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The advantages and benefits of the CAP surveillance project

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The advantages and benefits of the CAP Surveillance Project

Introduction

The Centrally Authorised Product (CAP) sampling and testing programme is a risk-based, public and animal health protection surveillance programme operating in the EU/EEA. It is under the auspices of the European Medicines Agency (EMA) and it has been in operation since 1999.

Its main objective is to check the quality and the compliance status of CAP products on the EU/EEA market against their authorised specifications. The suitability of pharmaceutical company test methods is also assessed as part of this programme.

At a day-to-day level, the programme is coordinated by the European Directorate for the Quality of Medicines & Health Care (EDQM), with support from the CAP Advisory Group at the OMCL Network (AdG-CAP). Sampling activities are usually performed by the Inspectorates at National Competent Authorities (NCAs) but may sometimes also be performed by OMCLs. Testing is performed by OMCLs right across the OMCL Network.

Key features of the programme are as follows:

- This programme is an independent and highly co-ordinated market surveillance programme, focussed on centrally authorised medicinal products available on the EU/EEA markets.
- It is designed to make maximum use of the analytical expertise and the availability of laboratory capacity across the OMCL Network.
- It promotes the principle of work-sharing between Member States - this not only applies to laboratory testing activities, but also to product sampling.
- A formalised risk assessment approach is applied during the development of the annual surveillance plans. This work is performed at the EMA, and takes into account the input of the CAP Advisory Group at the OMCL Network when developing the annual surveillance plans, as well as that from the EDQM.
- The programme is the only coordinated market surveillance programme in the EU/EEA that includes biotech and other biological products for both human and veterinary use, and testing on a prominent number of innovative expensive medicines, involving sophisticated analytical methods.
- It is currently one of the rare surveillance programmes which includes, on a regular basis, testing on Active Pharmaceutical Ingredients (APIs). In this regard, it supports the implementation of different new provisions of the Falsified Medicines Directive (FMD), 2011/62/EC.
- This programme also facilitates 'ad-hoc' testing activities recommended by the EMA's Scientific Committees (e.g. CHMP, CVMP) which may request the testing of a centrally authorised product in order to obtain rapid analytical results for one or several parameters.

As the programme involves product sampling across all member states of the EU/EEA, and as all EU/EEA Official Control Laboratories (OMCLs) of the Network are involved in the testing activities, it is an excellent example of work-sharing working in practice and in avoiding duplicative testing. This allows the best use to be made of the available laboratory resources and capacity across the Network.

