

HMA Working Group on Product Testing

**PRINCIPLES FOR MUTUAL RECOGNITION OF  
CONTROL RESULTS**

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**INTRODUCTION**

Mutual recognition of control results between Competent Authorities (CAs) is recognised as one of the key components of a collaborative approach to the sampling and analysis of medicinal products between Medicines Agencies. Sharing of workloads and acceptance of results is necessary for the success of this collaboration. It must be possible for Competent Authorities to take appropriate regulatory action on the basis of reports they receive without further confirmatory testing otherwise the concept of work sharing and collaboration fails. Equally it should be recognised that there are circumstances when re-testing is needed and they should be identified to avoid confusion.

Mutual recognition of control result needs to be considered in a number of contexts:

- i) The legal basis for mutual recognition of data and potential amendments to legislation.
- ii) The Official Medicines Control Laboratory (OMCL) quality system and its contribution to the assurance of laboratory results.
- iii) Additional accreditation needs for certain laboratory activities.
- iv) Exceptions to the general principle of mutual recognition of data.

## **THE LEGAL FRAMEWORK FOR SAMPLING AND TESTING**

Mutual recognition of test results is established within the framework of Directive 2001/83 in the context of the OMCL network and the official batch release of human vaccines and medicinal products derived from human blood and human plasma. To this end, Article 114 of the Directive requires MA holders to submit samples of individual batches of the products concerned to an OMCL or an equivalent designated laboratory for examination prior to release to the market (OCABR). Furthermore, where such a test has been performed in one Member State, these results will apply in all other Member States.

The same approach to the above is proposed in the Directive applied to veterinary medicines EC 2001/82.

The Centrally Authorised Product (CAP) sampling and testing programme is an annual post-marketing surveillance exercise sponsored by EMA, coordinated jointly by EMA and EDQM, and performed by OMCLs within the EEA Network. It is based on EC Regulation n° 725/2004, Article 57, and focuses on the quality testing of products which have undergone the centrally authorised procedure. Testing material, which is collected from the EU/EEA market along the distribution chain, preferably as closely as possible to the patient, include all biological and chemical CAPs with the exception of human biologicals, which are covered by the Official Control Authority Batch Release (OCABR) Procedure. Follow-up measures are coordinated by EMA.

The programme is based on the principle of work sharing and mutual recognition of test results, and has been adopted by all 30 EU/EEA member states and was implemented in 1998. For each product, one or two control laboratories at the most carry out the tests, according to a fixed protocol based on the marketing authorisation application. The results are mutually recognised by all EEA member states.

For further information on the activities of the OMCL network, see [Annex 1](#).

Article 111 of Directive 2001/83 establishes the principle of surveillance of the quality of medicines by means of GMP inspections. Within this article the CA is also empowered to take samples for independent analysis in an OMCL or equivalent designated laboratory. Information sharing and mutual recognition of inspections is achieved through certificates of GMP and the now established EudraGMP database as detailed in sub-paragraphs 6 and 7 of Article 111. Further requirements for communication of information from inspection reports, article 40 manufacturing authorisations, article 77 wholesale dealing authorisations and GMP certificates, are specified in article 122 of the Directive.

Other than the OCABR batch release, and the inspection activities, there is currently no legislative provision for mutual recognition of laboratory testing. If it is thought necessary there are two options available to address this.

1. Amendments to Directive 2001/83 as part of the current revision for this legislation and of the corresponding Directive for Veterinary Medicines, 2001/82.

2. A policy statement by HMA indicating that mutual recognition of test results is generally accepted and defining the scope of this policy, the monitoring of its application, and the exclusions that are to be applied.

Legislative amendments have the advantage that they would establish a legal basis for mutual recognition of data that would be open and transparent to all parties. However, it could be a protracted process that would not be implemented immediately. Furthermore, legal definitions can be restrictive and defining the scope of the collaboration whilst making provision for any necessary exemption could be difficult.

Producing an HMA policy position could be implemented quickly and there would be greater flexibility to define conditions and exemptions. It would be possible to manage the policy within Competent Authorities through performance objectives and Heads of Agencies would have visibility of it. It could be monitored as a part of the Benchmarking of Medicines Agencies Programme (BEMA) and review and improvements to the policy would be easily achieved. It would not, however, be legally binding but this should not be a major disadvantage.

### **QUALITY SYSTEMS WITHIN OMCLS**

There currently exist a number of mechanisms whereby OMCLs can implement and demonstrate compliance with accepted International Standards of laboratory quality systems. The basic principle of these is external assessment against the requirements of ISO 17025 and the relevant OMCL QA guidelines. This can be achieved through:

1. Accreditation to ISO 17025: General requirements for competence of testing and calibration laboratories.
2. The Mutual Joint Audit (MJA) programme of EDQM.

