

Section 5: Scientific Assessment Process: New Products and Referrals

1. SCOPE

The scope of this paper is to review the current scientific assessment process and consider ways in which it may change over the next 5-10 years. The scientific assessment process should always aim at protecting public and animal health. An evaluation of the collaboration of the member states and their rapporteurs in the assessment process across all regulatory systems, including the centralised procedure the mutual recognition procedure and the new decentralised procedure, including referrals, has been performed. It is deemed important to include all licensing procedure to ensure one consistent standard in the European network of Medicines Agencies (i.e., avoidance of double standards), This would ensure high quality assessment regardless of the procedure and thus earn the confidence of the European citizens. The safety, quality and efficacy of medicines, both for human and veterinary use that are on the European market would thus correspond to an appropriate standard.

It is recognised that not only is it important to come to a common standard in assessment but also to have common standards of Product information (SPC and PIL) to inform health care professionals and patients in Europe on a harmonised level.

European medicines authorities participate in the European regulatory systems to varying degrees, depending on their wishes and expertise, and this is considered entirely appropriate.

The assessment process relies on up-to-date scientific, regulatory and procedural knowledge. A quality management system is necessary to help in the attainment of a harmonised assessment and common standards in the European network. In addition, greater transparency in the scientific assessment process will be required as regularly procedures evolve.

2. CURRENT SITUATION

Currently there are two licensing procedures involving collaboration between Member States, namely the centralised procedure and the mutual recognition procedure.

In November 2005, a new procedure, the 'Decentralised procedure' will start. All procedures encompass phases of assessment and phases of decision making. The technical standards applied during the assessment should be identical across all procedures for all Member States as well as for competent authorities in those countries defined within the European Economic Area. These standards are based on agreed and common legal and technical regulations and guidelines, and common quality standards provided by the European Pharmacopeia.

Whilst in general it is recognised that the authorisation systems work well, it is also recognised that at times there are elements that can make it difficult to achieve the objectives of consensus and mutual confidence. In order to propose advances and improvements, certain aspects of the existing systems are considered to be particularly important.

a) Assessment

Centralised procedure

- An important strength of the system is a robust primary assessment performed by the Rapporteur with a further objective assessment performed by the Co-Rapporteur. Any proposal not to include a co-rapporteur's assessment is thought likely to weaken the system. It was concluded that it will be important not to replace the independent co-rapporteur's assessment by a peer review, but peer review could enhance the procedures by enabling the competent authorities, through their delegates to the scientific committees, to reach common scientific conclusions after the assessment performed by the rapporteurs.
- The input provided from all competent authorities via their CXMP delegates, in conjunction with the discussion at the Committee aimed at finding a consensus decision, wherever possible, is considered particularly valuable.

Mutual Recognition Procedure

- In this procedure, the primary assessment is performed by the Reference Member State (RMS). During the European phase of the mutual recognition procedure an independent assessment by the Concerned Member States (CMS) constitutes, in some respects, a quality assurance system. CMS assess the applications taking into account their own national conditions. Certain efforts will need to be made in order to avoid, wherever possible, that elements related to historical aspects/existing licences rather than with a critical evaluation of the safety, quality or efficacy are raised during the procedure and in referrals. Differences in licensing (SPC, PIL) between different European competent authorities would be difficult to understand by prescribers and patients, and therefore should be minimized.
- The need for a continuous improvement in the quality and consistency of the respective medicinal product assessment reports prepared by the RMS is recognised.

Decentralised Procedure

- This procedure, once introduced, should give member states more opportunity to reach an agreement at the European level prior to granting a marketing authorisation. More member states will be involved before the first licence is issued, thereby providing a greater level of quality assurance. Lack of agreement will result in referrals, which may therefore promote a focussing on more important issues for public and animal health.

Referral Procedure

This procedure is the means by which Member States refer national matters of scientific and regulatory concern to the CXMP for independent scientific review and arbitration. In the past, resolution of any differences in the interpretation of the relevant European standard could be avoided by applicants withdrawing their application from those concerned member states that raised objections to the licensing of the product. This situation has resulted in comparatively fewer referral procedures being initiated than would otherwise have been the case, thereby avoiding a harmonised approach. The withdrawal of an application will not, in the future, prevent the referral of the

disputed area to the CXMP for binding arbitration. Such arbitrations will assist in the elaboration a harmonised approach to matters of differing national opinion. In conjunction with the development of a database of scientific decisions that will be available to Member States in the conduct of the assessment process, this is expected to result in more consistency in the scientific assessment processes between medicines agencies in the future.