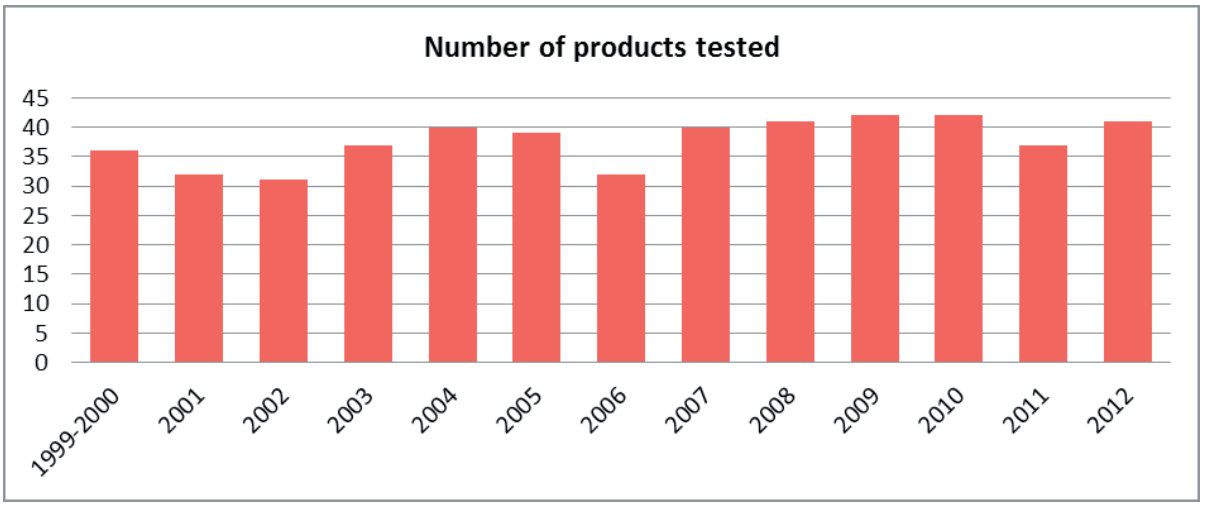
Protection of Public and Animal Health

The programme allows the compliance status of CAP products already placed on the market to be evaluated, following batch distribution activities along the supply chain. Thus, not only does it provide a measure of the adequacy of the manufacturing process associated with a product, it also provides a means of measuring any potential effects on the quality of the product via distribution and storage activities.

This adds value in terms of protection of public and animal health, because the programme is designed to sample products from as close to the patient and user as possible. This distinguishes the CAP Programme from the Official Control Authority Batch Release (OCABR) programme, where, in the latter case, the quality of specific biological products is assessed before their release to the market.

Findings of the CAP Surveillance Programme

By 2013, more than 1700 batches of CAPs were subjected to independent surveillance testing via this programme. This represents an appreciable amount of surveillance work.

