

## **Section 7: Inspection, Laboratory Control and Enforcement**

### **Objectives and Scope**

The objective is that the strategy will enable the full use of the resources of the European Medicines Regulatory Network (the Network) within its members together with other European regulatory bodies.

National risk management strategies based on inspections, standard laboratory controls and assessment may no longer be sufficient. Even though national policies and competences have to be preserved under national autonomy it is clear that the European regulatory system needs to add the network's dimension. In order to achieve this goal the Network should implement effective communication strategies and work towards mutual recognition of practices.

The Heads of Medicines Agencies (HMA) strategy clarifies the responsibility and accountability of the National Competent Authorities (NCA) within the Network. The HMA strategy should include activities for products authorised through all types of procedures. The role of the Network to carry out national tasks in specific areas could also be explored.

The new regulation makes explicit reference to OMCL that carry out the monitoring of centrally authorised products on the market on behalf of the EMEA through the EDQM. Furthermore, there is a system of recognition of inspections where it is made clear that every inspection done by a European Union (EU) inspector is done on behalf of the European Community. Inspection activities have been reinforced and extended in the new regulation and EMEA will have an important role in making available data on inspections through European databases.

In today's enlarged EU, in order to have a genuine synergy in the search for the best quality, efficacy and safety of medicines, assessment, control and inspection activities cannot and should not be dissociated. However, if it is true that the expertise for evaluation is distributed in a heterogeneous way within the EU, the strength of the inspection and laboratory control systems relies on the harmonisation of good practices and the excellence of all of its elements. It should also be noted that whilst other international bodies or organisations undertake audits only regulatory authorities perform regulatory inspections.

The ultimate goal of the Network is that a European citizen can get a treatment of the best and the same quality, efficacy and safety anywhere in Europe.

### **Reasons for improvement**

Two types of activities could be considered:

#### **1. Legitimate business development and its consequences**

##### **Quality of starting materials and medicinal products**

The 2001 Review of the legislation recognised the initial importance of the quality of starting materials in medicinal products and the need for inspection. This is due to emerging questions: diversity of sources; complexity of distribution chains; manufacturing outside EU; evolution of international standards regarding organic impurities (i.e. European Pharmacopoeia, ICH); current questions on toxic impurities (e.g. glycol ethers); new complex combinations of active ingredients (e.g. antiretroviral agents). This is of particular importance in the context of development of generic medicines and also for traditional herbal medicinal products which will now be regulated.

## **Restructuring and globalisation of manufacturing processes and distribution channels**

The movement of manufacturing operations out of Europe places an increased requirement for all Member States to undertake third country inspections and strategies are required to cope with potential international shortages arising from the consolidation of manufacturing in politically and geographically less stable areas.

There is an increasing need to look more thoroughly to distribution chains as the safety of medicines is also related to confidence in distribution channels.

## **New therapies**

The development of new therapeutic approaches and innovative medicines (e.g. gene therapy, cell therapy, biotechnology, tissue engineering, new ways of administration of medicines, "individual therapeutic" concept, nanotechnologies) raises several questions which must be anticipated by NCA: acquisition of new competences; definition of immediate needs in the standardization field (e.g. pharmacopoeia); anticipation of regulatory rules (e.g. batch release) and harmonisation of regulatory status; evaluation of level of production and level of therapeutic use; difficulty of access to certain categories of products for NCA; technical investments; capacity of manipulation in protected areas.

Collaborative work between industry and NCA for the convergence of methods and protocols of laboratory controls should be promoted.

There is a need to improve the processes for sharing information and developing expertise in NCA.

Training for inspectors is essential. The use of already implemented programmes is key to build trust and mutual recognition of practices and tools. Expert's circles such as the ones on tissues and cells and biotechnologies established by the PICS should be considered in this area.

## **Analytical Market Surveillance**

Usually analytical market surveillance will include:

- a general survey of the global market (e.g. generics, different sources of API).
- a specific survey of identified categories of products (e.g. radiopharmaceuticals, biotech products, vaccines, blood derivatives, medical gases),
- a specific survey of a limited number of parameters on selected products (e.g. sterility, particular tests, granulometry, dissolution),
- advanced and elaborated laboratory control tests, based on very specific techniques and competences to address new quality concerns.

In the context of a risk based approach to market surveillance, individual NCA may have differing priorities when identifying surveillance programmes. There is, however, a collaborative approach for sampling and testing centrally authorised products and products authorised by mutual recognition or decentralised procedures, which should be supported and maintained.

## **2. Deviations and illegal activities**

### **Misconduct of clinical and non clinical trials**

Misconduct in non clinical and clinical trials by lack of good practices or scientific dishonesty may expose subjects undergoing clinical trials to unreasonable and significant risk, and would impede/jeopardize the quality and the reliability of data obtained during these studies. Any false or misleading data submitted to a competent authority or published, would undermine the evaluation of the risk/benefit ratio for a medicinal product.

