Vol 11 No 6 June 2000

THE REGULATORY AFFAIRS JOURNAL

Features

Reference Information

Worldwide Update

Market Surveillance of Centrally-authorised Products

Ulla Paulsen-Sörman, Richard Wanko and Jean-Marc Spieser discuss the establishment of a common post-market surveillance system for products authorised via the EU centralised procebure in the EU/EEA

General trends in the quality control of medicinal products

EU centralised procedure: an example of collaboration and mutual recognition between CAs

Since the implementation of the «future systems» in 1995, close collaboration and mutual recognition between the Competent Authorities (CAs) of the EU and the European Economic Area (EEA) have become the norm for registration procedures. Innovative medicinal products are now introduced onto the market in the EU and EEA in a timely and efficient manner. To date, more than 140 medicinal products have been authorised through the centralised procedure.

Based on the experience of granting marketing authorisations through the centralised system and the achievement of closer collaboration between regulatory authorities of the EU/EEA Member States (MSs), there is also a move towards closer collaboration in other regulatory areas. One such area is the post-marketing surveillance of centrally-authorised products, where closer collaboration and work sharing should avoid duplicating activities, guarantee a clear focus of accountability and use available resources more efficiently. Throughout the EU and the EEA, there is a growing interest in closer collaboration between control laboratories, further rationalisation by sharing work and competence appropriately, and relying on the principles of mutual recognition of data between MSs. This kind of networking is based on national capabilities within the framework of European organisations, such as the EU and the Council of Europe.

Collaboration is also being seen in other regulatory areas

European Official Medicines Control Laboratories (OMCL) Network of the Council of Europe

Quality of marketed medicinal products is monitored by CAs

It is the right of the patient to receive medicinal products of good quality and CAs (organisations, administrations and agencies) have a duty to ensure that marketed products fulfil the quality requirements (e.g. those laid down in the marketing authorisation application). Official laboratory testing aims to support the regulatory authorities and to complement the Inspection Services in controlling the quality of medicinal products on the market by independent re-testing. Such re-testing by independent laboratories is scientifically based and encompasses necessary parameters essential for monitoring the quality of medicines on the market. Independent re-testing can be performed prior to granting the marketing authorisation, during the assessment period prior to placing a batch on the market, as official control authority batch release or after marketing the products.

With a view to creating a pool of resources, which provides technical expertise and a possibility of work sharing, an OMCL Network was formed in the mid-1990s under the aegis of the Council of Europe in Strasbourg, France. The Network's purpose is to co-ordinate the administrative and technical activities of the OMCLs, to facilitate the exchange of knowledge throughout Europe and to influence future development through harmonised common standards, based on the legal requirements for testing medicinal products. An inventory of available national resources within the OMCL Network has been developed, identifying the existing national structures in the human and veterinary areas and their various fields of expertise. This inventory will facilitate communication and the development of an efficient use of all existing expertise within the network.

OMCL Network, formed in mid-199Os...

The European Directorate for the Quality of Medicines (EDQM) of the Council of Europe (which is also responsible for the Ph Eur) began co-ordinating this Network in 1994. The general OMCL Network not only integrates the courtries of the EU, the EEA and Switzerland, but also most Central and Eastern European countries, notably members of CADREAC, which are already observers at the Ph Eur Commission. Some non-European countries (e.g. Canada and Australia) also participate Within the general OMCL Network, an EU/EEA specific OMCL Network (restricted to the EU /EEA MSs) has been set up. Its two main areas of interest relate to post-marketing surveillance of centrally-authorised products and official control authority batch release of biological products (human and veterinary) within the EU and the EEA.

…is co-ordinated by the EDQM

Ulla Paulsen-Sörman PhD, Scientific Officer, LDQM, Division IV/OMCL Network. Richard Wanko PhD, Scientific Officer, EDQM, Division IV/OMCL Network. Jean-Marc Spieser, Head, EDQM, Division IV.

Post-marketing surveillance of medicinal products

Market surveillance is performed to confirm that the registered quality of a medicinal product is met and maintained throughout its shelf-life. The surveillance includes various types of activity within the Inspection Services and in the control laboratories. To carry out testing activities, the authority must have access to an OMCL(s) within its own structure or, failing this, will have to subcontract the testing activities under special conditions.