Accreditation to ISO 17025 is an independent assessment by a National Accreditation Service against the requirements of the agreed International Standard. A number of OMCLs have chosen to seek this accreditation since at a national level it provides an assurance of competence when it is necessary to carry out regulatory actions or technical, forensic reports in legal cases.

The EDQM Mutual Joint Audit (MJA) programme has now been operating since 1996. It is a voluntary programme managed and facilitated by EDQM with the support of the OMCL network. Audits are conducted jointly by EDQM and accredited auditors from OMCLs and they assess compliance with the OMCL quality system as approved by the Network at its annual meetings. All guidelines from the OMCL Quality System have been agreed as recommendation documents by the European Accreditation Association (EA). The EDQM MJA programme is considered equivalent to ISO 17025 accreditation Laboratories receive an attestation of compliance following the successful completion of an audit. See Annex 2 for further information.

In the case of an OMCL failing to achieve the EDQM external assessment, support and assistance is available from the EDQM/OMCL Network to help reach this standard.

EDQM further supports the OMCL quality systems by conducting proficiency testing schemes that allow individual laboratories to assess the competency of individuals in the conduct of analytical techniques, which is an expected part of any laboratory quality system.

## **EXCEPTIONS TO MUTUAL RECOGNITION POLICY**

Any policy, if it is to be successful, needs to recognise the exceptions to its applications. The focus of the mutual recognition of results needs to be on the market surveillance activities of OMCLs, in particular the sampling and testing of centrally authorised products, mutual recognition products and decentralised products to confirm compliance with any registered specification. It is in the context of European collaboration for the analytical monitoring of these products that the HMA WG was initially set up and it is important that this remains its focus. Nonetheless there will be circumstances when the results of the analyses could lead to regulatory action, in particular if a quality defect is identified which would lead to a rapid alert and product recall.

There will be situations where it is necessary to perform additional analysis or to confirm the results of the original analysis when regulatory action needs to be taken against a manufacturing, wholesale dealing or marketing authorisation. For these reasons, legal requirements for mutual recognition may not be appropriate. As with inspection reports sharing of analytical reports should be established for these situations.

The one area where sharing of samples and mutual recognition of results may not be possible is for forensic or illegal samples. Continuity of evidence is of major importance with such samples and laboratories handling such samples need to be familiar with and comply with these requirements. Under these circumstances it is sensible and logical for such samples to be handled within the control system of individual Member State so that the individual legal requirements in Member States are met. If it is necessary to transfer legal samples between OMCLs then it is the responsibility of the parties concerned to ensure that the requirements are complied with.

## **RECOMMENDATIONS**

The HMA adopts a policy of mutual recognition of test results for the market surveillance and analysis of products authorised under the mutual recognition procedure (MRP) and the decentralised procedure (DCP) similar to the systems that already exist for CAP and OCABR, and based on the existing voluntary scheme coordinated by EDQM.

The HMA policy should require individual OMCLs to demonstrate that they work to an appropriate quality system which will confirm compliance with ISO 17025 and the relevant EDQM/OMCL Network QA documents.

The HMA policy should recognise the circumstances when MS may conduct their own investigations and analysis. These might be in relation to regulatory actions, and enforcement investigations in Member States.

The Benchmarking of European Medicines Agencies Standards should include performance indicators on collaboration and work sharing for the analytical market surveillance of the quality of medicinal products.

HMA WGPT  
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## ANNEX 1

### **Activities of the OMCL Network<sup>1</sup>**

The Network of Official Medicines Control Laboratories (OMCLs) was established in 1994 on the initiative of the EDQM in close co-operation with the Commission of the European Union. The Network is open to all countries that have signed the European Pharmacopoeia Convention as well as to observers to the European Pharmacopoeia Commission, provided that the criteria of the Network are fulfilled.

There are 2 levels of collaboration.

- *General activities* covering all areas of common interest and involving all member states of the Network such as work in the field of Quality Assurance (QA), Proficiency Testing Scheme (PTS), Market Surveillance Studies (MSS) and common Network strategies (risk-based approach for post-marketing sampling and testing, combating counterfeits and illegal medicines, establishment of centres of expertise, improvement of communication, etc.).
- *Activities restricted to the European Economic Area (EEA)*, in which a number of activities take place within the more restrictive regulatory framework for medicines in the EU/EEA, notably those connected to the Centralised Marketing Authorisation Procedure (CAP), the Mutual Recognition Procedure (MRP) / Decentralised Procedure (DCP) and the Official Control Authority Batch Release (OCABR) of blood and plasma derivatives, human vaccines and veterinary immunobiologicals.

‘Networking’ means sharing of know-how within a pool of experts, work sharing and mutual recognition of test results based on commonly agreed procedures, and consequently saving of resources and costs in the testing of medicinal products, enlargement of the national “coverage rate” of tested products for the individual Network members and finally reduction of duplication of work.