b) Decision Making

- In the centralised procedure, it was recognised that the CXMP strives to reach a consensus opinion at the European level, taking into account a more European than any national perspective. The relevant harmonisation task carried out by the preparatory work of the CXMP, its rapporteurs and its national assessors and experts through the CXMP-Working Parties and Rapporteur meetings is considered an essential element for the facilitation of the harmonisation and consistency of the European scientific opinions.
- It was recognised that for new medicines assessed during the mutual recognition (MR) procedure, a European view and consensus was normally achieved. However for some older medicines, there were difficulties in reaching a consensus because of non-harmonized standards that had been used during the national assessment products. It should be recognised that for old products disharmony is based on decisions made in the past by the different National Competent Authorities (NCAs). Much effort should be given to achieve common standards on product information in the interest of European citizens. The harmonising process requires not only scientific input but also a courageous and enlightened European decision making process.
- The timetable for MR procedures makes achieving a consensus more difficult. The time available for member states to discuss and resolve their different perspectives is limited, and in part this has led to withdrawals of applications from individual member states.
- It was also noted that there are currently differences in the availability of information released by member states following the licensing of products. The centralised procedure results in a European Public Assessment Report (EPAR) whereas there is no such equivalent in the mutual recognition procedure. There is a requirement from November 2005 on for NCAs to produce the equivalent of the EPAR for national and MR licences and this is expected to address the need for improved transparency.

In terms of overall standards, it is recognised that identical standards should be applied during the mutual recognition, the decentralised and the centralised procedures. All medicines licensed in the European Union must be of an appropriate standard. It is also important to ensure that this is the perception by the European citizens.

	ASSESSMENT	DECISION MAKING
CP	Rapporteur/Corapporteur Expert groups as appropriate CXMP members Including peer reviewers	All (CXMP) Standing Committee European Commission

	CXMP working parties	
MRP	RMS	RMS decides on 1 st authorisation
	CMS: assessment report optional. Normally only comments on the assessment report from the RMS should be expected.	CMS Same → Approval or → Referral different → Withdrawal
(future) DCP	RMS } CMS } All	All

RMS: Reference Member State
CMS: Concerned Member State

3. Suggestions for Improvements to Current Systems

The key elements for improving the system and enhance the collaboration between member states should be aimed to ensure that:

- i) The assessment process is robust,
- ii) Medicines licensed are of appropriate standards of quality safety and efficacy,
- iii) Licensing decisions reflect the European view,
- iv) Member states are free to participate in systems to a greater or lesser degree, depending on their resource and expertise,
- v) There should be no monopolies of competence,
- vi) There should be no difference in standards across the different systems,
- vii) Procedures should be efficient, transparent and responsive to needs.

It is believed that any changes should be the result of “evolution” rather than “revolution”. Specific proposals are made as follows:

3.1 Assessment processes

3.1.1 MRP (Mutual Recognition Procedure)

- Any disagreements should focus on important scientific issues.
- Recognition of the need to achieve a consensus at end of procedures wherever possible, and putting national (rather than scientific) differences aside.
- Important that MS participate to ensure full discussion of issues, adequate quality assurance, and “European” wide common view by support of, not only on scientific matters but also on the agreement on a uniform standard of product information (SPC and PL).
- Optional additional instruments aimed to avoid disagreements based on non scientific grounds may be considered. Before starting a MRP, pre-submission meetings or teleconferences between national agencies may be convened upon request of the RMS. The exact procedure for these contacts should be agreed by the HMAs.

- Different interpretation of guidelines is a main reason for disagreements which shall be minimised by creating opportunities for full participation of MS in ad-hoc groups for rapid critical analysis and reviewing of those leading to major cases of differences before they may constitute a potential matter of dispute.
- Encourage enhanced communication between Member states during the procedure.
- Review of withdrawals and reasons for referrals, aimed to define special training and guidelines. Need to share a scientific database of withdrawals and reasons for referrals between national competent authorities.
- The provision of an up-to-date dossier and assessment report at time of MR was recognised as being fundamental to the smooth conduct of the procedure and to the minimisation of potential matters of dispute.
- The training needs of assessors should be addressed in a methodical manner based on the priorities identified.

3.1.2 Decentralised Procedure

- It was suggested that in addition to the RMS, a second MS involved in the procedure should perform a full assessment, in order to provide an additional quality assurance. It was however recognised that in reality a number of MS may choose to do a full assessment on parts of the dossier anyway, given the limited timetable for CMS to provide comments if reliant on the RMS assessment report.
- It was recognised that this procedure may allow greater consensus to be achieved by member states as input can be provided before the first licence is granted.
- As commented under 3.1.1, pre-submission contact with the CMS may be requested by the RMS.
- The development of a scientific database of assessment decision was recognised to be an important priority.
- It was suggested that before submitting potentially difficult applications, the applicant should be encouraged to obtain scientific advice from the CXMP to assist in the smooth running of the subsequent procedure.
- A mechanism for the provision of updated translations of SPCs and PILs early in procedure was seen as desirable.
- The provision of training of assessors underpinned the success of the procedure in the future. Such training should be provided based on a specific set of agreed priority topics and delivered in a timely manner.
- (Link to the HMA Group on Decentralize procedure)

3.1.3 Centralised Procedure

The advantages of a Rapporteur and Co-Rapporteur system were appreciated and thought to be of pivotal to the future success of the system.

