



London, 10 January 2008
Doc. Ref. EMEA/INS/S&T/120857/2008

Sampling and Testing of Centrally Authorised Products

Development of risk based approach for the selection of products

Objectives

The objective is to make best use of Official Medicines Control Laboratories' (OMCLs) resources at the disposal of EMEA in carrying out the annual sampling and testing programmes for centrally authorised medicinal products (CAPs).

This will be done by selecting the products to be tested each year using a risk ranking approach by developing an easily worked system that takes account of information readily at hand to rank all centrally authorised medicinal products (CAPs) according to risk factors and weightings and to base the selection of products for inclusion in annual CAP sampling and testing programmes according to the assigned risk level. For medicinal products for human use the approach will be phased into the 2009 annual CAP sampling and testing programme and fully implemented in the 2010 programme and beyond. More work is needed on veterinary medicinal products but it is hoped that a similar approach can also be implemented in the 2010 programme.

Most of the information required for risk assessment should be already held by EMEA but some input from rapporteurs, GMP inspectorates and OMCLs will be necessary. It is intended to minimise, as far as possible, subjectivity in the ranking process.

It will be necessary to remain within the existing 5 year budget plan for the CAP sampling and testing scheme, which foresees approximately 40 products to be tested each year.

At a later stage the intention is to further apply the risk-based approach to the selection of the parameters to be tested.

Introduction

The primary objective of the sampling and testing programme is to supervise the quality of CAPs placed on the market and to check their compliance with the authorised specifications as referred to in Art. 57 of Regulation (EC) 726/2004. Details of the programme are available on the EMEA website in document EMEA/INS/S&T/5291/2005.

To achieve these objectives, the Agency has set up annual programmes involving its Scientific Committees, European Directorate for Quality of Medicines and Healthcare (EDQM), the GMP inspectorates and OMCLs of the Member States, to coordinate:

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

Document EMEA/INS/S&T/5291/2005 states that in the future products might be selected for testing on a risk basis. This paper examines how this approach is to be developed.

Selection of CAPs for testing under the current scheme

CAPs are selected for testing usually three years after the product has been granted a Community marketing authorisation. Typically 40 products are tested per year. At present CAPs are only tested on one occasion unless re-testing is recommended by the scientific committees.

The selection of products to be included in each annual programme is currently based on the following criteria:

- products (including new pharmaceutical forms) authorised three years before;
- products that have been recommended for re-testing by the rapporteurs as an outcome of previous testing;
- products authorised more than three years ago but which have never been tested, usually because they were not actually marketed at the time of initial selection.

Proposal for selection of CAPs for testing using a risk based approach

To understand what risk is actually being managed, since the primary objective of the programme is already being met under the current scheme, it is necessary to reflect on the outcome of each sampling and testing exercise. Experience shows that testing reports have one or more of the following outcomes:

- The sample complies with its registered specification
- The sample does not comply with its registered specification
- Issues are identified with respect to the testing methodology relating to its suitability or its robustness

Although the desired outcome is always that the sample complies with its registered specification, the other, “adverse”, outcomes are beneficial in that they lead to appropriate actions in the interest of public health. Therefore the risk-based selection of products attempts to maximise the possibility of identifying an adverse outcome. Arguably this also makes optimal use of the OMCL resources made available to EMEA.

Risk is defined as a combination of the impact of an event occurring and the probability of that event occurring. In the context of the Sampling and Testing scheme the event would be an “adverse” testing outcome and the risk is sample selection that does not maximise the possibility of identifying such an outcome. The proposal is to identify risk factors and allocate values so that a simple risk ranking tool can be used to select the CAPs to be included in any annual programme.

This new approach would replace the ‘three years after authorisation’ criterion that has been followed to date.