The development of generic compounds has shown the importance of surveillance of bioequivalence studies, often performed by CRO located outside the EU and included in Marketing Authorisation (MA) files for registration in European countries. Measures are

being implemented to improve the completeness and accessibility of trials and data (i.e. clinical trials databases, clinical trials registers), but Member States take responsibility for inspections within the context of the European strategy for inspections with exchange of information on the inspection concerns and outcomes for current, submitted and published trials. However, there is room for actions in terms of common inspection programs and exchange of information on GCP and GLP inspections.

### **Counterfeit products and sales on the Internet**

The regulations regarding distribution chains have a great influence on the emergence of counterfeit medicinal products on each national market in Europe. The diversity of distribution chains and pertaining regulatory rules, sales on the Internet and free movement of medicines provide increased opportunities for the emergence of counterfeit products. Issues such as accountability and responsibility should be clarified aiming to develop a common approach.

NCA must be prepared for this problem. Enforcement of medicines legislation is Member State's competency, but coordination between NCA and various national and international bodies involved in counterfeit fight is necessary. Ongoing activities in that area should be supported.

Actions related to the prioritization of "at risk" compounds; anticipation of ways of entry in the EU, implementation of new regulatory tools, setting up systems for rapid exchange of information, could be explored. This may not be appropriate if there is legal enforcement action.

From a national laboratory point of view, the assessment of counterfeit medicinal products requires specific methodologies, dedicated and improved competences in sophisticated analytical techniques.

In such a context, exchange of information on methods and results should be encouraged within a close and secure network. Investigations can be carried out in collaboration with the industry which can provide analytical methods and also help assess the risk to public health.

### **Activity of the existing networks**

#### **Interaction between NCA and other European and International bodies**

Each European or International institution has a clear status, well defined tasks and field of activities and is well organized in its contacts with NCA. There are places for exchanges and coordination at each level.

GMP and GCP related activities are covered by:

- Ad hoc Working Groups at the EMEA,
- API inspection programmes coordinated by the EDQM,
- PICS Committee of Officials (GMP for API and finished products),
- WHO programmes on vaccines and AIDS/TC/Malaria,
- International Conference on Harmonisation (ICH).

GLP activities are covered by:

- OECD,
- Ad hoc Working Group for GLP (sub-committee of the European Commission).
- GLP inspection services ad hoc meetings (EMEA)

The system has shown its effectiveness so far. Nevertheless, there should be developed a genuine link between assessment, inspection, laboratory control data from NCA which allows

a genuine “Global Risk Management Strategy” of medicinal products. Pharmacovigilance inspections should be further developed as part of the strategy.

### **Interaction between different tasks within the NCA**

Interactions at European level can only be improved if they improve at national level. When the tasks of assessment, inspection and control are distributed between more than one regulatory body, effective and operational coordination is necessary, for instance for the follow-up of out-of-specification (OOS) or questionable laboratory results.

There is today a lack of shared knowledge of the individual organisations put in place at national levels. HMA could share this information for the benefit of the Network. The EMEA Compliance Programme has been approved by HMA and is responsible for the Joint Audit Programme for centrally authorised products across Member States.

The information obtained from the HMA Benchmarking process would provide details of the approach of individual NCA to different tasks (e.g. handling of quality defects identified during inspection or laboratory analysis).

### **Ways for improvement**

#### **Facilitating the sharing of information**

Firstly, this requires a global visibility of all existing and future sources of information such as EMEA legally required databases and be sure that all kinds of needs have been considered. Secondly, after identifying what is available we could discuss additional requirements and how to organise the exchange of information related to assessment, inspection and laboratory controls findings within the Network. The issue of confidentiality of national data will have to be addressed. It is also important to ensure that information sharing does not lead to the re-assessment of MRP applications.

The Network’s information technology strategy should support the sharing activities and meet the Network requirements.

Finally, proposals for implementation could be made.

Currently there are a number of mechanisms for sharing information for example, the ad hoc inspectors working groups, PICS, OECD meetings, the rapid alert system, the OMCL network and EMEA databases. We should review the information exchange within these systems and identify gaps which we may wish to cover. This could be possible by modifying existing pathways.

The HMA Benchmarking procedure should provide information on conduct of regulatory functions by NCA and could be extended to include e.g. training programmes, inspection processes, and laboratory controls. This would allow best practice to be identified and promulgated.

The development of the EUDRAGMP database should be clearly supported by NCA. Sharing of information contained in this database should significantly improve accuracy and relevance of risk management programmes of inspections and laboratory controls.

For the content of the information to be shared there will be the need to agree on a common language.

For example, exchange of information may include:

- competences of all NCA members of the EMRN,
- information on products authorised through all types of procedures,
- training programmes for inspectors,
- methodologies and inspection tools,

- laboratory controls : programs and reports , quality defects identified by laboratory controls,
- information on performance and outcome of batch testing
- potential quality or product defects highlighted at the inspection phase,
- the expression of new needs for controls or standardization,
- the expression of inspection needs following laboratory control and assessment results,
- the involvement of inspectors at different stages of the assessment,
- MA changes highlighted by inspections (Rapid alerts),
- topics common for assessment, inspection and control tasks, either technical (e.g. packaging of medicines) or regulatory,
- programmes of scheduled routine inspections such as the pre-MA inspection in national procedures,
- pre-MA inspection findings in the field of GMP, GCP, GLP and bioequivalence studies, in addition to those that will be available in the European databases (EUDRAGMP,EUDRACT and EUDRAVIGILANCE)
- thematic reports of some inspection programmes,
- policing measures: suspension of companies, formal notices.