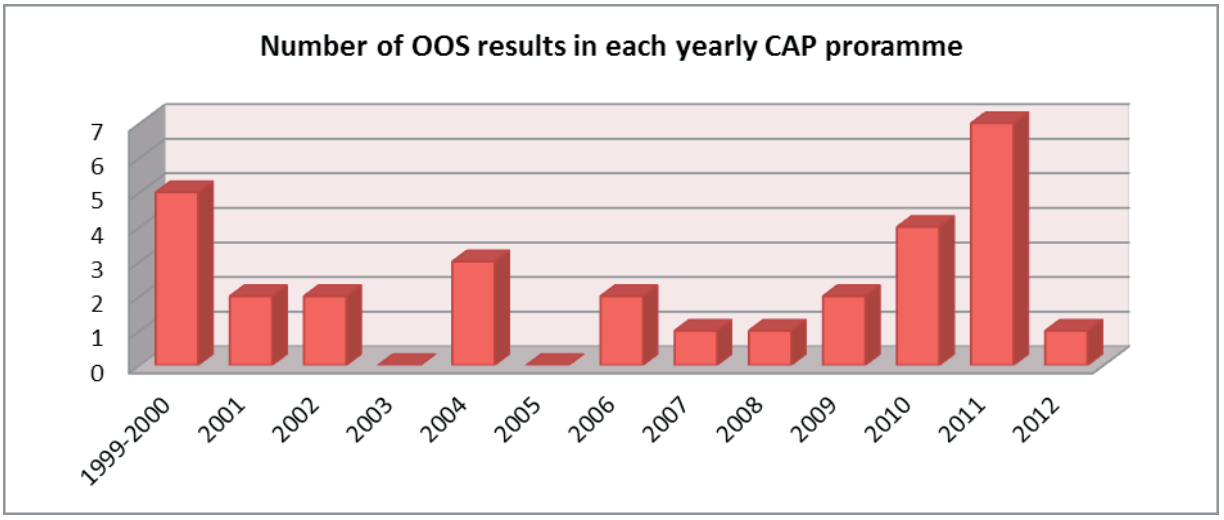


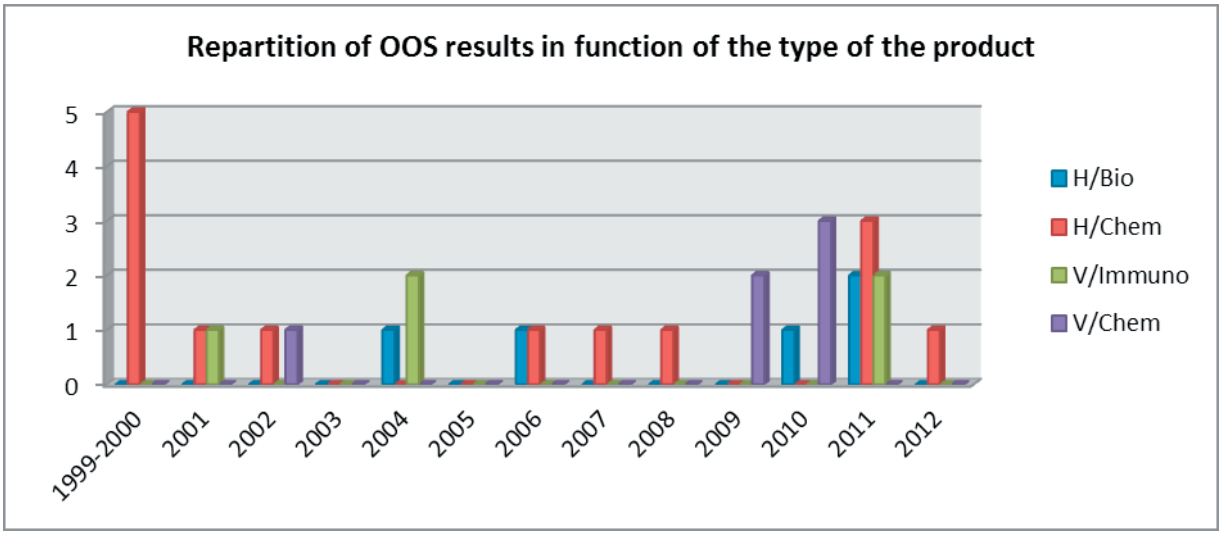
Over the years, the programme has demonstrated that the CAP products on the EU/EEA market are of a consistently high quality. This is shown by the relatively low number of confirmed out-of-specification results that have been obtained, (with an average 2 OOS findings per year). This is positive and is reflective of the outputs of other surveillance programmes of the OMCL Network, such as that for MRP and DCP products.

The majority of the CAP products tested in this programme have been found to comply with their authorised specifications. The relatively low number of out-of-specification test results should not be considered as indications of an ineffective sampling strategy or of an ineffective surveillance programme. In contrast, the wealth of within-specification test results obtained to date provides direct and independent evidence on the quality and safety of these products across the EU/EEA. This is important for patients and the public in general.

This programme has demonstrated that it is also capable of detecting sub-standard medicinal products on the marketplace, and that its outputs can directly be translated into effective risk-mitigation for patients and animals. This was demonstrated by the recall of one batch of a CAP product in 2006, following the finding of a serious OOS issue with that batch during surveillance testing. In 2010, a batch of an active substance was found to be OOS and this also resulted in regulatory action designed to protect patients.

The programme adds value in another way also. It provides direct evidence to confirm the inspection and marketing authorisation assessment work which takes place at NCAs across the EU/EEA, in relation to centrally authorised products and their sites of manufacture and distribution.





Evaluation of Analytical Test Methods

Another major feature of the programme is that it allows a detailed evaluation to be performed on the analytical test methods that the product manufactures use to test their products. When a CAP product is selected for testing, the OMCLs not only assess the quality of the batch sampled against its authorised specification, they also assess the appropriateness and robustness of the test methods used by the manufacturer.

Where deficiencies in company analytical methods are identified through the testing work, these are formally documented and reported, and work is done to ensure that those issues are corrected. This has resulted in many analytical method improvements being made to company test methods (and to their related Marketing Authorisation dossiers) since the inception of the programme.

As a result, this surveillance programme contributes significantly to the controls that are in place to assure the quality of the CAP medicines on the EU/EEA market.

The Value in Maintaining OMCL Testing Competencies

This programme ensures that OMCLs maintain their competencies in running innovative and sophisticated analytical methods and related items of equipment. This is highly valuable, in many ways.