Allocation of risk factors and values

Risk ranking requires the identification of risk factors and weighting of those factors. Normally, factors are either related to severity of impact or probability of occurrence and these are combined to provide a risk level. It is recognised that since all medicinal products are subject to the highest levels of assessment and are manufactured in accordance with GMP it may be inappropriate to suggest that certain products are more likely than others to result in an adverse testing outcome. It could be argued that in this context only severity of impact should be considered. A number of EMEA Working Parties and Groups with an interest in the sampling and testing scheme as well as the advisory group, consisting of representatives of the OMCL network set up to assist EMEA in its sampling and testing programmes, have been pre-consulted in order to identify possible risk factors. A large range of factors were suggested and although many of these relate in some way to probability of occurrence it has been decided to take some of these into account. For the purposes of the CAP sampling and testing scheme quantifiable data is not generally available on these factors in order to use the conventional risk ranking process where severity factors are multiplied by probability of occurrence.

It is proposed therefore to assign weightings to the factors identified and merely add these to the impact factors.

EMEA has given particular consideration to experience with other sampling and testing schemes not involving CAPs in which similar approaches have been trialled. Experience here has shown that the risk factors evaluated should be small in number and the information needed for the risk assessment should be readily accessible. For this reason, and also to promote common approaches, many of the factors chosen are taken from the risk factors used in those trials.

The risk factors therefore comprise of factors related to severity of impact (i), weighting factors (w) plus those weightings assigned by the assessors during evaluation, arising from a more detailed insight into the product and/or process (r).

Selection of products and contribution from Rapporteurs, Inspectors and OMCLs

The selection of products for inclusion in any annual programme will be those ranked highest on the list at the time the products are selected, which is usually done in preceding year:

$$\text{Risk level} = i \times (w + r)$$

EMEA proposes that the selection of products for inclusion in any annual programme based on risk ranking should at most make up 90% of the programme. 10% will be allocated at random.

Products will be included in any annual programme when specifically requested by the rapporteur. In addition although the list of risk factors identified includes any history of GMP non-compliance of any of the authorised manufacturing sites, Inspectors may propose in their inspection reports that a CAP be included in the next annual sampling and testing programme where in their assessment of conditions at the relevant manufacturing site such action would be appropriate.

OMCLs and EDQM may suggest inclusion of a product in any annual programme as a recommendation in testing reports.

The relevant Scientific Committees will continue to adopt the list of products to be tested.

Finally where possible, when the annual sampling schedule is developed, parallel distributed product will be targeted since these are more likely to have undergone more handling within the distribution chain than the original product.

Filtering

It will be necessary to conduct a filtering step to avoid the same products being tested in consecutive years. Products tested in the previous year will be filtered out unless specifically requested for re-inclusion. Products subject to "Official Control Authority Batch Release" (OCABR) will also filtered out as is current practice.

Next Steps

As CHMP has agreed to the basic approach outlined above, EMEA will develop the weightings in consultation with the CAP advisory group in time to implement the approach in the 2010 sampling and testing programme. In future years the rankings will be continuously updated by Inspections Sector at EMEA as new information is received. The scheme will be fine-tuned in line with experience and the report to the Committee on the 2010 programme will draw particular attention to the experience gained with a view to continuation, if deemed successful.

As the list of products for testing in the 2009 programme needed to be adopted by the Committees early in 2008 to enable the necessary information to be obtained from marketing authorisation holders and for EDQM to organise the logistics for sampling and testing with national GMP inspectorates and OMCLs, it is not possible to complete the detailed work necessary to conduct a full risk-based

programme for 2009. However in order to move towards making better use of resources as soon as possible, EMEA has used the risk ranking tool developed in the OMCL pilot for non-centrally authorised products as a partial implementation exercise. Products earmarked, according to the existing criterion for testing in 2009, together with those products identified for retesting as a follow up from previous sampling and testing programmes, will be scored in order to prioritise the 2009 programme along risk-based principles. This could mean that some products (a maximum of 25% of the products in question is proposed) authorised in 2006 will not be included in the 2009 programme because the testing of other products with a higher risk score will be given priority.

With regard to veterinary medicinal products, CVMP expressed concern that the factors for veterinary products would be different from those affecting products for human use and that a common approach may favour inclusion of products for human use over some veterinary products in any annual sampling plan. EMEA is therefore considering the development of specific factors for veterinary products and an approach that guarantees that an appropriate proportion of veterinary products are tested each year. In the meantime the existing approach is maintained for veterinary products for the 2009 sampling and testing exercise.