increasingly seeking information in a more active way about diseases and their treatment. This is an important element in the developing health care professional – patient interaction. Two important issues need to be considered in the context of the empowered patient concept: firstly, information and secondly, patient's safety. Such issues currently constitute a political priority at EU level [20)].

The involvement of patients in EMEA activities in general is not an entirely new concept. It has been first introduced in Community legislation in 2000, particularly through the Regulation on orphan medicinal products [8),45)]. Since then patients representatives have been members of the COMP.
New legislative provisions widen the scope of involvements in EMEA activities, for instance, patients' organisations are now also represented in the agencies Management board as stated in Article 65 (1) of the New regulation [20),46)].

As far as scientific advice involvement is concerned, Article 78(2) of the new regulation states that, the committees….and any working parties and Scientific advisory groups…shall in general matters establish contacts on an advisory basis, with parties concerned with the use of medicinal products…..Rapporteurs appointed by these committees may establish contacts with representatives of patient organisations and health care professionals associations relevant to the indication of the medicinal product concerned [46)]. This illuminates the new role of patients in the extended scope of scientific advice. Their consultation as appropriate will even be a substantial part of the new procedure, emphasising the new, politically supported attention dedicated to this group. The implementation of patients and health care professionals expertise is a further consequent step, as outlined in the annex of frame work interaction [20)].

The implementation of the article quoted above will be performed as follows:

- Consultation by the committees: the committees (CHMP, COMP and also HMPC) may consider it appropriate to consult patients and consumer organisations on very specific issues of a scientific or technical nature. Issues addressed during these consultations may include feed back on disease management, quality of life, and feasibility of risk management programmes.

- Consultation by the working parties or the Scientific advisory groups: The scientific Committee may request a scientific advisory group to consult patients and consumers organisations on very specific issues related to disease management or its impact on the daily life of the patients. The working parties may also consider the need to consult patients during the development of guidelines prior to finalisation of such documents. Issues such as quality of life, or feasibility of clinical trials may be addressed with patients

- Consultation by the rapporteurs: The rapporteurs appointed by the Committees may also establish contacts, on an advisory basis relevant to the medicinal products concerned [20)].

3.4.2.8 New regulation on SMEs including special SA provisions

Pursuant to the new regulation, the situation of micro, small and medium sized enterprises (SMEs) has to be considered separately. This has been laid down in the CR EC No 2049/2005 [9)].
SMEs are socially and economically important, since they represent 99 % of all enterprises in the EU and provide around 65 million jobs and contribute to entrepreneurship and innovation. However, they face particular difficulties which the EU and national legislation try to redress by granting various advantages such as certain incentives and funding programmes [47)]. The definition of an SME according to the EU commission has been set up in April 1996, based on the idea of EU wide harmonisation of the criteria for SMEs, so that the risk of distortion of competition is limited [7)]. Since then this definition has been revised to adapt economic developments. According to the current definition, into force since January 2005, an enterprise is considered to be any entity engaged in an economic activity irrespective of its legal form [9)]. Obviously, when it comes to the category of micro, small and medium size, criteria have to be set up in terms of limitation and differentiation of SMEs from usual enterprises. The most important criteria determining enterprise categories are the staff headcount and financial ceiling. Table 2 shows the ranges for these two main criteria laying down the size limits of enterprises for being categorised [1),47)].

Tab. 2) Main criteria determining enterprise categories: staff headcount and financial ceiling [47)]

Enterprise category	Headcount	Turnover	Or	Balance sheet total
Medium-sized	< 250	≤ € 50 million		≤ € 43 million
Small	< 50	≤ € 10 million		≤ € 10 million
Micro	< 10	≤ € 2 million		≤ € 2 million

Compared to the older definition, the increase of financial ceilings is designed to take into account subsequent price and productivity increases since 1996, however, the headcount ceilings remain fixed

Moreover, a typology of enterprises explaining the differences between the three organisation forms ‘autonomous enterprises’, ‘partner enterprises’ and ‘linked enterprises’ is another relevant part of the EU definition, introducing a calculation method for the thresholds in terms of consolidated accounts, so that a realistic picture of the economic strength of an enterprises is given. The definition also includes rules for headcounts [1),9)].

With this revised definition it is ensured that enterprises, which are part of a larger grouping and could therefore benefit from a stronger economic backing that genuine SMEs do not benefit from SME support schemes [9)] .

Experience since 1996 shows that the main financial and administrative entry hurdles for SMEs are the various steps involved in the premarketing authorisation procedures, such as seeking of SA as well as the submission of the MAA itself and subsequent inspections. The above named regulation focuses on these three aspects, and therefore foresees the adoption of specific provisions allowing a reduction or deferral of the usual fees. Looking at the special provisions for SA, the following can be noted: SMEs operating in the pharmaceutical section are often innovative companies, such as those active in the fields of gene or somatic cell therapy, which can notably benefit from pooling the scientific expertise at a community level. This is also in line with the extended emphasis on products intended for the new mandatory centralised procedures, as these emerging therapies are to be expected mainly within the scope of the annex of Regulation (EC) No 726/2004 (see section 3.4.2.2). Furthermore, the scientific evaluation of an MAA is more likely to be favourable in the case of MP which have obtained scientific advice. Therefore, access to the agencies scientific advice for SMEs seeking marketing authorisations should be facilitated through two major provisions [9)]:

- Firstly 90% reduction of fees payable to the EMEA for SA (For PA, like it is usually the case within the scope of an orphan drug application, also no fees will be obtained).
- Secondly additional incentives in terms of a conditional fee exemption should be given to applicants who have requested SA and have taken it effectively into account for the development of their MP. This means as outlined in article 6, that in such cases the fee payable to the agency for the evaluation of the MAA in the centralised procedure shall be due only if the MA has been granted [1),9)].

Further incentives also indirectly linked to SA are:

- Exemption of fees for administrative services: Free advice will be given by the new established SME office on the administrative and procedural steps necessary to comply with the requirements for the centralised procedure, also in workshops and trainings. A user guide especially for SMEs will be developed.
- A system for outsourcing translations of the documents required for the granting of the marketing authorisation [1)].

3.4.2.9 Other SA requests

Due to the NML further procedure types for MAAs are introduced. These are possible sources for other new kinds of SA requests, e.g. on the design of trials to assess safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies as defined in article 14 (11) of Regulation (EC) No 726/2004 or article 10 (1) fourth subparagraph of Directive 2001/83/EC, as well as SA requests on the design of trials to assess safety and efficacy in a new indication for a well established substance in accordance with article 10 (5) of Directive 2001/83/EC as amended and, last but not least, SA requests relating to paediatric development questions, which will come into the focus upon the implementation of the Regulation on Medicinal Products for paediatric use. It should be mentioned that the review of the Paediatric Investigation Plan will not fall under the scope of the provision of SA, although specific questions might be referred to the SAWP [37)].

4. A cooperative between both regions: Parallel Scientific Advice

4.1. General Principles

In a move to better coordinate regulatory approval, the FDA and the EMEA announced a pilot program allowing companies to seek parallel scientific advice (PSA) on testing their products from both agencies simultaneously [33)]. The legal framework for this initiative is laid down in the Confidentiality Arrangements concluded in September 2003 between the EU (the European Commission and the EMEA) and the FDA being an administration of the US Department of Health and Human Services in the context of regulatory co-operation and transparency between the US government and the European Commission. These Confidentiality Arrangements establish a framework for the possible exchange of information on advance drafts of legislation and regulatory guidance documents as well as non-public information related to ensuring the quality, safety and efficacy of medicinal products authorised or under review both in the USA and the EU [11)].

For this cooperation programme, which has been recently reviewed and agreed to be set forth and intensified in March 2006 [44)], a step-wise approach for implementation is envisaged. In the initial phase, the regulatory exchange consists of a) the establishment of an educational programme between the agencies including the possibility of staff exchange and b) the establishment of procedures for the request of documents/information to be exchanged. Under the scope of the latter two types of exchange can be distinguished. Firstly, the exchange on a regularly basis including quarterly routine listings of agreed information on applications, of inspections and guidelines, and secondly, ad-hoc exchange including, among others, the provision of parallel scientific advice based upon the formal pilot program mentioned above, as well as pharmacovigilance related issues [11)].

The goal of the pilot program to provide SA, as outlined in the 'General Principles'-document published in September 2004 to establish it for one year, commencing in January 2005, is to develop a mechanism for EMEA and FDA assessors and sponsors to exchange their views on scientific issues during the development phase of new medicinal products. The 'sponsor' refers to a sponsor of an IND or an applicant submitting an NDA or a Biologic License Application (BLA) in the US or a potential marketing authorisation applicant within the scope of the centralised procedure in the EU.

Increased dialogue between the two agencies and a pharmaceutical company from the beginning of the lifecycle of a new product, a deeper understanding of the bases of scientific advice and the opportunity to optimise product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies could be advantages expected. The first formal parallel scientific advice discussions took place in September 2003 for an orphan medicinal product. As the interest of agencies and pharmaceutical industry in such meetings has increased, the following general principles on how to perform these meetings have been agreed upon:

- The scope of products included in the pilot is limited to better evaluate the costs and values of the program. It should be focussed on important or breakthrough medicinal products (e.g. products for orphan indications and paediatric populations), especially if the product is being designed for indications for which development guidelines do not exist, or, if they exist, EMEA's and FDA's guidelines differ significantly [22)]. According to the new regulation, and according to the scope of the Confidentiality Agreements between the two agencies, in the EU such medicinal products are mainly evaluated or authorised in accordance with the centralised procedure and hence, such MPs are based on New

Molecular Entities (NMEs) in Investigational New Drugs (INDs) and/or NDAs/BLAs that should have been generally accorded 'fast track' status in the US [11),22)]. This scope could be extended upon increasing experience with the program.

