



## **NEW FRAMEWORK FOR SCIENTIFIC ADVICE & PROTOCOL ASSISTANCE**

### **The CPMP/CHMP Scientific advice procedure: a background**

Since the creation of the EMEA in 1995, the scientific advice (SA) framework has evolved and SA workload significantly increased.

In accordance with Council Regulation (EEC) 2309/93 the group responsible for advising applicants during the development phase started its activities as a CPMP consultation group (1996), as a Scientific Advice Review Group (1999) and as a formal CPMP Working Group (the SAWG) in 2003. It was formed, unlike other CPMP working groups or working parties, *as a Multidisciplinary Expert Group, based on complementary scientific competences not on a national representation*. As of 2001, with the introduction of Regulation (EC) No 141/2000, the activities of the group extended to providing protocol assistance (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 to 2 full days. New procedures for SA and PA were also put in place.

As of May 2004, the new Regulation (EC) No 726/2004 (Annex I) established the Scientific Advice Working Party (SAWP) as a standing working party of the CHMP with the sole remit of providing scientific advice, particularly regarding the development of new therapies. The SAWP was extended from 18 to 22 members in October 2004 and its current composition includes wide-ranging and specific expertise such as preclinical safety, pharmacokinetics, statistics and therapeutic fields for which there are frequent requests (e.g. cardiology) and those defined in the Annex of the new Regulation, i.e. oncology, diabetes, neurodegenerative disorders, and infectious diseases including HIV infection.

The SAWP currently faces a continuous increase in the number of procedures and meetings with applicants. A steep increase in the number of procedures was observed since 2001, nearly doubling in 4 years (109 procedures were finalised in 2004).

### **EMA/CHMP will implement a new procedure in line with Regulation (EC) No 726/2004**

The new Regulation outlines the principles for modernising the operating methods of the Committees and provides for more general and in-depth scientific advice with the aim of improving advice given to applicants.

The legislation gives this task to the EMA Executive Director to be achieved 'in close consultation' with the CHMP. For this purpose, a consultation phase was initiated, involving the CHMP chair, the SAWP chair, several SAWP members and CHMP members. This phase identified areas where developments are expected in order to fulfil the stakeholders' needs and ensure Public Health. The main stakeholder of scientific advice is the pharmaceutical industry. However, since better scientific

advice means better, more effective and faster development of safe and effective medicines, scientific advice is ultimately beneficial to patients and healthcare professionals as well.

As a consequence, a new procedure was adopted by the CHMP in April 2005. One of the key aspects of this procedure provides for earlier and greater involvement of internal assessors and external experts from the SA pre-submission phase to final SA. Based on this involvement starting from the SA pre-submission phase, it will be possible to streamline the procedure to allow finalisation within 40 or maximally 70 days (compared to the 100-day procedure in the current framework). This new framework will also consolidate the involvement of CHMP by formalising the peer review before final adoption of the letter to maximise the clarity and ensure consistency in the provision of scientific advice.

Another key aspect includes more interaction, communication and transparency with stakeholders, through extension of the scope and increased use of follow-up procedures, publication of standard Questions & Answers documents for frequently asked questions, and organisation of workshops and think-tank meetings on specific and rapidly evolving topics. The new SA framework also envisages more collaboration with academia, learned societies and patients' organisations. Moreover, new measures such as incentives to SMEs, additional specific expertise and new competences will be put in place to take into account the extended scope of Scientific Advice as defined by the new Regulation.

In view of the above and the increasing workload, practical aspects will be put in place to optimise the use of resources along the procedure.

A set of questions and answers (Q&A) is provided hereafter to better understand the changes that have been adopted by the CHMP in the new framework of SA:

- Q&A 1: How does the new regulation impact on the scope of scientific advice and protocol assistance?
- Q&A 2: What are the new aspects of the procedure for scientific advice and protocol assistance?
- Q&A 3: How will the new procedure increase transparency and communication with stakeholders?
- Q&A 4: What will be the impact of the new definition of a follow-up scientific advice or protocol assistance?
- Q&A 5: How will the new Scientific Advice Working Party be organised in the new scientific advice and protocol assistance framework?

This document was released for public consultation for 2 months on the EMEA website on 22 September 2005. Overview of contributions received from interested parties and EMEA recommendations on the new framework for scientific advice & protocol assistance are summarised in document EMEA/31649/2006.

## Q&A 1: How does the new Regulation impact on the scope of scientific advice and protocol assistance?

According to Article 57(1)(n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council, one of the tasks of the EMEA is, “advising companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products”.