Pharmaceutical control activities are normally carried out by public institutions and laboratories

In Europe, the pharmaceutical control activities are mainly performed by governmental laboratories (public institutions and laboratories). These are financed solely from. public resources (including fees for registration and/or control activities) and their independence is guaranteed by their status. The CA may subcontract testing of medicinal products to private laboratories. In that case, impartiality and confidentiality agreements covering conflicts of interest must be ensured.

The control laboratory tests samples of medicinal products to check whether they comply with the specifications laid down in the marketing authorisation. Specifications and methods described in the Ph Eur and other official specifications and guidelines (e.g. batch release guidelines for biologicals) are also considered.

Responsibilities of OMCLs

Traditionally, the OMCL(s) of each CA performs market surveillance of all nationally available medicinal products although the surveillance is now extended to control activities of centrally-authorised products. In addition, with high technology and innovative medicinal products currently being introduced onto the market, there is an increasing demand for research and development of new analytical procedures, both in the chemical and biological field. Consequently, OMCLs will need to implement these new procedures.

A pilot study on the post-marketing control of nine centrally-authorised products was carried out in 1998. The purpose of this trial was to check the feasibility of a common approach to sampling and testing and to deal with organisational issues. The outcome demonstrated the value of work sharing based on commonly agreed procedures.

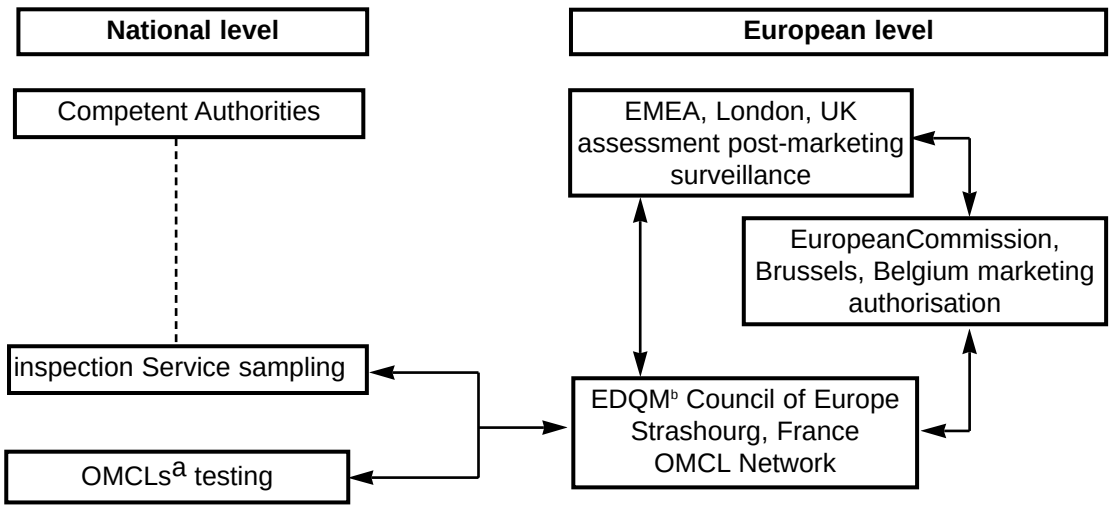
Establishment of a general procedure for sampling and testing

General procedure for sampling/testing of centrally-authorised products approved in 1997

Responsibility for monitoring the quality of medicinal products, authorised under the centralised system, rests with the CAs of the EU and the EEA . A general procedure for sampling and testing of centrally-authorised products, based on collaboration between the EMEA, the EDQM and the national authorities (see Figure 1), has been developed and was approved by the Pharmaceutical Committee in June 1997. In this procedure, the EMEA has overall responsibility and the EDQM has been given responsibility for co-ordinating the sampling and testing of the product, based on its long experience of laboratory work and organising collaborative studies in the field of pharmaceuticals.