- The parallel scientific advice meetings usually should be requested by the applicant but may also be initiated by either EMEA or FDA. Parallel scientific advice meetings should focus on specific questions involving the development of a medicinal product on which the pharmaceutical company desires to have further scientific input from both agencies. Although the applicant is taking part in the main meeting scheduled, the two agencies alone will usually hold a pre-meeting and may hold a follow-up conference in the aftermath of the meeting with each other in order to discuss further the issues posed by the sponsor (joint discussion processes).
- The parallel scientific advice meetings themselves as well as preparation- and debriefing meetings of the agencies should preferably occur via tele- or videoconference. Travelling of agency staff is limited to rare occasions.
- The number of parallel scientific advice meetings is limited to no more than one meeting per month during the pilot phase.
- Due to the given time frame and the limitation in number, parallel scientific advice meetings are to be considered as a single occurrence focused on the specific development issue raised. Therefore, follow-up meetings are not part of the pilot.
- Parallel scientific advice meetings are voluntary. Upon sponsors request, they should be focused on milestone meetings such as the 'end of phase 2' meeting or specific issues or questions. These meetings will be in the lieu of PDUFA meetings (e.g. Pre-IND, EOP 2), but will not be subject to the PDUFA performance goals. Hence, on contrary to the usual single SA-procedures of each agency, the request for parallel scientific advice is no guarantee that such a meeting will be granted, because one or both agencies could decline their participation. In such cases sponsors a free to pursue a regular SA procedure with each agency individually.
- Requests for participation in the pilot should be addressed as follows: one single 'Request for parallel scientific advice' -letter is submitted simultaneously to designated contact points at the EMEA and the FDA in order to allow for the most efficiently evaluation of the request by both agencies and for obtaining documentation as needed. Apart from the usual contents of such a Letter of Intent and the briefing document attached regarding the product characteristics and the issues to be clarified, two important additional items should be included: a) a justification or rationale why a discussion with the assessors of the two agencies in parallel would be beneficial to the development of the product in question and b) an explicit authorisation of the comprehensive exchange between the two agencies of all information relevant to the subject product (especially including trade secret information). Both agencies committed themselves to maintain the confidentiality of all such information.
- Upon agreement to conduct a parallel scientific advice meeting by both agencies, the sponsor receives an acknowledgement of such agreement by E-mail also stating the primary contact person per agency, who will work with the sponsor on final logistics of the meeting including timelines for submission of pre-meeting background information to both agencies, and will in so far have a similar function as an SA co-ordinator. The current

timelines for the two agencies for scientific advice type meetings are not too discordant: a type B meeting in the US is to be scheduled in 60 days from the request; for the EMEA, the advice letter is issued mainly 70 days from the start of the EMEA procedure. Therefore it was decided to schedule the parallel scientific advice meeting with the sponsor usually around day 60, in the margin of the SAWP meeting.

- The SA provided to the sponsor by each agency via this parallel pilot program is independent and processed according to their usual formal schedules (see section 3.4.1 and annex). The advice of each agency may still differ after the joint discussion. Sponsors should neither expect to receive similar recommendations from the two agencies in any case regarding drug development issues in terms of SA nor expect always to receive similar decisions by the two agencies regarding a marketing application made following to a parallel scientific advice meeting, even if the recommendations are implemented. It is rather anticipated that following such PSA meetings it should be clearer to sponsors what the respective requirements and perspectives of the two agencies are with regard to the development programme discussed, and the reasons for any divergence.
- Both agencies remain committed to the domestic meeting processes and review goals and timelines; therefore they will react as flexible as possible in exhibition of PSA, but only as long as their formal domestic performance expectations are not touched. The agencies will assure to maintain records to facilitate an assessment of the benefits and detriments of the pilot.
- Fees will be paid within this programme as if two single usual SA processes at each agency would have been provided [22)].

4.2. Experience and outlook

A company using the parallel SA procedure for a clinical SA procedure reported the following experience:

The process was initiated by submission of the same background documentation to EMEA and FDA in April 2004. The corresponding SAWP meeting took place on July 5, 2004; there was no request of an oral explanation with the sponsor. The meeting of the sponsor and the FDA took place on July 12th, 2004. The final EMEA advice letter was received still in the same month.

The reported key messages indicated the following: There was no joint meeting of the SAWP and the FDA because the SAWP meeting coincided with an FDA holiday. Shortly after this meeting, the SAWP was not prepared to send the joint report to the sponsor. However, they agreed to send it to the FDA prior to the meeting on July 12, 2004. Consistent advice regarding the major issues was achieved in this case, although some differences between both agencies remained.

Another company also experienced different meeting dates with separated participants. More or less, first both agencies met in the joint meeting without the applicant, later on the applicant and the SAWP met in the scope of an oral explanation. The key messages of this report were, that the differing positions were discussed, and then individual and different advice letters were provided. However, in the view of the reporting company, the joint meetings are rather useful to identify the key concerns and improve the understanding of different scientific approaches, so that nonetheless the global development of drugs will be facilitated.

In an general outlook, the companies consider the procedure to be very positive due to the following:

- Involvement of both agencies at the same time and visibility of the different concerns allowed for comprehensive review and very significant advice
- Though resource intensive during the procedure, it saved time and resource compared to separate meetings which would be most probable sequential
- PSA allowed to progress very quickly with the development design based on the advice received from the agencies.

Hence, the following preliminary suggestions for improvement could be concluded: One of the agencies should take a clear leadership, e.g. in chairing the meeting. The applicants should have opportunity to participate at the meetings and to summarise understanding of the agencies guidance to agree upon conclusions, if separate minutes are issued. Responses from both agencies should be synchronised and specifically address sponsor's questions. The issuance of a consolidated position in one set of minutes in writing should be considered by EMEA/FDA. Hence, the scope should be expanded after the pilot programme, so that other than fast track products will become eligible [36)].

5. The situation for SA in the USA

If a company would like to obtain a future NDA/BLA in the US, it is recommended to convene meetings with the FDA. Up to a certain extent an FDA scientific advice process (it is possible to have all kinds of meetings for the same product) could be used as a precursor for further applications in other regions, although scientific advice usually is not legally binding because of the imponderability of new scientific knowledge for a certain indication or safety results in the future. In the case of the FDA, early communication with the FDA during the development process should be established, containing the benefit to learn at a very early stage that the development of a medicinal product might be stopped and will never come to the US market, which saves money and resources.

5.1 Legal basis and scope for SA in the USA

The corresponding law dealing with the legislation, approval and survey of medicinal products and their development in the USA is the Federal Food, Drug and Cosmetic Act (FD&C), originally issued 1938, amended until today by the Prescription Drug User Fee Act (PDUFA) starting 1992 and by the Food and Drug Administration Modernization Act of 1997 (FDAMA). Hence, the permanently updated Code of Federal Regulations (CFR) which could be seen on the same level as EU regulations has also to be taken into account when it comes to registration issues. Both ruling documents the FD&C act as codified or amended and the CFR are legally binding. Additionally, there are dockets and guidance documents containing recommendations which should be followed, comparable to Notice to Applicants and guidelines. Scientific advice is embedded in the US-legislation at least since the PDUFA initiative started (1992). A relevant article from FDAMA regarding special protocol assistance, a specific scientific advice procedure in the USA, is for instance recommending that FDA/Sponsor meetings should be held for the "…purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim" in a new drug

application [19]. This quote reflects the mission of the FDA to act as a partner to the industry in terms of accelerating the development of a drug and always acting in the interest of the public health as well. Hence the mission explains the strategy of the US-Agency to accompany the drug development from the bottom to the top. CFR title 21, subchapter D, Parts 312.47 and 312.82 describe the scope and procedure of scientific advice provided usually in the setting of FDA meetings such as e.g. End-of-Phase 2 (EOP2) meetings "In general, meetings are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extend that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extend that FDAs resources permit. The general principle underlying conduct of such meetings is that there should be free, full and open communication about any scientific or medical question that may arise during the clinical investigation" [6].

5.2 Procedural aspects: Meetings with the FDA

From a procedural point of view, SA in the USA is very often linked to FDA-meetings. The optimal time for such meetings to solicit input is when a particular landmark is reached in the therapeutic development process, which is a similar situation to the EU SA procedures (see section 2.1). Depending on the phase of drug development, there are in general three sorts of milestone meetings, coinciding with the typical landmarks, in which SA is provided by the FDA upon request of the pharmaceutical industry: Pre-IND meetings, EOP2 or End-of-Phase 2 a (EOP2a) meetings and pre-BLA/NDA-meetings.
Compared to the situation in the EU, there is not such a strong difference made on whether the information provided in an FDA meeting is regarding regulatory issues or regarding purely scientific issues. In general, all milestone meetings can consist of both kind of information. However, depending on the meeting sort and type, in some cases the focus is more on the regulatory part than on the scientific part. This should be applicable in the case of the pre-NDA/BLA-meetings, which are comparable to the presubmission meetings when a centralised procedure is planned in the EU. Therefore these meetings will not be described any further within this thesis.
On the other hand, pre-IND meetings and EOP2 meetings (as well as Chemistry and Manufacturing Control (CMC) meetings) consist of typical SA topics, and will therefore be discussed further.