The CHMP has established the Scientific Advice Working Party (SAWP) as a standing working party with the sole remit of providing scientific advice and protocol assistance to applicants.

Scientific advice (SA) may be requested for all medicinal products for use in human beings irrespective of eligibility for the centralised procedure or not. Protocol assistance (PA) applies to designated orphan medicinal products, in accordance with Article 6 of Regulation (EC) No 141/2000 on orphan medicinal products. SA and PA deal with scientific issues. Regulatory aspects are handled separately by the EMEA Secretariat. SA and PA requests should contain prospective questions concerning quality (chemical, pharmaceutical and biological testing), non-clinical (toxicological and pharmacological tests) and clinical aspects (studies in human subjects in either patients or healthy volunteers, including clinical pharmacological trials designed to determine the efficacy and safety of the product for pre or post-authorisation activities) relating to the proposed future development of the medicinal product. Specifically for PA, requests may include questions relating to demonstration of significant benefit within the scope of the designated orphan indication and issues addressing similarity/clinical superiority in case other potentially similar orphan medicinal products have market exclusivity in the concerned therapeutic indication.

According to the new Regulation, in addition to the above-mentioned provision, the EMEA/SAWP may deal with the following new aspects:

- Broader and more general advice for specific types of medicinal products or treatments, in collaboration with the relevant Working Parties
- Products intended for the new mandatory centralised procedure, i.e. acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes and, as of 20 May 2008, auto-immune diseases and other immune dysfunctions and viral diseases
- Emerging and new therapies, by maximising the involvement of all EU expertise available
- Safety aspects of scientific advice, including review of pharmacovigilance plans (pre-authorisation/post-authorisation phase) and risk-management programmes
- Advice about the *justification* on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in Article 2 and fulfils the condition laid down in Article 4(1)(c) of 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
- SA requests on acceptability of the development programme for conditional marketing authorisation, which are defined in Article 14(7) of Regulation (EC) No 726/2004
- Advice about the *justification* for applying for a marketing authorisation under exceptional circumstances (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)
- SA requests on acceptability of the development programme for marketing authorisation application under exceptional circumstances, which are defined in article 14(8) of Regulation (EC) No 726/2004
- SA requests 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
- 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 as by Directive 2004/27/EC

- SA requests for medicinal products intended to be marketed exclusively outside the Community, in the context of WHO collaboration as defined in Article 58(2) of Regulation (EC) No 726/2004
- SA requests on paediatric developments

In addition, specific needs of small and medium-sized enterprises (SMEs) will be taken into account.

The following remain outside of the scope of the scientific advice procedure:

- Pre-assessment of data that will be used to support future marketing authorisation applications<sup>1</sup>
- Compassionate use as defined in Article 83 of Regulation (EC) No 726/2004
- EMEA advice prior to submission for qualification of a request for an accelerated assessment procedure [Guideline on the Procedure for Accelerated Assessment Pursuant to Article 14(9) of Regulation (EC) No 726/2004 (EMEA/419127/05)]
- Paediatric Investigational Plans as defined in the Regulation on medicines for children when implemented
- Regulatory aspects which are handled by the EMEA Secretariat

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<sup>1</sup> In particular, requests directly related to marketing authorisation applications are not accepted in the critical period shortly before submission (e.g. once rapporteur and co-rapporteur have been appointed) or once the assessment of the application has begun.

## Q&A 2: What are the new aspects of the procedure for scientific advice and protocol assistance?

The scientific advice or protocol assistance provided to companies is the result of collegial work by the coordinators, the experts, the different Working Parties or Scientific Advisory Groups, the Scientific Advice Working Party, the COMP (for questions related to demonstration of significant benefit within the scope of PA) and the CHMP. The answer is prepared by the coordinators and then submitted if necessary 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 and/or the COMP for formal adoption.

One of the key aspects of this new procedure is the **systematic involvement of coordinator(s) and their assessors/experts in the planning/pre-submission phase** in all types of advice. The presubmission meetings remain optional. However they are strongly recommended, in particular for first time users of the SA procedures, for Protocol assistance, for SMEs, for SA on “specific types of medicinal products and therapies”, and “broad and more general advice”. Pre-submission meetings will be an opportunity for applicants to introduce and receive feedback from coordinators on their proposed development programme for the medicinal product concerned, receive feedback on the list of issues, identify additional issues to be included in the request and obtain more detailed information concerning the procedure. In addition presubmission meetings offer an opportunity to ask regulatory questions which are outside the scope of scientific advice. It will enable companies to establish contact with the coordinators and the EMEA staff closely involved with the application as it proceeds. The presubmission meeting will also allow identification of additional expertise to be involved at an earlier stage in the procedure.