Figure 1. Sampling and testing of centrally-authorised medicinal products in the EU and EEA

EMEA holds overall responsibility and EDQM is responsible for the procedure for sampling and testing of products



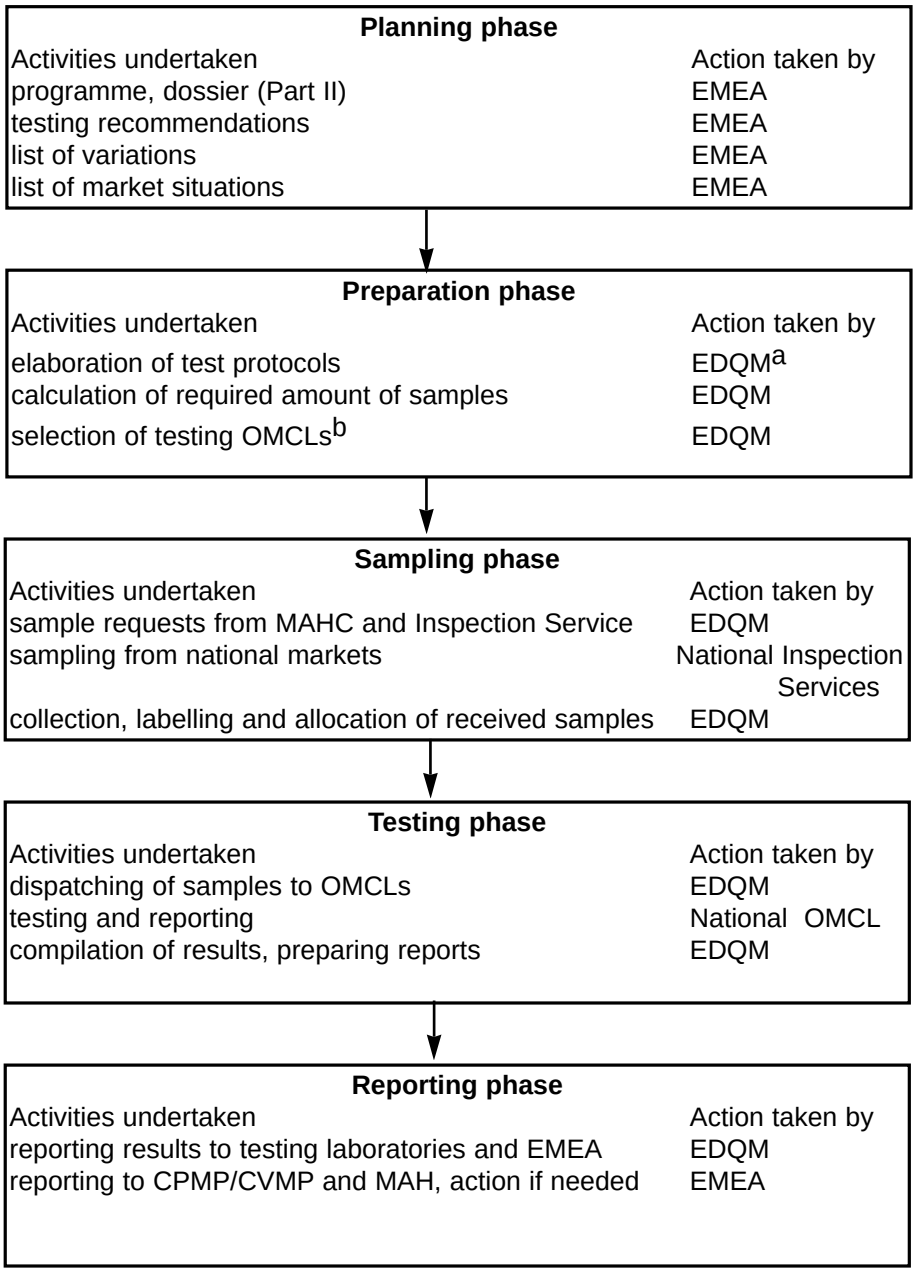
Notes
a Official Medicines Control Laboratories
b European Directorate for the Quality of Medicine

To assist in the development of the general procedure (see Figure 2) an Advisory Group of the EU/EEA OMCL Network was established to help install the procedure and to ensure continuity of the post-marketing surveillance. The Advisory Group consists of five to six representatives recruited from the pool of OMCLs within the EU/EEA OMCL Network and the EDQM Director. The EMEA and the European Commission are also represented. The Network is supported by the EDQM Secretariat (Division IV/OMCL Network). With the help of this Advisory Group, special procedures have also been developed to deal with unsatisfactory test results and emergency control of centrally-authorised products. The procedure in the case of emergency control is linked to the EMEA crisis management document.

