European Medicines Agency
Inspections

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Sampling and Testing of Centrally Authorised Products
Objectives and description of the Programme

Introduction
This paper outlines proposals for improving the Sampling and Testing of Centrally Authorised Products (CAPs). During the seminar in September 2003 and subsequent meetings it was agreed to look afresh at the entire programme, its objectives, the role and responsibility of all parties involved and the communication and reporting.

Background
As a joint initiative of the European Commission, the European Medicines Agency (EMEA), the European Directorate for the Quality of Medicines (EDQM) and the network of Official Medicines Control Laboratories (OMCLs) in the EEA a sampling and testing programme of centrally authorised products was initiated in 1997.

After a trial phase in 1997-1998, the programme has been fully implemented with products being systematically tested in the 12 months following the third anniversary of their authorisation. Following 3 complete years of annual programmes, it was time to summarise the experience gained. A Seminar was organised in September 2003 to review the programme and procedures with the aim of improving its operation.

One of the outcomes of the seminar was to re-examine the objectives of the programme. This paper focuses on the legal basis for the sampling and testing programme, the objectives of the programme and the means of achieving these objectives. The sampling and testing programme has been reviewed with the aim to make use of existing systems and optimise resources, to avoid duplication in testing, to provide for work sharing in the EEA and to ensure mutual recognition of testing results in the EEA.

Legal basis
The legal requirements for the sampling and testing of medicinal products are laid down in the Council Regulation No 726/2004 replacing 2309/93 and the Directives 2001/83 Art 111 (Human medicinal products) and 2001/82 Art 80 (Veterinary medicinal products), Title XI, Supervision and sanctions, as amended by Directives 2004/28 and 27, respectively. For medicinal products authorised through the centralised procedure, the EMEA coordinates the sampling and testing to avoid duplication by Member States.

Council Regulation (EC) No 726/2004, Article 55 stipulates that the **Agency shall be responsible for coordinating** the existing scientific resources put at its disposal by Member States for the evaluation, **supervision** and pharmacovigilance of **medicinal products**.

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In particular, the agency shall undertake the:

- coordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community (Art 57(c))

- coordination of the supervision of the quality of medicinal products **placed on the market** by requesting testing of compliance with their authorised specifications by an Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose Art 57(r).

In addition, the Scientific Committees at the EMEA, in order to prepare for an opinion, may request than an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose test the medicinal product for human and veterinary use, its starting materials and, if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory (Article 7 and 32 respectively). Testing in the pre-authorisation phase is not an integral part of the Sampling and Testing Programme, however such testing may be coordinated through the programme.

Objectives of the Sampling and Testing Programme for CAPs

The objectives of the post-marketing sampling and testing programme are derived from the legal requirements:

- to supervise the quality of medicinal products placed on the market;
- to check compliance of the medicinal product placed on the market with its authorised specifications.

In a wider sense this may include:

- to check the quality of the finished product in all parts of the distribution chain throughout the authorised shelf-life;
- to ensure that the control methods are satisfactory;
- to investigate suspected quality defects of CAPs - when requested;
- to assist in testing of counterfeits of CAPs - when requested.

The objectives of the coordination of sampling and testing of CAPs are drawn up to make best use of existing competencies and available resources by avoiding duplication. This will save money for both industry and regulators. In addition this coordination provides for work sharing and mutual recognition of testing results in the EEA. It establishes the capability for independent testing of all CAPs, to be used in case of emergencies.

To achieve these objectives, the Agency set up a sampling and testing programme involving the Scientific Committees at EMEA, EDQM, the inspectorates and OMCLs of the EEA countries to coordinate:

- the selection of CAPs and parameters to be tested;
- the sampling of selected CAPs from the European market;
- the testing of these CAPs for parameters identified and;
- reporting.

The work sharing and responsibilities of all partners involved are described in the relevant procedures.

The Sampling and Testing Programme for CAPs is part of the overall supervision of medicinal products and is complementary to other important areas e.g. pharmacovigilance and inspection of manufacturers.

Selection of CAPs for testing
Centrally Authorised Products are selected for testing usually three years after the product has been granted a Community Marketing Authorisation. Typically 40 products are tested per year.

In addition to this annual testing scheme, in the future products may be selected based on a risk analysis. Such risk analysis would be based on findings at assessment, GMP inspections, submitted variations, findings in similar products or presentations. Selection criteria could include risks identified for active substance, patient profiles, poor stability of product, production process, pharmaceutical form and data from previous controls.