5.2.1 Performance data showing the impact of SA in EOP2 meetings on review cycles

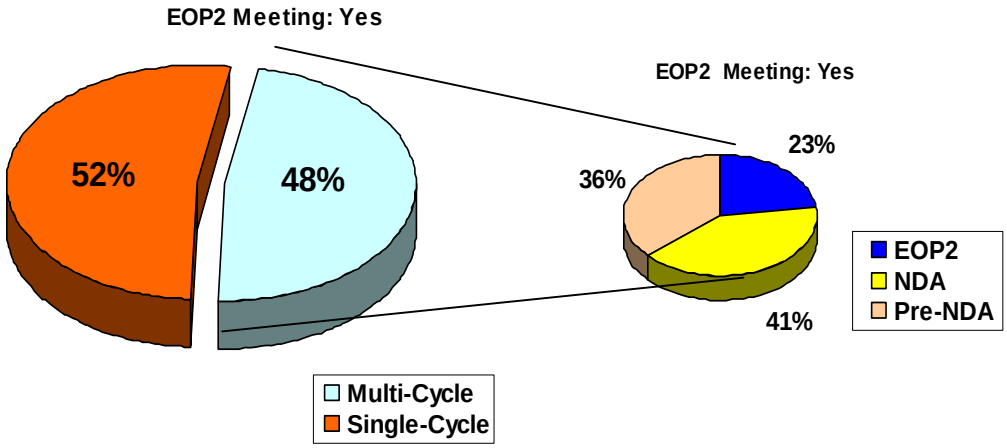
For NMEs submitted as NDAs or BLAs from 2002-2004, the FDA provided a retrospective analysis report on performance data in the scope of PDUFA, in which the following result was provided [4]:
EOP2 meetings or especially the discussion of scientific issues in this context have a positive impact on first-cycle approval rate. Of 46 products with EOP2 meetings, 52% received first-cycle approval (Fig. 4 a), vs. only 29 % for products that did not have such a meeting in general (Fig. 4 c).
However, there seems to be room for improvement: of the multiple-cycle applications that had an EOP2 meeting, 23% of these applications had the critical issue preventing first-cycle approval

identified at this very meeting, indicating an inability to resolve the problems prior to submission. At least, it has been detected, while 36% of the critical issues preventing first-cycle approval were identified at a later meeting, and 41% during the review (Fig. 4 b).

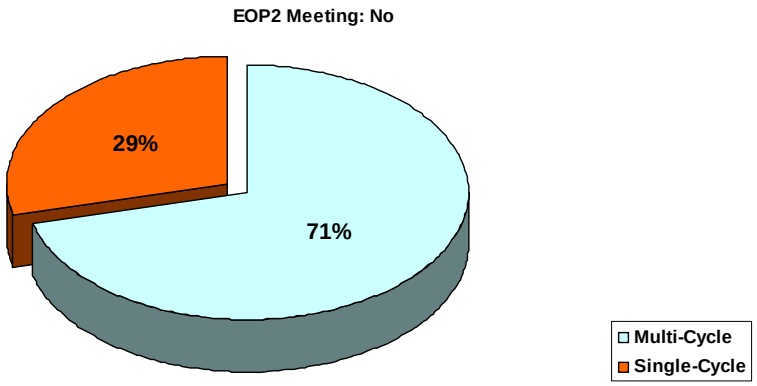
Fig. 4) Impact of EOP2 meetings on product review cycles and timing of issue ID (modified according to [4])

a) Product review cycles with EOP2 meeting (n = 46)

b) Timing of issue ID for multi-cycle review products (n = 22)



c) Product review cycles without meeting: (n = 21)



The results in this report show the positive impact consulting with the FDA before beginning the final phase of human testing can have on first cycle approval rates. Although this is displayed here exemplatory for the EOP2 meetings, and these are one unique aspect of FDA's SA programme, a tendency can be derived in general, that earlier consultation and feedback from FDA in terms of SA on sponsor's development programme is critical to ensure safe and effective study designs. Hence, EOP2 meetings can shorten approval times.

5.2.2 Examples for the most important Milestone meetings

End-of-Phase 2 /End-of-Phase 2 a meetings

Phase II studies may continue for a variety of conditions, but usually when a potential for benefit has been identified, a formal meeting will be scheduled [31)]. The purpose of such a meeting is to determine the safety of proceeding to the clinical development phase III, to evaluate the appropriate development plan and the protocols as well as the adequacy of current studies and plans to assess safety and effectiveness, also in the paediatric environment, and to identify any additional information necessary to support a planned marketing application for the indications under investigation in terms of an NDA[6)]. Hence, all safety issues, scientific issues and/or potential problems should be identified and resolved, if possible, prior to initiation of phase III studies. In this context, CMC plans are also evaluated to ensure that meaningful data will be generated during phase III [25)] .
These meetings are to be considered as most important to the FDA and the company in question, and although this is not given in the law explicitely, they are more or less inevitable for a successful NME developmental programme. The focus of an EOP2 meeting is to design a development plan that would produce the relevant data which form the source from which a use claim may be made. Typical topics could be:

- Determination of the key endpoints
- What is the nature of the anticipated benefit? Is it clinically meaningful?
- Is the benefit measured directly or through a valid surrogate?
- Is the comparator for a controlled study appropriate?
- Note if the data analysis plan is stated in advance and addresses the endpoints and potential benefits
- Is the target patient population representative of people with the disease or condition? [31)]

Pre-Investigational New Drug (IND) meetings

Most products have a development phase prior to use in humans (pre-clinical). Once the use in humans is contemplated, some potential sponsors request a pre-IND meeting to discuss approaches to manufacturing, recommended animal studies and approaches to determine human dosing and preliminary toxicity characteristics to plan Phase I study designs [31)]. The primary purpose of this meeting is to review and reach agreement on the design of the animal studies needed to initiate human testing [6)]. Hence, CMC issues as they relate to the safety of an IND proposed for use in initial clinical studies [25)].
This very early consultation is applicable for all NMEs, but strongly recommended for drugs intended to treat life threatening and severely debilitating illnesses (fast track candidates), which are in the focus of PDUFA.
Although these meetings are arranged prior to filing a formal Investigational New Drug (IND) application to use a product in humans upon FDA approval, which is not comparable to the situation in the EU, where the local HAs and Ethic Committees are responsible for the evaluation and approval of a Clinical Trial Application (CTA), they are listed in this context. This is done due to the fact, that, although the EMEA does not approve CTAs, it encourages pharmaceutical companies to seek SA in the critical phases of drug development. The start of the clinical phase is critical for drug development,

and therefore many scientific issues in context of dosing in humans, toxicity characteristics, the appropriate types of animal studies are same in SA procedures applied for at the EMEA, especially at the timepoint when a drug is in this development phase, as well as in pre-IND meetings. Therefore not all goals of the pre-IND meetings are comparable to SA procedures in the preclinical area, but when focus is made on the pure scientific goals, these are comparable.

In comparison to the items listed in table 1, all these topics described there are applicable in the context of this system of milestone meetings as well. It is possible to have all sorts of meetings once for the same product and it is necessary to establish a very early communication with the FDA in the life-cycle of a product. Hence, Follow-up meetings may be warranted in the event that new issues arise during phase III studies that affect the drug development programme. Annex 2 shows an overview about meeting type classification (A, B or C-meetings) and pertinent time schedules.
While these milestone meetings described above are the most common forum to obtain Scientific advice and also to clarify regulatory issues, the context for other meetings also offered by the FDA with a stronger focus on scientific questions rather than regulatory issues is given within the scope of special products for which the PDUFA initiative was created.

5.3 Prescription Drug User Fee Act (PDUFA)

In 1992, the US congress passed the Prescription Drug User Fee act. As this initiative contained a sunset provision for automatic expiration in 1997, it was reauthorised by the FDAMA 1997 and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. The special concept of PDUFA was the authorisation of the FDA to collect fees from companies that produce certain human drug and biological products. Any time a company wants the FDA to approve a new medicinal product in the sense of a new molecular entity (NME) or biotechnology derived MP prior to marketing, it must submit an application along with fee to support the review process. In addition, companies pay annual fees. Previously, taxpayers alone paid for product reviews through budgets provided by the Congress [43)].

5.3.1 PDUFA products as source for SA requests

The products PDUFA is focussing on are MPs which are new on the US market. This means: New Drug applications (NDA), especially for a new molecular entity (NME) and Biologic applications (BLA) are the products to which the US public should receive earlier access. Therefore, for standard and priority original NMEs in each submission cohort there will be the same performance goals as for all of the original NDAs (including NMEs) in each submission cohort but shall be reported separately. For biological products, all original BLAs will be considered to be NMEs. Products intended to treat life threatening and severely debilitating illnesses (according to subpart E or subpart H of 21 CFR 312 and 21 U.S.C 508) are another focus and are designated to be candidates for fast track approval and the new project of the continuous marketing application [43)].

In so far, these products in the focus of PDUFA are comparable to the products listed in the annex I of the Regulation (EC) No 726/2004 in context with its article 3 which are mandatory for the centralised procedure (see section 3.4.2.2).

These are also the areas for which scientific advice is mainly necessary and requested.

How do the PDUFA products and goals have impact on SA ?

In the new program, industry provides the funding in exchange for FDA agreement to meet drug review performance gaols, which emphasises timelines. The main advantage is that the FDA is now enabled to accelerate its drug evaluation process without compromising review quality-and vice versa, the industry has the right to insist on the fulfilment of the PDUFA goals. This initiative could be interpreted as a ‘contract’ between the agency and the industry, however, undoubtedly the agency is still acting independently, they are only bound to their self committed goals.