Peer review, whilst perhaps adding value by a more in-depth review by CXMP members should not replace the very important in-depth assessment by the Co-Rapporteur. Peer review should concentrate on the quality of the assessment procedure. Peer review is actually enhancing the procedures by enabling the competent authorities, through their delegates to the scientific committees, to reach common scientific conclusions after the assessment performed by the rapporteurs. Indeed this is a crucial point where competent authorities should look for a SOP to bring effective involvement of their strategies and responsibilities via their CXMP

delegates and get scientific input through the delegates to increase certainty and rigorous basis for consensus criteria of excellence within the current scientific assessors teams.

Thus, also an active plan of updating and communication of information in relation to future EMEA scientific database shall be implemented.

The EMEA scientific database, which is currently being developed, should be made available to all European NCAs to ensure consistency across procedures.

3.2 Collaboration between member states and future models for participation in European procedures

- It is recognised that all MS should be free to participate in all procedures, dependent upon their expertise and available resource, providing they have the ability to perform at agreed EU standards (benchmarking exercise) (transparency).
- All Member States should have the opportunity to participate and contribute with valuable scientific inputs for the assessments, by promoting rigorous framing of scientific questions and also helping to build a more trustworthy regulatory system.
- All Member States have to assist public in their trust in regulatory institutions and its scientific advisory and assessment system, so openness and transparency are widely necessary, and shall be guaranteed through building trust in the European network regulatory agencies' use of science.
- It is suggested that in each procedure involving at least several member states, at least 2 MS should perform a full assessment.
- The systems in the future should allow MS to concentrate on key scientific issues rather than non-scientific historical issues.
- It is recognised that it is important to avoid any sort of monopoly whereby a single member state has the only expertise or competence or ability to perform assessment in a particular area.
- Risk and uncertainty in the fields of scientific assessment process is best handled if the provision of scientific advice, decision-making and communication with the public is a key point not underplayed or overplayed for political advantage. Thus, scientific uncertainties should be made explicit and their implications transparently taken into account in decision-making in European harmonised procedures.
- It is recognised that it is important that a number of MS participate in any licensing decision affecting a number of member states, to enable a balanced European view. It is important that decisions reflect the wish of whole Community, therefore participation of MS from different countries of the European Economic Area is also important.

3.3 Should Member States specialise in certain areas?

The group considered this and concluded the following:

- It would be important to keep access to expertise
Some agencies will remain full service agencies, and should do so if they wish. Due to a large number of nationally licensed products most agencies will need to continue to be able to cover all therapeutic areas. Experience in the assessment of veterinary medicines shows that the emerging new

technological and disease areas are adequately covered within the current framework and do not merit the establishment of specialist agencies.

Member states need to have access to expertise to assess every new therapies and diseases covered within the existing framework and this is expected to remain the case for the present.

- Some agencies may choose to specialise
 - specialisation means concentrating expertise, in particular therapeutic and/ or discipline area.

However it was noted that specialisation may not be permanent as it is often dependent upon a few key staff.

- Specialisation may also result in an increased variability of work load volumes.
- Some agencies may choose to contribute less resources and expertise to European systems than others and this would be acceptable. These Member states rely on the expertise provided by other NCAs. On the other hand it is important that most agencies do contribute to some extent to ensure that decisions continue to reflect the wish of the whole Community.

3.4 Work -sharing model

In this model, the different modules of the assessment (quality, non-clinical and clinical) are split amongst two or more different member states. This model, although occasionally has been done, is not thought to be optimal as a rule because it does not allow as much interaction between assessors as would normally be required for optimal assessment. Moreover, it might result in the dilution of the responsibilities on the final result of the assessment process. However, there may be opportunities for work-sharing between NCAs on a case-by-case basis.

3.5 Achieving common standards

This is thought to be a critical issue, relevant to all MS and all procedures. Without common standards, confidence in a system or MS would be eroded to the detriment of public health for the citizens of Europe. Achieving this requires:

- Common interpretation of legislation and guidelines
- Common training
- Focus on important scientific issues
- MS having a willingness to work together to achieve consensus in MR, Decentralised and centralised procedure. This will require MS to be more flexible and open minded, however it is important that this is achieved without compromise to scientific standards. However for old medicines flexibility is needed to agree to common standards of product information.

4. An Agreed Plan for Training of Assessors: Reinforcing Confidence in a Network of Excellence

One of the ways for improving consistency and achieving common standards would be to have more opportunities for networking amongst assessors, to learn from experience and past disagreements. This could be achieved by:

- Regular meetings between assessors.

- Common training in areas of interest (could be achieved through funds).
- Establishing a *European Assessors Academy*. There is a need to establish formalised training courses on a regular basis. This should be in addition to the more procedural and regulatory courses at EMEA. A module on quality, one on safety and a number on efficacy, covering a series of therapeutic areas could be foreseen. The courses should be directed towards new assessors. The faculty for the various modules should be experienced assessors from different agencies.
- Fostering a “collegiate” behaviour amongst assessors, with greater mutual respect and understanding
- Staff exchange between agencies

It was recognised that some of these activities may be costly and resource intensive, and therefore the costs would need to be justified in the context of potential benefit. Therefore, modern techniques of communication such as video and on-line conferences should play a key role.