Repeated testing of CAPs
Currently CAPs are only tested on one occasion. In the future however, repeated testing may be carried out based on a risk assessment as above and on the following considerations:

- Problems (product related or method related) which have arisen during the first testing.
- A product may present inherent risks due to production, specific application or dosage form presentation aspects. Priorities should be set for repetition of CAP studies. Particular consideration should be given to an inherent variability of the production process, poor stability, the potential presence of toxic impurities, problematic bioavailability, and biological standardisation of potency.
- Unfavourable reports of GMP inspections may initiate a study.
- A generic of a CAP may justify studies to compare specific quality aspects.
- After a major variation of the quality part of the dossier it should be assessed if re-testing should be performed
- Any product that has been tested three years after granting of the authorisation, may be selected for re-testing at any time, on a random basis, for continued control.

The design and timing of any re-testing will not be identical for every product.

Parameters to be tested
The parameters to be tested should be critical indicators of the quality of a product. The parameters are selected by the Rapporteurs from the product and starting material specifications and assessment results. In view of advances in technology such as process analytical technology and emerging new pharmaceutical forms it may become necessary to revisit current selection criteria.

Organisation of the Sampling and Testing Programme for CAPs
An operational procedure for sampling and testing of Centrally Authorised Products has been developed based on collaboration between EMEA, EDQM and the national authorities. A contract was signed in June 1999 and renewed in 2002 between EMEA and EDQM that will govern yearly programmes for the surveillance of medicinal products on the European market. The role and responsibility of the partners and the organisational steps are as follows:

EMEA
The EMEA is responsible for the choice of products to be included in annual testing programmes in consultation with its Scientific Committees and Working Parties. The selection of parameters to be tested is based on the recommendations of Rapporteurs / Co-Rapporteurs. The EMEA communicates with the marketing authorisation holders for the selected products and coordinates any follow up measures. The EMEA holds the overall responsibility for the Sampling and Testing Programme.

EDQM
EDQM then establishes and coordinates the sampling and testing of the selected products based on the information made available by the MAH (test methods, validation data). It reviews the documentation and requests reference material and specific reagents. EDQM coordinates the EEA OMCL network and organises the Quality Assurance system of the network. EDQM defines the sampling and selects the inspectorates.

National GMP Inspectorates
Inspectorates sample the products from three different countries on average to be representative of the European market. Samples are collected in principle throughout the entire medicine distribution chain (e.g. wholesalers, community or hospital pharmacies, distribution centres). Samples of each product are sent to EDQM, which allocates them to one or several OMCLs for testing in accordance with protocols derived from marketing authorisation dossiers.

National Laboratories and testing scheme
In the past CAPs were usually tested by two OMCLs. From 2005 onwards chemical products will be tested by a single OMCL only with the objective to implement this scheme fully for the 2007 programme. The OMCLs that have successfully undergone external assessment of their QA system would progressively be given the preference. Nevertheless the principle of having an optimal distribution of workload between the different OMCLs of the network will still be kept. In the future this might be extended to other CAPs based on the experience gained.

The analysis and results from the tests together with advice concerning the test methods are sent by the involved OMCLs to EDQM. A report is established and sent to the EMEA for any follow-up that might be needed.

Rapporteurs / Co-Rapporteurs
EMEA communicates the testing results to Rapporteurs / Co-Rapporteurs and Marketing Authorisation Holders ensuring that all partners in the Sampling and Testing programme are informed and any follow-up measures initiated.

Funding of the programmes
The annual sampling and testing programmes are funded by using part of the annual fee revenue. The contribution to EDQM is provided in relation to the number and type of products in the programme, to finance its co-ordination of the programme and to contribute towards the costs of the participating inspectorates and OMCLs. Additional costs are covered by national authorities. The samples taken from the market are replaced by the MAH through a voucher system.

Pre-authorisation testing
In addition to the sampling and testing of CAPs in the post-authorisation phase, the Rapporteur has the possibility to identify special analytical methods during the assessment phase which should be tested by an OMCL before the marketing authorisation is granted. This pre-authorisation testing should help to identify quality problems at an early stage and facilitate the CAP programme later on.

Follow up and reporting
EDQM prepares and sends to EMEA reports detailing the testing results on an ongoing basis. These reports are sent to Rapporteur and Co-Rapporteurs for advice on follow-up actions. A summary report is provided to MAHs. If any issues are identified EMEA follows up any regulatory actions.

The detailed reports are available on the GMP Inspection Database (for regulators only) and annual summary reports on the sampling and testing programme are published on EMEA's website.