The process to collect additional resources is based on a three step program, each part of which is planned over a five year period. The PDUFA I five year plan mainly consisted of the systematic collection of the industrial fees. FDA primarily spent the new resources to hire additional personnel to review human drug applications and to update the IT technology and infrastructure so that review times will be decreased. During PDUFA II and III periods, new resources were collected and invested, also to accomplish increasingly challenging major performance goals in terms shortened drug development times. In this respect, sound financial footing and an enhancement of interactions between agency and industry during drug development and review is in the focus in order to make safe and effective drugs available to the public more quickly.

Table 3 gives an overview on, among others, the most relevant PDUFA performance goals focussing on SA related topics (modified according to [43)]):

Tab.3) PDUFA performance goals, including goals focussing on SA related topics *(italics)*

PDUFA I, II, III	PDUFA I	PDUFA II	PDUFA III
Industry paid a fee per	FDA provides	FDA provides	FDA provides
Submission of new drug application (NDA/BLA) Manufacturing establishment Product annually	**NDA/BLA Priority reviews** (incl. efficacy supplements) **and** **NDA/BLA resubmission reviews** (90% in 6 mon) **NDA/BLA Standard reviews** (incl. efficacy supplements) (90% in 12 mon) **Reviews of manufacturing supplements** (90% in 6 mon)	***1) Special protocol assessment (SA procedure)***: 90% in 45 days ***2) Formal meetings (for SA)*** schedule 90% within 14 days ***3) Formal meetings (for SA) Convene*** 90% within 30/69/75 days (depending on meeting category) ***4) provide industry with meeting minutes*** (90% within 30 days) **5) Clinical hold response:** 90% in 30 days **6) NDA/BLA Priority reviews** incl. efficacy supplements (90% in 6 mon) **7) NDA/BLA resubmission reviews** (Class I: 90% in 2 mon; Class II 90% in 6 mon **8) NDA/BLA Standard reviews** (incl. efficacy supplements) (90% in 10 mon) **9) Reviews of manufacturing supplements** (90% in 6 mon and in 4 mon if needed prior approval)	**1) - 9) same as PDUFA II goals** plus: ***10) Continuous Marketing application***: Pilot 1: discipline review letters for presubmitted reviewable units of NDAs/BLAs and ***Pilot 2: Frequent scientific Feedback and interaction during drug development*** ***11) Independent Consultants for biotechnology*** clinical trial protocols **12) Pre and peri-NDA/BLA Risk management Plan Activities** **13) First cycle review performance goals**: incl. Notification of issues identified during filing review earlier than within 60 days Good review management principles guidance **14) Improvement of FDA performance management**

Italics: these goals refer to scientific advice procedures

As the PDUFA initiative is providing an extended procedural frame, there are certain product classes or groups for which scientific advice is requested more frequently than for others, irrespectively whether a license is planned in the EU or in the USA. Three of them should be now further investigated exemplatory, and in this context especially the three scientific advice related PDUFA goals (PDUFA goal ***1), 10), 11)*** in italics in table 3) should be described.

5.3.2 Special Protocol Assessment

According to table 3, the SPA procedure is listed as PDUFA goal ***1)*** for SA. Potential registration studies may be reviewed as special protocol assessment (SPA) [31)]. The exceptional provision of this

framework for SA on a specific clinical trial design is, that, if the FDA agrees to the protocol, a commitment exists to accept the study results for filing. In so far, SA in the setting of SPA is binding for both sides, and this is the only existing SA procedure in USA and EU in which binding advice is given.
Upon specific request to clearly label the submission of an SPA, the FDA will evaluate certain protocols and issues to assess whether the design is adequate to meet scientific requirements [43)]. Specific questions about the protocol design must accompany the submission or else it is not considered a protocol for Special Assessment [31)]. Such questions could be e.g. whether the dose range in a carcinogenicity study is adequate, considering the intended clinical dose [43)]. The FDA review time frame is 45 days compared to the standard protocol review of 30 days [31)], as outlined in PDUFA (see section 5.3).
The review usually is performed internally at the FDA by the appropriate disciplines and also ad hoc by external consultants. Once completed, the FDA will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the agency does not agree that the protocol design, execution plans and data analyses are adequate to achieve the goal of the sponsor, the reasons for disagreement will be explained.
For this programme, protocols on carcinogenicity, stability and phase III protocols for clinical trials forming the primary basis of an efficacy claim are qualified. Other protocols may be eligible in the context of investigational drugs with fast track status.

If a protocol is reviewed under the process outlined above and a written agreement with the agency is reached on design, execution and analyses and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, the agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the protocols reviewed under SPA the agency will not later alter its perspective on the issues of design, execution or analyses unless unexpected public health concerns occur [43)].
However, the sponsor may also not deviate from the written agreement in any respect.
It is important to mention that the FDA is not making a commitment for later approval, which will depend on the quality of all data submitted [31)].

5.3.3 SA in the setting of biotechnology procedures (independent consultants)

This SA procedure refers to PDUFA goal ***11)*** in table 3. As far as scientific advice is concerned, the biotechnology setting is also in the USA a hot spot for SA requests. One of the reasons is possibly lying in the fact, that the definition for biological product is quite short and general: “Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment of cure of diseases or injuries of man (21 CFR 600 subpart A, section 600.3). This means in regulatory practice, that the following kinds of MPs are considered as a biological product, and therefore any new application for such a product is to be considered as a BLA

- Monoclonal antibodies (mABs)
- Growth factors, cytokines, and mAB intended to mobilise, stimulate, decrease or otherwise alter the production of haematopoietic cells in vivo

- Proteins intended for therapeutic use, including enzymes (thrombolytics) and other novel proteins derived from plants, animals or microorganisms, and recombinant versions of these products.
- Immunomodulators

These categories are much more on the side of biotechnology and emerging therapies. Some of them are evaluated by the Centre of Drug Evaluation and Research (CDER). Hence, they are in a certain respect comparable to the products defined in the Annex of the Regulation (EC) No 726/2004 in the EU legislative, although their manufacturing process is not clearly specified to exclusively belong to a certain category.

- Cellular products, including products composed of human, bacterial or animal cells (e.g. pancreatic islet cells)
- Blood, blood components, plasma derived products (eg. albumin, immunoglobulins, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives, as well as blood substitutes, plasma volume expanders and erythrocyte reagents.
- Vaccines, antitoxins
- Allergenic extracts for the diagnosis and treatment of allergic diseases

These belong much more to the conventional source of biologics, being reviewed and scientifically evaluated by the Centre of Biologics Evaluation and Research (CBER). In a comparison to the EU, for these products in most cases the free eligibility of the approval procedure (centralised, decentralised or national) applies (with some exceptions, e.g. recombinant and transgenic plasma derivatives).

When it comes to scientific advice in this context, in many cases the first four categories will be in the focus, especially when biotechnology products such as rDNA derived products or products in the setting of gene therapy or cell therapy should be licensed. SA, usually provided in the context of a meeting, will be quite often obtained in a multidisciplinary meeting, especially in the IND stage, involving Agency personnel in clinical, pharmacology, pharmacokinetics, pharmacogenomics, chemistry, microbiology, molecular biology, statistics, and other disciplines. Of particular importance are clinical and CMC related issues that affect other disciplines. Appropriate technical experts (chemists, microbiologists, molecular biologists) representing the company and the agency should be present during all discussions of CMC related issues. Meetings should focus primarily on addressing the specific question listed in the information package. The agency may also wish to discuss relevant questions on safety issues, e.g. biosafety or viral safety, or various scientific and /or regulatory aspects of the drug. These can arise from agency guidance documents, the reviewing divisions experience, the manufacturing industry's experience, or scientific literature [25)].

Typical meeting issues for biotechnology BLAs from the first four categories (see above) could be the following:

EOP2 meetings:

- Environmental impact considerations, if pertinent
- Adequacy of physicochemical and biological characterisation (e.g. peptide map, amino acid sequence, glycosylation sites and structures, other posttranslational modifications)

- Appropriateness of planned bioassays (specifity, precision)
- Adequacy of cell bank characterisation
- Removal of product-and process-related impurities (e.g. misfolded proteins, aggregates, host cell proteins, nucleic acid)
- Bioactivity of product related substances and product related impurities relative to desired products [25)]
- Discussion of the ongoing clinical projects in relationship to phase III [23)]

As given in table 3, PDUFA includes the possibility to involve independent consultants as additional external experts for biotechnology clinical trial protocols, as discussed in the context of EOP2 meetings.
During the development period for a biotechnology product, a company may request that FDA engage an independent expert consultant, selected by the FDA, to participate in the agency's review of the protocol for the clinical studies that are expected to serve as the primary basis for a claim. The product in question must be a biotechnology product (e.g. DNA plasmid products, synthetic peptides of fewer than 40 amino acids, mABs for in vivo use, and recombinant DNA-derived products) that represents a significant advance in the treatment, diagnosis or prevention of a disease or condition, or have the potential to address an unmet medical need. Hence, the product may not have been the subject of a previously granted request under this program.
To take part into the program, the company must submit a written request for the use of an independent expert consultant, describing the reasons why the consultant should be involved (e.g. as a result of preliminary discussions with the agency the applicant expects substantial disagreement over the proposed protocol). The request should formally be designated as a request for appointment of Expert consultant and submitted along with a formal meeting request, typically during the end of phase II meeting or a Type A meeting. A list of recommended consultant should be attached for consideration by the agency. The selected consultant will either be a special government employee, or will be retained by FDA under contract. The consultants role will be advisory to the agency, the FDA will remain responsible for making scientific and regulatory decisions regarding the clinical protocol in question. It is in the agency's discretion to accept or deny the request for the independent consultant. In case of a rejection, a written rationale will be provided to the applicant within 14 days of receipt.
In case of acceptance, due to the time required to select the consultant for potential conflicts of interest and to allow the consultant sufficient time to review the scientific issues involved, the PDUFA performance goal for scheduling the formal meeting may be extended for additional 60 days. During 2006, a study should be conducted to evaluate the costs and benefits of this program for both the applicant and the agency [43)]. This FDA-offer has no pendant in the EU.