Formation of an Advisory Group helped to develop the procedure

Figure 2. Important steps in the Post-marketing Surveillance Programme

Programme comprises five phases



Responsibility for varicus activities is indicated

Notes

a European Directorate for the Quality of Medicines
b Official Medicines Control Laboratories
c marketing authorisation holder

Based on the experience gained in the trial phase, the general procedure has been set up for the flrst routine centrally-authorised product programme for the period l999-2000, which is currently in progress.

Role and responsibilities of the EMEA in the programme

EMEA selects the medicinal products to be included in annual programme...

The choice of medicinal products to be included in the annual testing programme is made by the EMEA. The Agency then prepares the list of potential candidate products for testing in the forthcoming year and arranges the final adoption of the programme by its scientific committees (i.e. the CPMP and CVMP). All correspondence with the rapporteur/co-rapporteur (who are responsible for the evaluation of applications for marketing authorisations and who recommend testing parameters for the centrally-authorised product programme) is co-ordinated by the EMEA. The documentation requests (updated with variations) and enquiries from the marketing authorisation holders (MAHs) about the market situation of the medicinal products in the programme are also the responsibilities of the EMEA.

...and informs the CPMP/CVMP and MAH of the results

The EMEA communicates all results of the testing phase to the CPMP/CVMP and their related working parties and also to the MAH. Moreover, it gives general information on the progress and feasibility of the programme on a regular basis. Any action required due to adverse test results is to be arranged by the EMEA in close collaboration with the EDQM. The EU/EEA OMCL Network should also be included in collaboration if additional testing is required.

Role and responsibilities of the EDQM in the programme

EDQM co-ordinates the Network and sampling of products from different EU/EEA markets

The EDQM is responsible for the co-ordination of the EU/EEA OMCL Network, the organisation of a quality assurance system for OMCLs and the development and maintenance of procedures and methods related to the programme on sampling and testing of centrally-authorised products. All relevant documentation for the programme is communicated directly from the MAH to the EDQM, where it is archived. The list of available products on the EU/EEA market, received from the EMEA, is updated if necessary by the EDQM.

The EDQM is responsible for requesting reference material and specific reagents from the MAH. It also co-ordinates sampling of products from different EU/EEA markets. Selection of OMCLs to carry out the testing samples is the responsibility of the EDQM, along with the development and distribution of test protocols. After the testing phase, the EDQM compiles all the results and reports, and prepares regular updates on the progress of the programme. Meetings of the Advisory Group and annual meetings of the EU/EEA OMCL Network are arranged to discuss all issues relevant to the correct technical and scientific execution and follow-up of the centrally-authorised product programme.

Role and responsibilities of the national authorities in the programme

National authorities are responsible for sampling of centrally-authorised products from their markets

The procedure on sampling and testing has been set up to make best use of national expertise in the different MSs. One responsibility of the national authorities is sampling of centrally-authorised products from their markets, following a request by the EDQM. This is carried out by their Inspection Services. Another responsibility is the testing of the sampled products, which is their mariets performed at selected OMCLs througLout the EU/EEA OMCL Network. In the centrally-authorised product programme, the OMCLs contribute to the rationalisation by testing samples from other markets and by sharing the results with their colleagues, thus applying the subsidiarity principle governing medicines in Europe.

First routine centrally-authorised product programme on sampling and testing

First routine programme started in July 1999 and will run until 31 December 2000

The centrally-authorised product programme for 1999/2000 was endorsed by the CPMP/CVMP in June 1999. It started on 1 July 1999 and will close by the end of the year 2000. More than 30 medicinal products for human and veterinary use are on the list for testing and products fulfilling the following criteria may be tested:

- all products authorised via the centralised procedure for the past three years;
- special products identified for priority testing by the expert scientific committees of the EMEA on the basis of specific scientific issues, raised during the assessment of the application and/or post-authorisation quality problems.

For the purposes of the programme, the rapporteur and/or co-rapporteur of the application file for each medicinal product have given advice on the main test parameters in the product specifications. These are of special importance for ensuring quality and need to be tested as a post-marketing control. In the case of some biological products, where essential quality parameters cannot be analysed on the finisLed product, testing of the active substance is exceptionally included in the testing programme.