Based on this involvement starting from the pre-submission phase, it will be possible to streamline the procedure to allow **finalisation within 40 or maximally 70 days** (compared to the possibility of 100-day procedure in the current framework).

Formal links between SAWP and EMEA Working Parties and Groups, including the Scientific Advisory Groups, will be established in order to maximise the use of available expertise.

In order to maximise the 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 letter. The practicalities of the peer review will be defined in the near future. This will involve reviewers from SAWP, CHMP and COMP, in addition to the EMEA Secretariat, whose responsibility is to ensure quality-assurance throughout the procedure.

Finally, the 24-hour consultation phase intended to provide applicants with the opportunity to request clarifications just before formal adoption by the CHMP on parts of the draft final letter that were not found clear has been removed from the new procedure. This new step was introduced in December 2004 and was still under a pilot phase. It was considered that, due to time constraints, especially at the end of the procedure, it would be more valuable to consolidate the involvement of CHMP by formalising the peer review and leave more time to applicants to seek clarification at a later stage. Therefore, in the event that applicants feel that part of the advice provided needs further explanation, it will be possible to ask for clarification at any time after receipt of the final advice letter. An expedited process will be implemented to provide clarifications immediately after the SAWP meeting.

1a) Planning phase with Presubmission meeting

<b>DAYS (calendar days)</b>	<b>ACTION</b>
~ 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	<ul style="list-style-type: none"> <li>▪ Submission of the SA or PA request.</li> <li>▪ EMEA appoints in-house personnel, with following actions: <ul style="list-style-type: none"> <li>○ EMEA review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review.</li> <li>○ Additional Experts/patient representative <b>identification</b>.</li> </ul> </li> </ul>
Pre-submission meeting with company	Pre-submission meeting with coordinator(s) (and/or coordinator's experts), secretariat <ul style="list-style-type: none"> <li>▪ 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.</li> <li>▪ Identify requests for which expertise is particularly needed</li> <li>▪ WP consultation (ad-hoc).</li> </ul>
~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

<b>DAYS (calendar days)</b>	<b>ACTION</b>
~ Well in advance (<< ~ D -30) <b>Letter of intent + Appointment of coordinators</b>	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) <b>Letter of intent + Appointment of coordinators</b>	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 <b>Validation</b>	Submission of draft SA or PA request  <ul style="list-style-type: none"> <li>- EMEA review of evidence: scientific memory (previous and ongoing MAA), including checking existing EPARs and previous advice, literature review.</li> <li>- Additional Experts/patient representative <b>identification</b>.</li> <li>- List of Comments (LoC) for request is forwarded to company.</li> </ul>
~D-10 <b>Validation</b>	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

<b>D 0 – SAWP 1</b>	<ul style="list-style-type: none"> <li>▪ The coordinators introduce the company's request highlighting the main issues.</li> <li>▪ Formal WP consultation.</li> <li>▪ <b>Additional expert appointment.</b></li> </ul>
~D+20	<ul style="list-style-type: none"> <li>▪ The coordinators send their <i>first</i> reports to the EMEA Secretariat.</li> <li>▪ The reports are forwarded for comments to the SAWP, the relevant Working Parties, the additional experts and to the COMP (for PA).</li> <li>▪ <b>EMEA quality-assurance:</b> scientific memory (previous MAA), literature review, checking existing EPARs and previous advice.</li> </ul>
~D+30 – SAWP 2	<p><b>Discussion of the first reports</b> focusing on <b>controversial</b> 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 <b>list of issues</b> 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.</p> <p>The SAWP may request the applicant to address issues in writing only.</p>

	<p>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.</p>
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## 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.