5.3.3.1 GT-products: A challenging example for the role of SA for innovative drugs

As with the EU situation, there is also an ongoing controversy scientific dialogue in terms of Gene therapy products. The reasons are mainly lying in the developmental history of this emerging therapeutic field. As the very first steps starting 1990 with the GT of the SCID disease in context of a clinical research project at the National Institute of Health (NIH) were promising, proceeding experience revealed, that the efficacy results were not of that extent as the scientific theory would have

made expectable. Hence, the upcoming safety issues led to a flurry of activity to minimise the chance of future accidental deaths after one patient suffering from ornithine transcarboxylase deficiency (OTCD) died upon receipt of an experimental GT treatment in a clinical trial in 1999, most probable by an excessive immunological reaction on the adenovirus carrier [49)]. Further investigation revealed, that in several GT trials the researchers did not follow the rules of proper serious adverse event (SAE) reporting. Among other actions such as the clinical hold of several GT clinical trials in which the deviations of protocol and GCP-requirement occurred, extensive FDA inspections and the implementation of the Gene Therapy Clinical Trial Monitoring Plan, the US Congress received the proposal for a new legislation to authorise civil monetary penalties for researchers and institutions found to be in violation of regulations governing human clinical trials. In January 2005 this so called Gelsinger Case was clarified by a final settlement, containing fines for the scientists but also that the researchers do not admit any responsibility for the patient's death [13),49)].

The reason for the sometimes lean efficacy and the safety issues in context with GT products is lying in molecular biology itself. Apart from the challenge to transfer new genes into as many as possible target cells, the success of the treatment depends on the fact that a transferred gene, once inserted, is becoming active in terms of expression. But the genome developed different mechanisms of gene expression control during the evolution to protect the coding sequences of an organism, so that the existing genes stay active and the possibility to be destroyed by enabling mutations is reduced. Especially the expression of foreign or transferred genes is essentially suppressed, as this is a very old evolutionary concept to cope with transferred DNA inserted into the genome 'naturally', e.g. by a viral infection. Although techniques have improved, today's scientists still face these challenges. As far as the safety issues are concerned, major difficulties include shortcomings in many of the current gene transfer vectors and still most often an inadequate understanding of the biological interactions of these vectors with the host [49)]. How critical the viral safety issues are, especially over time, even in the setting of research projects or INDs approved by agencies and official institutions like e.g. the Recombinant DNA Advisory Committee RAC and the FDA, not only the drastic Gelsinger case shows. Another approved trial in France for the X-linked severe combined immunodeficiency (X-SCID) initially led to enthusiastic results so that the French scientists reported convincing evidence that they successfully treated four babies at the Necker children's hospital in Paris with gene therapy, leading to a near complete recovery of their immune systems in April 2000 [49)]. But during the course of the French trial, although 17 children have been successfully treated for X-SCID using GT, two patients developed leukaemia (in one case fatal) in late 2002 after a vector inserted near an oncogene. These two leukaemia cases occurred in infants treated at 3 months of age or less, leading to speculation that cells with the oncogene insertion proliferate more readily in very young children, while older children would be protected by their more mature cellular development. But in January 2005, it was reported that a third child from the trial developed leukaemia, which was treated at 9 months, and this is suggesting that older children may also be at risk. And this risk can occur with years of delay [13)].
This ups and downs of the GT field over 15 years causes different and reluctant views on this therapeutic area by agencies and official research and governmental institutions. Although it is still promising, the risk management in terms of viral safety does not seem to allow for an easy handling.
Today the following general risk factors are identified for the risk of delayed adverse events:

Firstly, persistence of the viral vector in association with latency could lead to continued expression of the gene or delayed effects of viral infection. Secondly, integration of genetic material into the host genome raises the risk of malignant transformation. Thirdly, prolonged expression of the transgene as well as altered expressions of the host genes may both be associated with long-term risks resulting from unregulated cell growth, malignant transformation, autoimmune-like reaction to self antigens and unpredictable adverse events [24)].

While the EU in general is still interested in GT development and its regulatory control, the USA and France are keeping it down at the moment, although there is no movement to forbid the GT research projects as such. Since August 2005, there is a draft FDA guidance available dealing with recommendations for the observation for delayed adverse events in GT clinical trials, but it is still not finalised, while ongoing discussions at meetings and conferences, especially by the Biological Response Modifiers Advisory Committee (BRMAC), the American Society of Gene Therapy (ASGT), the CBER and industrial organisations show that there is a long way between scientific dialogue and legal decision on a certain issue. To date, FDA has not yet approved any human gene therapy medicinal product for marketing [5),24)].

It is clear that in this field of viral safety and the finding of appropriate preclinical testings thinking of difficulties to find target animal species in a setting where especially the human immune system is to respond, scientific advice will be sought and the options given by PDUFA will be helpful. The draft guidance clearly indicates that the industry is encouraged to discuss the study designs with the Agency before starting the trial because there are many variables that will affect the outcome ad interpretation of the in vivo biodistribution of each vector type [24)].

5.3.4 Frequent scientific interaction in the scope of Continuous Marketing Application

The PDUFA goal ***10)*** refers to SA in the context of the Continuous Marketing Application (CMA) (table 3). To test whether providing early review of selected applications and additional feedback and advice to companies during drug development for selected products can further shorten drug development and review times, FDA agreed to conduct two pilot programmes. The pilot 1 refers to a regulatory procedure for the submission of NDAs/BLAs in portions, the ‘reviewable units’. The pilot 2 (see table 3) consist of additional opportunities for SA: Frequent scientific feedback and interactions during drug development: The pilot applies to drugs and biologics that have been designated to be fast track drugs or biologics pursuant to section 112 of FDAMA, that are intended to treat serious and /or life-threatening diseases, and that have been subject to an end-of-phase 1 meeting. The pilot programme has been limited to one fast track product in each CDER and CBER review division over its course [43)]. A Fast track designation is intended for the combination of a product and a claim that addresses an unmet medical need and facilitates close and early communication between a sponsor and the FDA [31)]. In this respect orphan drugs under development could also fall within the scope of this pilot.

For drugs and biologics that meet these criteria, FDA may enter into an agreement with the sponsor to initiate a formal programme of frequent scientific feedback and interactions regarding the drug development programme. The feedback and interactions may take the form of regular meetings between the division and the sponsor at appropriate points during the development process, written feedback from the division following review of the sponsors drug development plan, of important new protocols and of study summaries or complete study reports submitted by the sponsor.

Decisions regarding which study reports would be reviewed as summaries and which ones would be reviewed as complete reports are to be made in advance upon discussions between the division and the sponsor of the proposed drug development programme. In making these decision, the review division will consider the importance of the study to the drug development, the nature of the study and the potential value of limited versus more thorough division review. The pilot started in 2004 and will continue through 2007. A preliminary evaluation on the outcome of this programme will be generated by an external consultant during 2006.

5.4 Biosimilars: An example for discussions in legal classifications of special therapeutic proteins and the impact on access to SA

For biosimilars, or follow-on proteins, the situation in the USA is not yet legally finalised. According to an FDA draft guidance in 1999, the § 505(b) (2) of the FD &C Act could be used to get approval of therapeutic protein products an sponsors could make changes to a reference listed drug if the change were supported by clinical data. This means , that biosimilars in the USA are considered to be treated and approved like generic drugs, although, as shown in section 3.4.2.2.2, it is clear that from a scientific view they are rather ‘similar to’ than ‘the same as’ a reference listed drug.
Therefore innovator companies filed several citizen petitions challenging the use of the legal basis for a generic drug also for follow-on proteins. The rationale was that a biologic could not be approved without a full complement of non-clinical and clinical data. The agency responded that its legal interpretation on 505(b) (2) applications was long-standing and it would resolve related scientific issues in the future.
In late 2004 and 2005, follow-on proteins garnered significant attention in the US. However, although several initiatives started, until now no guidance documents on different scientific issues for follow-on proteins are finalised. Moreover, since July 2003 a generic application for Omnitrope has been under review at the FDA without any results. A lawsuit initiated by the applicant did not yet result in a product approval in the USA, while things moved forward in the EU [32)].
As a consequence, this means that, although FDA allows for generic applications for biosimilars, they are not processed to approval as appropriate due to the difficulties in classification as described above. In the context of SA, this means, that none of the additional meetings as described in the PDUFA setting such as SPA, or SA in the setting of biotechnology procedures including independent consultants can be used for applications for biosimilars, because they are treated legally like ‘normal’ generics. As a result, EU regulators have taken the lead in attempting to define a policy of legal framework for biosimilars, including useful opportunities for SA. The EU-opinion and decision on Omnitrope could, however, give the FDA scientific cover for an approval of the pending application as well and may stimulate the efforts to renew and adapt appropriate legislation, which may also take into account more opportunities for SA in the future [32)].