#### *Definition of OMCL*

An Official Medicines Control Laboratory (OMCL) is a public institution, which only performs laboratory testing for a Competent Authority, independently from the manufacturer, for medicinal products prior to and/or after marketing for the general surveillance of medicines in relation to the safety of human patient and/or animals.

Nevertheless, where such institutions or specific technical competences are not available, the Competent Authorities or OMCL may have another laboratory act as their control laboratory, which does not necessarily give this laboratory the status of an OMCL within the Network. The laboratory should then sign a technical agreement as well as an impartiality and confidentiality agreement which also covers conflicts of interest.

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<sup>1</sup> Terms of Reference for the General European OMCL Network (GEON) of the Council of Europe PA/PH/OMCL (07) 79 12R and its annexes.

## ANNEX 2

### **Harmonised Quality Assurance (QA) approach within the OMCL Network**

In the early 90s, the General European Official Medicines Control Laboratory (OMCL) Network (GEON) agreed on the need of implementing harmonised quality management systems (QMS) throughout the OMCL Network as the basic pillar for building mutual confidence in the laboratory procedures and for a mutual recognition of tests results.

With this purpose, the ISO/IEC 17025 standard “General requirements for the competence of testing and calibration laboratories” was selected as the most appropriate to fulfil the needs of the OMCLs for the implementation and maintenance of a QMS. Complementarily, in view of the particular activities carried out by OMCLs and taking into account their specificities, QA guidelines and documents are continuously being drafted since then to give support to the OMCLs in the implementation of the ISO/IEC 17025 standard.

Several of these QA guidelines and documents have obtained the status of recommendation documents after their adoption by the European Co-operation for Accreditation Laboratory Committee (EA/LC). Thus, their use is strongly encouraged during external audits at the facilities of OMCLs, performed either by an Accreditation Body member of EA, or by the experts of the OMCL Network and EDQM, in the frame of a Mutual Joint Audit (MJA) or Mutual Joint Visit (MJV).

The following QA OMCL guidelines have been adopted by EA:

1. Validation of Analytical Procedures
2. Uncertainty of Measurement - Part 1 (compliance testing)
3. Scope of Accreditation of OMCLs
4. Qualification of Equipment - Core document
5. Annex 1: Qualification of HPLC equipment
6. Annex 2: Qualification of GC equipment
7. Annex 3: Qualification of UV-Visible spectrophotometers
8. Annex 4: Qualification of IR spectrophotometers
9. Standard aide-mémoire for the MJA of OMCLs
10. Aide-mémoire for environmental conditions and treatment of biological models

These and other guidelines can be downloaded from the European Directorate for the Quality of Medicines & HealthCare (EDQM) website ([www.edqm.eu](http://www.edqm.eu)). The OMCL Network intends to reinforce the collaboration with EA to ensure that the same status is gradually obtained for other OMCL guidelines.

## Quality Assurance (QA) Programme within the OMCL Network

With the aim of promoting and later on verifying that a harmonized QMS approach is taken within the OMCL Network, the EDQM Department of Biological Standardisation, OMCL Network & HealthCare (DBO) has established and coordinates a QA Programme, with a high level of participation and satisfaction amongst OMCLs, consisting of: Mutual Joint Visits (MJV), Mutual Joint Audits (MJA), Tutorials (TU), and Training Visits (TV).

The main objective of an MJV is to assist the OMCLs implementing a QMS in accordance with the ISO/IEC 17025 norm and the relevant OMCL guidelines by giving recommendations for improvement, while MJAs are aimed to verify the level of compliance of the laboratory with these reference standards once the QMS is established. Tutorials are aimed to coach OMCL staff on QA or technical subjects, to help the OMCL developing a QMS according to ISO/IEC 17025 and the OMCL guidelines. In all cases, the audit/visit/tutor team is composed of duly qualified experts of the OMCL Network and a team co-ordinator from the EDQM, all specifically trained for the quality audit. The EDQM organises also Training Visits in which members of an OMCL requiring training on QA or technical topics, visit the facilities of another OMCL.

In Figure 1, the total number of MJA, MJV, TV/TU performed in OMCLs within the EU/EEA area is presented. The QA programme has a high level of participation and the requests are increasing every year, showing the commitment of OMCLs to reaching excellence in QA and promoting the harmonisation in the field of medicines control throughout Europe.

In two occasions, a MJA was performed jointly with a National Accreditation Body (Austria and Germany), upon request of the audited OMCL. The experience showed that the approaches taken are equivalent.

**Figure 1:** Total number of MJV, MJA, TV/TU performed within the OMCL Network EU-EEA area, from December 1997 until July 2009