### **Strengthening coordination**

Coordination between NCA already exists. The ad hoc inspection groups, the OMCL network and the informal network of enforcement group all give a degree of coordination. EMEA working parties also aim for a co-ordinated approach. These should be developed and consideration be given to what additional mechanisms need to be set up. The Benchmarking process should provide further coordination and enable best practice to be identified and implemented in NCA, leading to a continuous improvement cycle.

Preserving NCA own field of expertise, the EMRN should take advantage of the wide range of skills that are available to ensure that objectives are met and all regulatory activities are covered to some degree. We should also identify areas of best practice for optimising use of resources and build on these.

Global risk management based strategies, notably for market surveillance programmes and follow up of quality problems should include sharing of expertise from assessment, inspection and laboratory control and the coordination of activities between the NCA. HMA should define common approaches and main orientations for coordinated actions between EMEA and EDQM.

### **Encouraging communication**

Some possible areas for communication could be:

- between NCA to develop a common view on the complementarity's of different tasks,
- between NCA and EMEA for sampling and testing products authorised through all types of procedures, which should be supported and maintained,
- between NCA, EMEA and EDQM to define common approaches and main orientations for coordinated actions,
- between NCA, EMEA and PICS to define common tools on inspection and related training courses,
- between HMAs and EDQM in order to influence the strategic orientations for the OMCL network and to discuss the conditions of a genuine mutual recognition of controls,
- between HMAs, EMEA, European Pharmacopoeia and manufacturers in order to better define the expectations regarding new needs of standardization,
- between OMCL and manufacturers to allow a proactive approach to developing competencies and investments.

## **Promoting harmonisation**

Harmonisation of good practices and also harmonisation of concepts and strategies are the basis for the mutual recognition of activities. It is the first step towards a more consistent approach with improved efficiency.

Areas for harmonisation could be:

- National practices in terms of alerts on quality defects and on implementing batch withdrawals in particular for products not authorised via the centralised procedure,
- Inspections reporting,
- Follow-up of OOS laboratory results,
- Methods and protocols of laboratory control (e.g ICH guidelines),
- Quality Management Systems (Benchmarking exercise),
- Quality system for GMP inspectorates (EU Joint Audit Program, PICS Joint Reassessment Program),
- Quality system for OMCL (coordinated by the EDQM).

## **Developing common training and sharing of experience**

Participation in existing training schemes could be improved through better communication and new training opportunities could be explored, for example, developing information mechanisms between NCA and the large international training providers (DIA, PDA, ISPE) as well as the wider use of in-house agency training programmes. It is recommended that a European Training Group be established.

Support should be given to the EDQM's initiative to organize common training for OMCL and, in this regard, to have a proactive approach of NCA in proposing topics of interest and in including such trainings in the national strategies.

In the field of GMP, PICS Seminars and various experts' circles (API, medicinal gases, computerized system, blood, tissues and cells, biotechnologies) could be used with potential contribution from the European Commission and the EMEA.

Exchanges with "newcomers" in the EU are also a crucial point of interest.

The possibility for reviewers and pharmaceutical analysts to participate in inspection activities and the participation of inspectors or laboratory assistants in assessment working groups at NCA could be envisaged.

## **Enforcement**

In the field of enforcement, the first actions could be to:

- Define the various areas in which this concept is applicable,
- Identify the national stakeholders and in particular establish a link between enforcement officers and HMA,
- Identify the European networks already in operation in this field,
- Structure the activity by defining common policies, and develop the communication tools between the various enforcement officers.
- Develop sound processes and provide adequate resources in order to improve the management of enforcement activities.

The EU Medicines Enforcement Group is recognised as a key body for progressing the above actions and implementing the HMA strategy. The former provides for exchange of information on enforcement issues arising with particular manufacturers and a process for exchange of information between enforcement officers and inspections. Other enforcement related fora include the Permanent Forum on International Pharmaceutical Crime and the Council of Europe ad-hoc Group on Counterfeit Medicines.

In the area of counterfeit activities it could be useful to identify the most counterfeited products and specific methods of identification on a regular basis.

A Global Risk Management Strategy of medicinal products must not forget to pay attention to the distribution channels. Inspections activities should not stop at GMP and it is necessary establish GDP requirements in all Member States and to enforce GDP inspections and sampling of products at different levels of the distribution chain.

**Glossary:**

<b>Term</b>	<b>Description</b>
OMCL	Official Medicines Control Laboratories
EDQM	European Directory for the Quality of Medicines
PICS	Pharmaceutical Inspection Cooperation Scheme
API	Active Pharmaceutical Ingredient
CRO	Contract Research Organisation
OECD	Organisation for Economic Co-operation and Development
DIA	Drug Information Association
PDA	Parenteral Drug Association
ISPE	International Society for Pharmaceutical Engineering
GMP	Good Manufacturing Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GDP	Good Distribution Practice

# Annex I : Drug Life Cycle