6. Discussion and outlook

The introduction of the new EU medicines legislation provides a grater mandate to give SA particularly regarding the development of new therapies with direct responsibility for the Executive director to establish effective structures for the provision of SA. The streamlined procedure allows

finalisation within maximally 70 days or earlier, compared to the 100 days procedure in the former setting. Moreover, the introduction of a formalised peer review maximises the clarity and ensures consistency in the provision of SA. More interaction and communication is included with stakeholders, through the extended scope and increased use of follow- up procedures, publication of standard Q&A documents and further measures to develop and improve existing guidelines, especially for rapidly evolving topics [42)].
Compared to the former situation, the new framework for SA provides more transparency in procedures and involvement of external experts and non regulatory groups, and, upon establishing the SAWP, the responsibilities are made clear. This allows for a decision making on a broader and more complex scientific basis. Risk management activities are now included, moving the scientific competence of the EMEA forward to a risk management oriented way of action rather than to focus on hazard prevention [3)]. Moreover, new measures such as incentives to SMEs, additional specific expertise and new competence are put in place to follow the extended scope as defined by the new regulation [42)].

The parallel SA procedure includes a mechanism for the EMEA, FDA and companies to exchange views on scientific issues during the development phase of new breakthrough drugs. Although there is not always given identical advice by both agencies, all participants are trying to find the most pragmatic approach, and it helps the sponsor to know the scientific view of both agencies at the same time and hence to follow the advice including the higher requirements for the development of the appropriate clinical programme. This means for the sponsor to have a clear master plan in place, including enough alternative solutions to reach for a good compromise[36)]. Experience shows, that industry and agencies have appreciated the good results, but there is still room for improvement - however, this initiative has been extended and the next steps have been outlined lately by the EMEA for a programme on processing requests for parallel Joint FDA-EMEA voluntary genomic data submission (VGDS) briefing meetings to provide SA on the collection and interpretation of pharmacogenomic data, which are not yet a mandatory part of the CTD for approval, but are of paramount scientific interest [30)].

In an overview, the consequences of the NML for SA mainly consist of the extension of its scope, and of an accelerated procedure. As shown in section 3.2, in many cases SA had a positive impact on approval, when it has been implemented, in so far an extended scope and an accelerated SA procedure can drive approval procedures to a certain extent.
Compared to the situation of SA in the US, the following main differences have been demonstrated:

- SA in the USA is much more linked to several sorts of meetings with the FDA. While the EU mentality is more process oriented, considering the idea of follow–up procedures, the interactions between the sponsors and the FDA are highly concentrated on the clarification of the issues in question at once in a direct discussion. Although preparation meetings are held for the review division internally, everything that can not be identified or clarified in a special sponsor meeting scheduled will remain a potential reason to hinder the later approval process (see section 5.2.1).
- SA in the USA is not so clearly separated from regulatory issues as SA in the EU. While all SA guidelines point out that regulatory issues are not within the scope of SA

procedures, US guidance includes regulatory issues in milestone meetings, while only the extend to which scientific issues are dominating a certain meeting depends on the sort of the meeting (see section 5.2).

- The more SA issues a meeting sort contains in the US, the more it is restricted to innovative medicines such as NMEs, fast track drugs and emerging therapy drugs (e.g. GT products). Special sorts of meetings provided in the context of PDUFA products, such as SPA or SA in the scope of the pilot 2 for CMA are only applicable for innovative breakthrough products.
- There is a different view of both agencies upon the 'value' of certain kinds of MPs, which was shown for two examples: A) The EU has made a clear difference between biosimilarity and a 'classic' generic medicinal product by applying a definition of the latter within the new NML. Hence, while Biosimilars in the EU are to be licensed via the centralised procedure if they are based on biotechnology and therefore can be a subject to all EU SA procedures, follow-on proteins in the USA are still legally considered as 'generics' and therefore not being innovative on a first view. Although movement is made to clarify the differences between 'similar' and 'the same as', there is still no solution provided in the US-legislation. Hence, many possible SA meetings with the FDA do not apply for follow-on proteins, while in the EU all guidelines on biosimilarity recommend additional SA to discuss the clinical studies as appropriate. B) GT products are a focus in the EU procedures, and specific guidance has been developed to cope with their challenges, although not all MS are in favour of these MPs. In the US, due to the controversy lying in its disappointing developmental history an the public distrust, there is a reluctant approach to this issue demonstrated by the fact that a draft guideline for GT products has been created but not yet been finalised for one year. However, GT products can be the subject to PSA procedures and the future will show in how far the cooperation of both agencies will help to establish a progress in this respect in the US.
- Binding character of SPA: The USA, on the other hand, has established the only SA procedure known in both regions to have a binding character: The SPA.
- Innovative Products within the scope of PDUFA: Special SA procedures as the pilot 2 for CMA can not be compared to a single similar procedure in the EU. However, as this is created as a close and early cooperative with the FDA for innovative products, most probably similar scientific questions will be the subject of the scope of this pilot 2 in the USA and also in an EMEA SA/PA procedure, for instance within an orphan drug development, an development under exceptional circumstances or an innovative product by an SME, where close consultation with the CHMP and the SAWP is recommended and partially supported with incentives.
- The USA already has implemented a paediatric rule, while this will become available in the EU, so that the scientific advice procedures for paediatric developmental issues in the EU will increase upon implementation of the new paediatric regulation.
- Companies in the EU can take advantage out of the provision of SA by the local HAs. Due to its federal character the EMEA has a wide ranging network with access to a variety of internal and external experts from the MS with different cultural background, giving their precious input in workshops an think-tank meetings, which is a different situation to the centralised character of he FDA and its divisions. However, in the USA there already

exists a much tighter network of exchange between universities, research and academia with high quality expertise and the US agency FDA via governmental institutions such as the NIH, as the example described in section 5.3.3.1 may show.

For both regions scientific advice is the earliest source for upcoming scientific issues to be clarified generally in new guidance documents, as shown in the case of GTs und biosimilars.

To conclude a general outlook, each initiative to improve SA procedures in any of the regions will lead to better, more efficient and faster development of safe and effective medicines. It will moreover help to put each decision making process on a broader scientific bases, making it more profound and reliable. SA will gain an increasing impact on the success of the future approval procedures. It will continuously identify the need for new guidance, reflecting the increased impact of academia knowledge on regulatory implementation by closer involvement. The closer cooperation between regions will lead to an earlier and better exchange of scientific views and to more integrated advices.

7. Summary

The EMEA has provided SA to sponsors since 1996. The introduction of the new EU medicines legislation provides a grater mandate to give SA particularly regarding the development of new therapies with direct and clearly distributed responsibilities and effective structures for the provision of SA by the SAWP and its expert's network.

The new framework for SA allows for earlier and greater involvement of internal and external assessors. Therefore it is made possible to streamline the procedure to allow finalisation within maximally 70 days or earlier. Moreover the involvement of the CHMP will be consolidated by formalising of a peer review to ensure consistency in the provision of SA. More interaction and communication is included with stakeholders, through the extended scope and increased use of follow-up procedures, publication of standard Q&A documents and further measures to develop and improve existing guidelines, especially for rapidly evolving topics [42)]. Moreover, new measures such as incentives to SMEs, additional specific expertise and new competence are put in place to follow the extended scope as defined by the new regulation [42)]. In the context of co-operation with other non EU authorities EMEA and FDA have agreed upon a programme for companies to obtain parallel or joint SA from the 2 agencies. The parallel SA procedure includes a mechanism for the EMEA, FDA and companies to exchange views on scientific issues during the development phase of new breakthrough drugs, with a positive adoption from the industry as well as from the agencies.

SA in the USA is linked to different sorts of milestone meetings with the FDA, which are displayed in sections 5.2 and 5.3. The PDUFA initiative provides a framework for specific SA procedures (as outlined in table 3) such as SPA, SA in the setting of biotechnology procedures including independent consultants and the frequent scientific interaction in the scope of CMA (pilot 2), which are restricted to PDUFA products. For both regions scientific advice is the earliest source for upcoming scientific issues to be clarified in guidance documents with the examples for GT products and biosimilars or follow-on proteins. The same examples also show on the other hand that a different value and political and historical issues lead to different legal classification of certain types of biotechnology drugs, resulting in different possibilities for these drugs to be subject of SA procedures. In the discussion a comparison is provided, listing the main differences for SA in both regions (see section 6.).