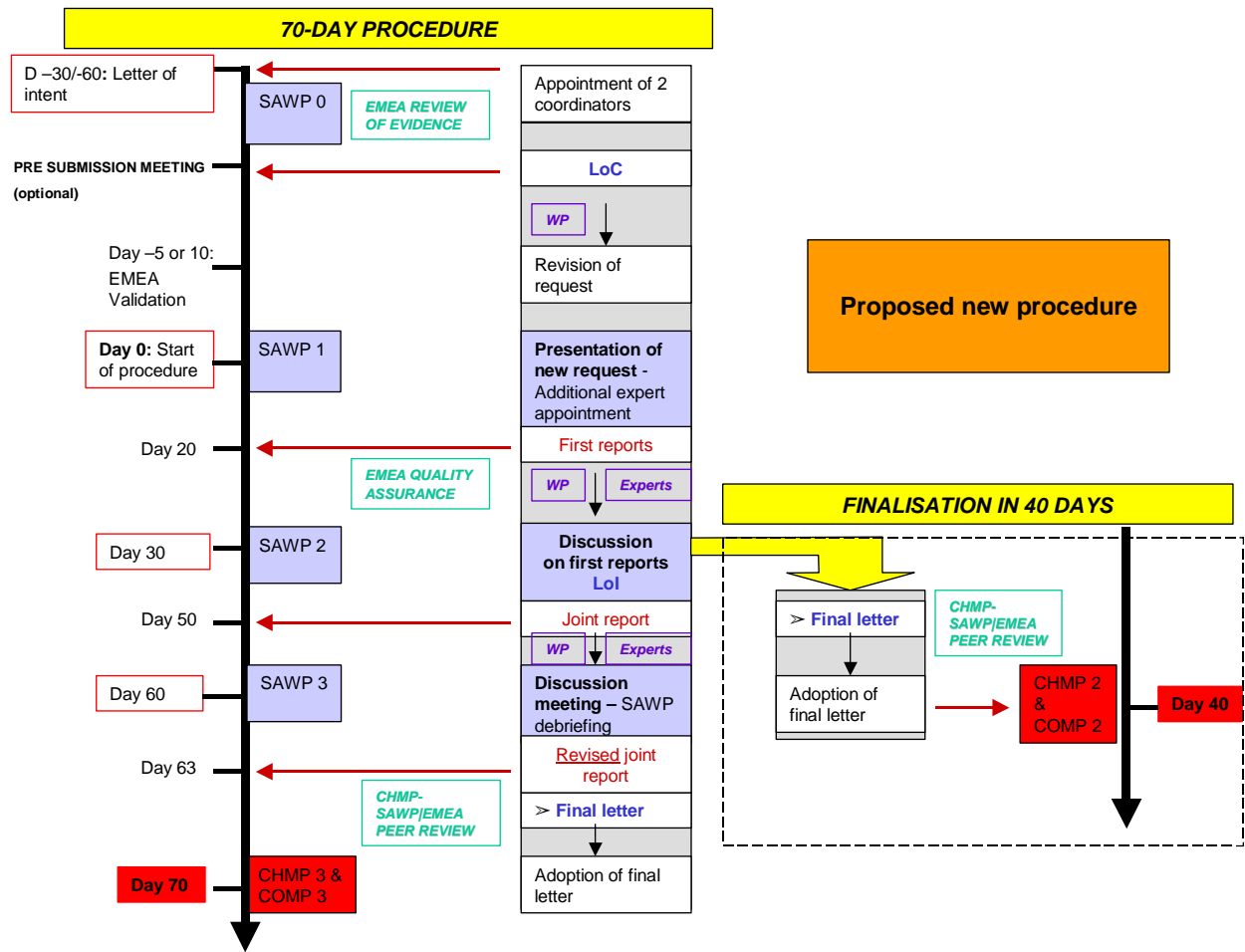
~D+33	<ul style="list-style-type: none"><li>▪ The coordinators send their <b>joint report</b> to the EMEA Secretariat. The joint coordinators' report and the draft advice letter to the company are adopted by the SAWP through a <i>written procedure</i>.</li><li>▪ <b>CHMP/SAWP/EMEA peer review</b> (content consistency/coherence).</li></ul>
~D+40 <b>CHMP 2</b>	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 <b>joint report, highlighting the controversial issues from SAWP 2 discussion</b> , 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	<b>Discussion meeting with company and SAWP.</b> 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	<ul style="list-style-type: none"><li>▪ The coordinators send their <b>revised joint report</b> to the EMEA Secretariat.</li><li>▪ The joint coordinators' report and the draft advice letter to the company are adopted by the SAWP through a <i>written procedure</i>.</li><li>▪ <b>CHMP/SAWP/EMEA peer review</b> (content consistency/coherence).</li></ul>
~D+70 <b>CHMP 3</b>	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



### **Q&A 3: How will the new framework increase transparency and communication with stakeholders?**

The new framework for scientific advice and protocol assistance will allow more interaction, communication and transparency with stakeholders by developing new dialogue phases and opportunities for feedback and by intensifying existing practices. This is especially relevant with regard to protocol assistance and the new aspects defined by the Regulation where SAWP may deal with SMEs or emerging therapies and new therapies (please also refer to Q&A 1).