Specifications, as well as complete documentation, on relevant analytical procedures (working methods) and validation data, both for the active ingredient and finished product (mainly Parts IIC, E and F) together with other relevant documentation, are stored in a separate archive room at the EDQM. Access to these data are restricted to the persons directly involved in the programme.

Product sampling is allocated randomly to the Inspection Services, usually to three different EU MSs for each product. Climatic differences and actual marketing of the product to be sampled are considered. The sample amount is calculated based on the test methods recommended by the rapporteur/co-rapporteur team and the standard operating procedures received from the MAH. The necessary repeats commonly agreed to ascertain statistical validity of the results is another factor to be taken into account. Sets of samples are collected from the maket from a wide range of sources within the distribution chain (e.g. community pharmacies, wholesale dealers and hospitals). It is recommended that each set of samples should originate from the same batch, so that results can be related to given batch numbers and are representative of individual national markets for the benefit of the entire EU/EEA market.

Sets of samples should be from the same batch of product

The strategy of this sampling system saves resources and prevents unnecessary consumption of valuable samples. In parallel to the requests on product samples, a sufficient amount of a recently manufactured product batch is included in the testing programme. This is used as a common test sample and serves as a quality marLer when exchanging and comparing results between OMCLs. The common test sample, relevant reference material and specific reagents needed for testing are requested directly by the EDQM from the MAH. When the testing phase is initiated, all samples are dispatched from the EDQM and, along with the relevant documentation needed to carry out the actual laboratory testing, sent directly to the testing OMCLs.

MAH supplies the common test sample reference material and specific reagents required

Similar to the rotating system used by the EMEA for the selection of the rapporteur/co-rapporteur, two OMCLs per medicinal product usually perform the testing programme on behalf of the EU/EEA OMCL Network. Candidate OMCLs are selected on a rolling system from a priority list. This is mainly according to their scientific and technical expertise, their connection with the rapporteur/supervisory authority and the co-rapporteur, or previous experience with similar products. Selection is made on a voluntary basis, keeping in mind the aim of an even worklond between the control laboratories throughout the EU/EEA.

Reports are distributed to interested parties...

Individual product reports are set up by the EDQM on an ongoing basis, as soon as results from b o th testing labora to ries are av ailable . Th e rep orts are dis tribu to d to th e tes ting labora tories and the EMEA. The EU/EEA OMCL network, the MAH and the European Commission are also informed about the outcome of the testing in due course. In cases of problems (e.g. deficiency of the qu ali ty or analytic al pro cedure s) an d any em ergency si tua tion, special action will be initia ted by the EMEA. If the need arises, key issues of the programme will be communicated to all interested parties.

Conclusions

The general procedure for sampling and testing of centrally-authorised products relies on an efficient network of competent and dedicated experts, who agree to share the work and responsibilities, and offer their expertise by contributing synergistically to this programme. There are benefits for all parties in developing a common approach on post-marketing control of products authorised through the centralised procedure. The main advantages can be highlighted as follows:

Advantages to CAs and OMCLs...

• for the CAs and their OMCL(s):
- to share the workload and avoid duplication of work;
- to be able to access recent high technology and selective analytical procedures;
- to use resources and establish pools of expertise in case of emergency situations for rapid testing;

...EU/EEA, EMEA and EDQM

• for the EU/EEA, the EMEA and the EDQM:
- to save public money by pooling expertise and human resources;
- to take advantage of an already existing network of OMCLs;
- to avoid having to develop a separate system for centrally-authorised product testing; - to make best use of resources available throughout the EU/EEA OMCL Network;

...and MAH are detailed

• for the MAH:
- to cut costs by avoiding unnecessary duplication of sampling and testing;
- to limit the number of test samples and reference/reagent material required;
- to apply the defined procedure at a given time for all EU/EEA MSs through one co-ordinating body.

The networking effect of expertise serving both authorities and manufacturers is an independent tool to benefit the European patient. Work sharing based on a common approach to quality assurance will establish mutual recognition between OMCLs in the EU/EEA OMCL Network and will favour the development of centres of excellence. It is foreseeable that with the same resources available throughout the network, efficient market surveillance will devélop and lead to optimal medicinal product testing.