8. References

1) Authorisation of medicines: Commission makes life easier for SMEs, IP/05/1618, 15 December 2005, available at: http://www.emea.eu.int/

2) Baader E. (2005) International Registration - European Union: Scientific Advice, presentation, presented at the Course for Master of Drug Regulatory Affairs (MDRA) 06, Module 9: International Registration, Bonn, January 2005

3) Ballantine B. (2005): Better regulation - Enhancing the role of Science in the decision making of the EU (working paper 17), published by: The European Policy Centre (EPC), Belgium, available at: http://www.theepc.be/, accessed: 13.3.2006

4) Booz/Allen/Hamilton (eds) (2006) Independent Evaluation of FDA's First Cycle Review Performance – Retrospective Analysis Final Report (Prescription Drug User Fee Act III – Initiatives & Evaluations), published by the FDA, available at:
http://www.accessdata.fda.gov/scripts/oc/ohrms/dailylist.cfm?yr=2006&mn=2&dy=7, accessed:5.4.06

5) Cellular and Gene Therapy, published by: FDA (CBER), updated online April 2006, available at: http://www.fda.gov/CBER/gene.htm, accessed: 2.5.2006

6) Code of Federal Regulations (CFR), Title 21: Food and Drugs, Chapter I: Food and Drug Administration Department of Health and Human Services, Subchapter D: Drugs for Human Use, Part 312: Investigational New Drug Application (IND), Sections 312.47 and 312.82, available at: http://www.accessdata.fda.gov/, accessed: 12.4.2006

7) Commission Recommendation of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (2003/361/EC), Official Journal L 124, 20/5/2003 p. 36-38

8) Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority', Official Journal L 103, 28/4/2000 p. 5 - 8

9) Commission Regulation (EC) No. 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises, Official Journal L 329, 16/12/2005 p. 4-7

10) Commission Regulation (EC) No. 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, Official Journal L 92, 30/3/2006 p. 6 - 9

11) Confidentiality arrangements concluded between the EU (EC and EMEA) and the US FDA/DHHS-
Implementation Plan for Medicinal Products for Human Use, 16 September 2004, published by: EMEA, available at: http://www.emea.eu.int/, accessed on: 13.3.2006

12) Council Regulation (EEC) No 2309/93 of 22 July 1993
laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, Official Journal L 314, 24/8/1993 p. 1 (outdated)

13) Couzin J., Kaiser J. (2005) Gene Therapy - As Gelsinger Case Ends, Gene Therapy Suffers Another Blow; Science, Vol. 307 no. 5712, p. 1028, 18.2.2005

14) Decentralised Procedure Member States' Standard Operating Procedure, October 2005, CMD(h), published on: MRFG Guidance Documents in the Mutual Recognition Procedure and Decentralised Procedure, http://heads.medagencies.org/

15) Dejas-Eckertz P. and Schäffner G. (2005) Beratung im Vorfeld klinischer Prüfungen durch die Bundesoberbehörde und Scientific Advice bei der EMEA, Bundesgesundheitsbl-Gesundheitforsch-Gesundheitsschutz 4 2005. 48: p. 423-328

16) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use *(Official Journal L 311, 28/11/2001 p. 67 - 128)* as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC. The consolidated version is published in Official Journal L 311, 28/11/2004 p. 67 – 128; further amended (annex) by Commission Directive 2003/63/EC of 25 June 2003, available at Official Journal L 159, 27/6/2003 p. 46 - 94

17) EMEA Guidance for companies requesting Protocol Assistance regarding Scientific Issues, EMEA/H/238/02 Rev 1, June 2003, available at: http://www.emea.eu.int/

18) EMEA Guidance for companies requesting Scientific Advice (SA) and Protocol Assistance (PA), EMEA/H/4260/01 Rev 3, December 2005, available at: http://www.emea.eu.int/, current version accessed: 1.6.2006

19) Federal Food, Drug and Cosmetic Act as codified (FD&C Act of 1938), amended by the FDA Modernisation Act (FDAMA of 1997), Chapter 5, Subchapter A: Drugs and Devices, section 505 (b) (4) (B) (in FDAMA under section 119 'Content and review of applications' (a)), available at: http://www.fda.gov/, accessed: 12.4.2006

20) Framework on the Interaction Between the EMEA and Patients' and Consumers' Organisations, Doc. Ref. EMEA/354515/2005-Final, February 2006, available at: http://www.emea.eu.int/

21) Function and Tasks for CMD(h), February 2006, available at: CMD(h), Activities, http://heads.medagencies.org/

22) General Principles-EMEA-FDA parallel scientific advice meetings, Pilot Program, September 17, 2004; available at: http://www.emea.eu.int/

23) Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products, February 2000, published by: FDA (CDER, CBER), available at: http://www.fda.gov/

24) Guidance for Industry: Gene Therapy Clinical Trials - Observing Participants for Delayed Adverse Events; Draft Guidance, August 2005, published by: FDA (CBER), available at: http://www.fda.gov/

25) Guidance for Industry: IND Meetings for Human Drugs and Biologics - Chemistry, Manufacturing and Controls Information, May 2001, CMC, published by: FDA (CDER and CBER), available at: http://www.fda.gov/

26) Guideline on Comparability of Medicinal Products containing Biotechnology-Derived Proteins as Active Substance – Non-Clinical and Clinical Issues, EMEA/CPMP/3097/02/Final, December 2003, available at: http://www.emea.eu.int/

27) Guideline on Procedural Aspects Regarding a CHMP Scientific Opinion in the Context of Cooperation with the World Health Organisation (WHO) for the Evaluation of Medicinal Products Intended Exclusively for Markets Outside the Community, EMEA/CHMP/5579/04 Rev.1, November 2005, available at: http://www.emea.eu.int/

28) Guideline on procedures for the granting of a Marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004, EMEA/357981/2005, 15 December 2005, available at: http://www.emea.eu.int/

29) Guideline on Similar Biological Medicinal Products for Human Use, CHMP/437/04, November 2004, available at: http://www.emea.eu.int/

30) Guiding Principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement, published by EMEA online on 31 May 2006, available at: http://www.emea.eu.int/pdfs/general/direct/pr/FDAEMEA.pdf

31) Hirschfeld S., Obtaining scientific and Regulatory advice from the FDA and Additional Special Topics, presentation slides, accessed by e-mail from Dr. E. Baader on 24.5.2006

32) Hogan & Hartson LLP (eds) (2006) EU Moves Closer to a "Biosimilar" Approval: What This Means for the EU and U.S. Markets, Update Pharmaceutical and Biotechnology February 2006, p.1-5

33) Katsnelson A., FDA and EMEA pool scientific advice, Nature biotechnology, published online: 6. December 2004; doi: 10.1038/ nbt 1204-1490, accessed 13.3.2006

34) Mandate, Objectives and Rules of Procedure of the Scientific Advice Working Party (SAWP), EMEA/CHMP/SAWP/69686/04 Rev 5, adopted by the CHMP on 31 May 2006, available at: http://www.emea.eu.int/

35) Marketing authorisation under exceptional circumstances, EMEA, published online 2006, available at: http://www.emea.eu.int/htms/human/presub/exepcircum.htm, accessed: 6.6.2006

36) Netzer T. (2005) Parallel Advice EMEA/FDA: Status report on industry experience October 2005, presentation, presented at the EFPIA INFO DAY 2005, accessed by e-mail from the author on 2.6.06

37) New Framework for Scientific Advice & Protocol Assistance, EMEA/267187/2005/FINAL, 26 April 2006, available at: http://www.emea.eu.int/

38) Note for Guidance on Planning Pharmacovigilance Activities, (ICH E2E Pharmacovigilance Planning PVP), CPMP/ICH/5716/03, December 2004, available at: http://www.emea.eu.int/

39) NOTICE TO APPLICANTS VOLUME 2A, April 2006
Procedures for marketing authorisation, CHAPTER 3, Referrals, and CHAPTER 4, Centralised Procedure, The Eudralex Collection, Enterprise and Industry, published online by the EC, available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

40) Papaluca Amati M., Pignatti F., Nolte A, Amerasinghe N., Gustafsson D., Moulon I. Le Courtois P. (2002) EMEA and Gene Therapy Medicinal Products Development in the European Union, J. Biomed. Biotechnol. 2003; 2003(1): 3-8

41) Performance indicators for the EMEA in 2003, EMEA/5217/04, February 2004, available at: http://www.emea.eu.int/

42) Plastow R. (2006) The stamp of approval, Next Generation Pharmaceutical (NPG), published online 2006, available at: http://www.ngpharma.eu.com/pastissue/aricle.asp?art=25583&issue=144/ accessed on: 15.3.2006

43) Prescription Drug User Fees-Overview - Enclosure PDUFA Reauthorization Performance Gaols and Procedures (incl. PDUFA III Five-Year Plan), published by: FDA, available at: http://www.fda.gov/oc/pdufa/, accessed: 10.5.2005

44) Press release: Cooperation on medicines regulation intensified, Doc. Ref. EMEA/93090/2006, February 2006, available at: http://www.emea.eu.int/

45) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, Official Journal L 18, 22/1/2000 p. 1 - 5

46) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Official Journal L 136, 30/4/2004 p. 1 - 33

47) SME Definition (2006), Enterprise and Industry, published online by the EC: 9.3.2006, available at: http://europa.eu.int/comm/enterprise/enterprise_policy/sme_definiton/index_en.htm, accessed: 29.3.06

48) Survey on the performance of EMEA scientific procedures for medicinal products for human use 2004-Management Board March 2005, EMEA/CHMP/103479/2005, available at: http://www.emea.eu.int/

49) Thompson L. (2000) Human Gene Therapy - Harsh Lessons, High Hopes, FDA Consumer magazine, published online: September-October 2000, available at: http://www.fda.gov/fdac/features/2000/500_gene.html, accessed: 2.5.2006

50) Verfahren der wissenschaftlichen und verfahrenstechnischen Beratung durch das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Erläuterungen für Antragsteller (Revision 1*), 23.05.2006, replacing former version: Wissenschaftliche und verfahrenstechnische Beratung durch das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (Ergänzende Hinweise des BfArM zur Gemeinsamen Bekanntmachung des BfArM, BgVV und PEI vom 4.9.1998 mit Erläuterungen für Antragsteller (Februar 2003)), published on http://www.bfarm.de, June 2006

51) Wissenschaftliche Beratung durch das BfArM von der präklinischen Testung bis zur Zulassung und der Aufrechterhaltung der Zulassung – presentators: Dr. K. Broich, Dr. P. Dejas-Eckertz, Dr. U. Granzer, Forum Institut für Management GmbH Intensive Course, Heidelberg, Meeting on 3. April 2006, Hotel Günnewig, Bonn

Annex 1

Schedule for an SA/ PA procedure at the EMEA according to the new framework becoming effective in July 2006 [37)]