- Earlier and greater involvement of internal assessors and external experts from the SA pre-submission phase to final SA will be provided in all types of advice (please also refer to Q&A 2).
- More opportunities will be dedicated for discussion meetings by increasing the duration of meetings to 3 days (please also refer to Q&A 5).
- The definition of the follow-up procedure will be widened to encourage applicants to seek scientific advice or protocol assistance as many times as necessary throughout their development programme (please also refer to Q&A 4).
- Collaboration with patients' organisations, especially in the context of protocol assistance, will be developed.
- Standard Questions & Answers documents for frequently asked questions will be developed in collaboration with the relevant working parties and published on the EMEA website.
- Workshops and think-tank meetings on specific and rapidly evolving topics will be organised by EMEA involving regulators, pharmaceutical companies, academia/learned societies and patients' representatives, to share the available non-confidential knowledge. The topics of these workshops and think-tank meetings will be defined in the near future and announced on the EMEA website well in advance.

#### **Q&A 4: What will be the impact of the new definition of a follow-up scientific advice or protocol assistance request?**

Until now, a follow-up request to an initial request could only be requested to reconsider the scientific advice or protocol assistance already given in the light of **new information** available to the company or in case of **changes or amendments** to the development programme **for which scientific advice or protocol assistance was initially given**. An initial request is the first request for scientific advice or protocol assistance introduced in relation to the submission of an application for marketing authorisation or a variation, whatever the authorisation phase (pre- or post-authorisation).

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 area(s)** as the initial request. Area in this context means quality, preclinical and/or clinical development, including pharmacovigilance/risk-management aspects).

By widening the definition, the applicants are not restricted to follow-up on the topics brought up by the questions raised in the initial request. 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 same therapeutic indication and area(s) of the advice). When submitting a follow-up request to the initial request for scientific advice or protocol assistance, applicants should still make reference to the previous CHMP advice received. It is also reminded that the questions should still remain prospective, as it is not within the scope of scientific advice or protocol assistance to provide pre-assessment of data. To ensure continuity, one of the 2 coordinators involved in the initial request will be proposed for reviewing the follow-up request.

This broadened definition of a follow-up request is an incentive to encourage applicants to seek scientific advice or protocol assistance as many times as necessary throughout their development programme, to ensure continuity in the support by the CHMP of the development of their medicinal product and reduce the uncertainties of the marketing authorisation process outcome.

**Q&A 5: How will the new Scientific Advice Working Party be organised in the new scientific advice and protocol assistance framework?**

The SAWP is formed, unlike a number of other CHMP working groups or working parties, as a multidisciplinary expert group, based on complementary scientific competences and not on national representation.

To face the increasing workload and the new legal requirements, the group will be extended from **22** members to **26 members** and the duration of meetings will be systematically increased to **3 days** also increasing the slots for discussion meetings.

The SAWP will involve an increased number of internal and external experts at an earlier stage in the procedure and formal links between SAWP and EMEA Working Parties and Groups, including the Scientific Advisory Groups, will be established.

In order to streamline the work of the coordinators and their internal experts at national level, an **information tracking system** will be developed by the EMEA and made accessible to national competent authorities. This will allow exchange of information on scientific advice, ensure consistency between advice given at national or Community level and ensure consistency with ongoing or finalised marketing authorisation applications through the centralised procedures. An EU Best Practice Guide for all EU regulatory authorities concerning EU-wide advice will also be created in the near future.

In order to facilitate the involvement of coordinators at the pre-submission stage and of experts supporting at the national level the coordinators present at EMEA during SAWP meetings, a **greater use of tele, video and web conferencing** will also be put in place. The EMEA and National Authorities are currently working in collaboration to optimise the use of resources and appropriate equipment to make the scientific advice process more efficient.

## Annex I

### **Legal requirements from Regulation (EC) No 726/2004 of the European Parliament and of the Council**

Article 56(3): “The Executive Director, in close consultation with the Committee for Medicinal Products for Human Use and the Committee for Medicinal Products for Veterinary Use, shall set up the administrative structures and procedures allowing the development of advice for undertakings, as referred to in Article 57(1)(n), particularly regarding the development of new therapies. Each committee shall establish a standing working party with the sole remit of providing scientific advice to undertakings.”

Article 57(1): “... the Agency, acting particularly through its committees, shall undertake the following tasks: ... (n) advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products.”

Preamble (25): “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, small and medium-sized enterprises should be put in place ...”

Article 78(2): “The committees referred to in Article 56(1) and any working parties and scientific advisory groups established in accordance with that Article shall in general matters establish contacts, on an advisory basis, with parties concerned with the use of medicinal products, in particular patient organisations and health-care professionals' associations. Rapporteurs appointed by these committees may, on an advisory basis, establish contacts with representatives of patient organisations and health-care professionals' associations relevant to the indication of the medicinal product concerned.”

Article 58(1) and (2):

- “The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.”
- “The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.”