For example:

- In crisis situations, when governments and Competent Authorities need to independently check the quality of certain products and active substances on the market, there is a network of OMCLs in a position to do such work.
- In the field of biosimilars, where it is necessary to identify differences and comparisons between biological products, the CAP surveillance programme ensures that competencies in this area are maintained. This is of paramount importance in this particular field, considering the expected increase in the number of new biosimilars that are expected to arrive to the market and the complexity of the analytical methods involved.
- In addition, as the threats posed by falsified APIs and falsified medicines continue to increase, it is vital that governments and Competent Authorities have access to independent testing facilities with sophisticated and highly sensitive testing equipment and methods, to support investigations and Enforcement work. The CAP surveillance programme is important as it ensures that such items of equipment and techniques are readily available, and that the necessary analytical expertise is also available.
- Also in this context, API testing in the CAP surveillance programme is increasing in its importance (and relevance), especially with the introduction of generic CAP products. These often include active ingredients from different sources, and API surveillance testing allows additional data to be obtained on the quality of those

APIs over and above what is in the dossier for the product. This is of value, because it represents a means of monitoring the quality of those APIs. Also, in the event that an unauthorised API has been used in the manufacture of a CAP medicinal product, this aspect of the surveillance programme provides a means of detecting this.

- The programme also provides a means of responding to emergency test requests from EMA's Scientific Committees (e.g. CHMP, CVMP), in order to obtain rapid analytical results on specific centrally authorised products.

Overall Benefits

In terms of the benefits for all the parties involved, the main advantages can be highlighted as follows:

• *For Patients and Users of CAP products*:
- the programme provides independent assurance in the quality and the compliance status of the CAP products on the EU/EEA market;

• *For the NCAs and their OMCL(s):*
- the programme provides a means of sharing surveillance workload and avoiding duplication of effort;
- It provides access to novel high technology and selective analytical procedures;
- It allows for an efficient use of resources and for the establishment of pools of expertise in the case of emergency situations requiring rapid testing;

• *For the EU/EEA, the EMA and the EDQM:*
- the programme facilitates the saving of public money, by pooling expertise, laboratory capacity and human resources throughout the EU/EEA OMCL Network;
- it allows NCAs to take advantage of an already existing network of OMCLs;
- it helps avoid having to develop a separate system for centrally-authorised product testing;

• *For MAHs:*
- the programme reduces costs by avoiding the unnecessary duplication of regulatory sampling and testing;
- it limits the number of test samples and reference/reagent material that are required;
- it provides for one defined surveillance procedure applicable to all EU/EEA MSs through one co-ordinating body;

• *For the CHMP/CVMP:*
- the programme facilitates the best use of laboratory resources and expertise in the case of emergency situations for requiring testing;
- it allows for the rapid testing of CAP products when quality defect issues arise.

The networking aspect of the programme among OMCLs helps to facilitate and promote work-sharing activities based on a common approach to quality management. This helps establish mutual recognition processes between OMCLs in the EU/EEA OMCL Network and it supports the development of centres of expertise.

Future Considerations

Looking to the future, it is important that the competencies and infrastructure that are required to provide a comprehensive, independent and technologically advanced surveillance programme, based on the principles of work-sharing, quality risk management and making best use of available laboratory resources and capacity, be maintained.

It is recognised that key stakeholders, such as NCAs, the EMA, the Heads of Medicines Agencies and others, need to be continually assured in the usefulness of such surveillance programmes and of the benefits that they bring. This paper sets out some of the key features and benefits to patient and animal well-being of the CAP surveillance programme.

Like many surveillance programmes, it requires resources and funding to operate and to develop, but these are offset by the level of public and animal health protection that this programme provides.

There are also opportunities for further developing the programme. For example, surveillance capabilities relating to Immunological Veterinary Medicinal Products (IVMPs) and radiopharmaceuticals are generally lower than for other product types, as there is currently limited laboratory capacity across the Network for such work. It is recommended that these areas be reviewed with key stakeholder groups so that solutions may be found.

It is important to note that the CAP programme has been under formal continuous improvement initiatives since its initial development. For example, in 2010, the programme was redesigned to make annual sampling and testing activities more formally based on risk. This was a very useful initiative. It also facilitated the inclusion of previously tested products in ongoing annual plans, so that additional surveillance data may be generated on those products. The programme also allows for the random selection of products. (These aspects of the programme are useful as they give a clear signal to manufacturers that the testing of a CAP can happen at any time, and not only once during the life-cycle of the product.)

It is the intention of the EU/EEA OMCL Network to bring this Position Paper to the attention of the decision makers in the NCAs to underline the importance of the OMCLs' contribution to the success of the CAP surveillance programme.