1a) Planning phase with Presubmission meeting

DAYS (calendar days)	ACTION
~ Well in advance (<< ~ D –60) Letter of intent + Appointment of coordinators	If applicable potential Parallel Advice with the FDA will be requested to and agreed by SAWP
~ D -60 (SAWP meeting 0 taking place 2 months before SAWP1) **Letter of intent + Appointment of coordinators**	The company submits a letter of intent for SA or PA requests to the EMEA Secretariat The company's letter of intent for SA or PA requests is forwarded by the EMEA Secretariat to the SAWP for appointment of 2 coordinators and, where appropriate, a third coordinator for questions relating to significant benefit (PA).
~D-60 to Date Pre-submission meeting Organisation of Pre-submission meeting	▪ Submission of the SA or PA request. ▪ EMEA appoints in-house personnel, with following actions: o EMEA review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review. o Additional Experts/patient representative **identification**.
Pre-submission meeting with company	Pre-submission meeting with coordinator(s) (and/or coordinator's experts), secretariat ▪ List of Comments (LoC) on the request is forwarded to the company. This document will be prepared by EMEA in order to improve validation of SA requests, flag issues identified at the presubmission to the SAWP. ▪ Identify requests for which expetise is particularly needed ▪ WP consultation (ad-hoc).
~D-10 Company consult-ation on LoC	The company revises the request and includes potential additional issues.
~D-5 Validation	Submission of final SA or PA request The validated SA or PA request is forwarded by the EMEA Secretariat to the SAWP and to the relevant Working Parties.

1b) Planning phase without Presubmission meeting

DAYS (calendar days)	ACTION
~ Well in advance (<< ~ D –30) Letter of intent + Appointment of coordinators	If applicable Parallel Advice with the FDA will be requested to and agreed by SAWP.
~ D -30 (SAWP meeting 0 taking place 1 month before SAWP1) **Letter of intent + Appointment of coordinators**	The company submits a letter of intent for SA or PA requests to the EMEA Secretariat The company's letter of intent for SA or PA requests is forwarded by the EMEA Secretariat to the SAWP for appointment of 2 coordinators and, where appropriate, a third coordinator for questions relating to significant benefit (PA).
~D-15 Validation	Submission of draft SA or PA request - EMEA review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review. - Additional Experts/patient representative **identification**. - List of Comments (LoC) for request is forwarded to company.
~D-10 Validation	Submission of final SA or PA request The validated SA or PA request is forwarded by the EMEA Secretariat to the SAWP and to the relevant Working Parties.

2) Evaluation phase

D 0 – SAWP 1	▪ The coordinators introduce the company's request highlighting the main issues. ▪ Formal WP consultation. ▪ **Additional expert appointment.**
~D+20	▪ The coordinators send their ***first*** reports to the EMEA Secretariat. ▪ The reports are forwarded for comments to the SAWP, the relevant Working Parties, the additional experts and to the COMP (for PA). ▪ **EMEA quality-assurance**: scientific memory (previous MAA), literature review, checking existing EPARs and previous advice.
~D+30 – SAWP 2	**Discussion of the first reports** focusing on **controversial** issues. The SAWP confirms at this stage whether the advice can be adopted at Day 40 or whether it is necessary to invite the applicant for a discussion meeting (Day 70 procedure e.g in case of disagreement with the proposed development). In the latter case, a **list of issues** to be addressed by the company at the discussion meeting is adopted by the SAWP and sent to the company. The applicant may also propose in writing to the EMEA additional points for discussion that are not part of the adopted list of issues and submit in writing ahead of the Discussion meeting an amended development programme. The SAWP may request the applicant to address issues in writing only. In this case a list of issues to be addressed by the company in writing is adopted by the SAWP and sent to the company. In this case the 70-day procedure will apply.

2a) 40-day procedure

SAWP decides that there is no need for a discussion meeting and that the procedure can be finalised in 40 days.

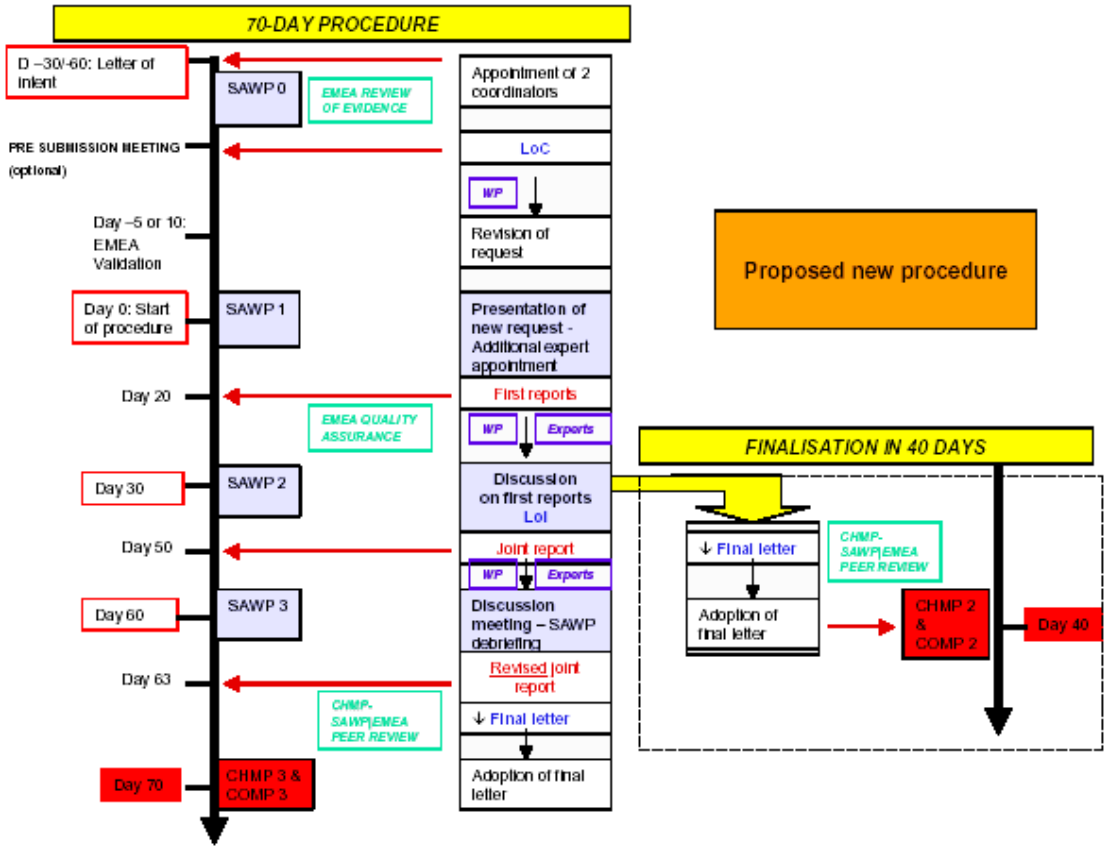
~D+33	▪ The coordinators send their **joint report** to the EMEA Secretariat. The joint coordinators' report and the draft advice letter to the company are adopted by the SAWP through a *written procedure*. ▪ **CHMP/SAWP/EMEA peer review** (content consistency/co-herence).
~D+40 **CHMP 2**	The final advice letter is adopted by the CHMP (and by the COMP in case of question on significant benefit for PA) and sent to the company.

2b) 70-day procedure

SAWP decides that there is a need for a discussion meeting and that the procedure be finalised in 70 days.

~D+50	The coordinators send their **joint report, highlighting the controversial issues from SAWP 2 discussion,** to the EMEA Secretariat. The report is forwarded for comments to the SAWP, the relevant Working Parties, the additional experts and to the COMP (for PA).
~D+60 – SAWP 3	**Discussion meeting with company and SAWP.** The coordinators present a preliminary conclusion at the end of the discussion meeting. The coordinators present the outcome of the discussion meeting to the SAWP.
~D+63	▪ The coordinators send their **revised joint report** to the EMEA Secretariat. ▪ The joint coordinators' report and the draft advice letter to the company are adopted by the SAWP through a *written procedure*. ▪ **CHMP/SAWP/EMEA peer review** (content consistency/coherence).
~D+70 **CHMP 3**	The final advice letter is adopted by the CHMP (and by the COMP in case of question on significant benefit for PA) and sent to the company

Overview of Procedure



Annex II

Time schedules for sponsor meetings with the FDA

From the procedural aspect of timelines, since PDUFA at the latest, the FDA offers three categories of meeting-schedules an applicant might request: Type A meetings**,** Type B meetings and Type C meetings:

- Type A meetings are considered to be immediately necessary, because otherwise the product development could be stopped by 'clinical hold'. This can be typically triggered by a safety or severe quality issue, and has to be scheduled within 30 days of request. They are made up mostly to avoid 'clinical hold', which is the immediate advise by the US-agency to interrupt a clinical trial for safety concerns.
- Type B meetings are the most customary meetings. They refer to the critical phases of drug development when decisions have to be made whether a new active substance is worth being further promoted in development in terms of safety and efficacy: Pre IND-meetings, end of phase 2/Phase 2a meetings and pre NDA, pre BLA meetings are mainly held within this schedule. They should be scheduled within 60 days of request
- Type C meetings can be summarised as all other meetings not covered by categories A and B. They are to be scheduled within 75 days of company's request [23)].

It is possible to have all kinds of meetings once for the same product and it is necessary to establish a very early communication with the FDA in the life-cycle of a product [25)].

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Sachsenkam, den_____

Ellen Güttler

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