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API Surveillance: Position Paper for OMCLs

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API SURVEILLANCE

POSITION PAPER FOR OMCLs

1. SCOPE

This position paper exposes some of the general risk issues with APIs and the need for API surveillance.

The purpose is to provide useful discussion points for OMCLs on the manner in which API surveillance may be performed, on the challenges presented by it, and on the different ways that surveillance in this area may be achieved.

It is intended to be of use to OMCLs and their associated inspectors who may be involved in designing surveillance programmes and in performing material sampling.

2. INTRODUCTION

General risk issues with APIs

The worldwide threat of falsified medicinal products has indeed rapidly increased during the past decades. By far, most of these falsifications are reaching patients in the western world via the Internet. But infiltration of falsified medicines into the legal supply chain in Europe is also rapidly increasing though it still is a relatively rare phenomenon. A related problem is the falsification of Active Pharmaceutical Ingredients (APIs). Any form of tampering or falsification that will affect the quality of an API constitutes a direct threat to the health of patients. A series of health scares involving large numbers of casualties happened when pharmaceutical ingredients intentionally were contaminated with large quantities of a relatively cheap and toxic substance that escaped detection in routine analytical testing. The latter has been the case with heparin and glycerin and these events have increased the awareness that API falsification is an important health issue.

Need for API surveillances

The marketing authorisation holder (MAH) has the key responsibility to ensure that not only the API but also the intermediates and excipients have the approved quality before formulation of the finished product. Several systems have been set up to safeguard the quality and safety of medicinal products; however criminal groups have bypassed these regulatory requirements and systems.

The 2011-2012 Annual Report of the HMA Strategy expresses that the effects of globalisation have created new needs for quality assurance of medicines and APIs sourced from one or more third countries, as well as the need for robust measures against falsified and counterfeit medicines. Also, Directive 2001/83/EC has been updated and many of its provisions in relation to falsified medicines and active substances are coming into effect on Jan 1st 2013. These will strengthen the EU systems to prevent unsafe, inefficient and low quality products infiltrating the legal supply chain. The changes include strengthened requirements for medicinal products for human use such as controls and inspections, record-keeping for wholesale distributors, on-line sale to the public, and the

introduction of an obligation to put authenticity feature on the outer packaging. It also includes new controls over imported APIs together with a clear legal basis to audit API sites, in the EEA and in 3rd countries. The OMCL Network can support and contribute to these initiatives by increasing the amount and type of surveillance work that is performed on APIs. These changes present opportunities for more coordinated and transparent approaches to API surveillance across the OMCL Network and their associated inspectorates.

The importance of API surveillance has been acknowledged by the OMCL Network. The OMCL Network Counterfeit paper ("OMCL Network Support for the Implementation of the CoE MEDICRIME Convention", PA/PH/OMCL (09) 87 3R) that was adopted at the 2010 Annual Meeting, for example, made a clear recommendation for increased API surveillance, as did the "Heparin Learnings" discussion paper (PA/PH/OMCL (11) 64 R) agreed at the 2011 Annual Meeting.

Several initiatives have already been launched by the Network and published over the last 3 years such as:

- The Clopidogrel CAP generic testing project in 2011 also involving APIs;
- Sweden's Simvastatin Work 2010 using LC-MS-TOF;
- France's work on APIs as part of their generics surveys of 2009-2010;
- Denmark's API project 2009-2010.

Several more initiatives involving API testing occur at national level, which not necessarily are reported back to the Network members as a recently performed questionnaire revealed. In this connection some out of specification results could be observed.

This was also the conclusion on the CAP/MRP/DCP meeting in Lisbon in 2011, when the participants were confronted with the low level of data input into the MRP/DCP Database on APIs. However, as it was pointed out, the OMCL Network does not have an established reporting system on "national controls". One possibility is to explore whether the MRP/DCP database could be expanded to include both proposed national controls and their results (from national surveys). However, the current database may not be suited for reporting data on documentation or drum label controls nor highlight the use of or development of other analytical methods than routine methods used for the API surveillance. Therefore, the need to ensure sufficient and effective communication between the OMCLs and also their stakeholders must be addressed.

3. POTENTIAL DESIGNS FOR API SURVEILLANCE PROGRAMMES

Different designs for API surveillance programmes may be run, so different factors may have to be defined: a) the selection of the APIs, b) the type of surveillance, c) the testing parameters, and finally d) the sampling.

a) Selection of APIs:

The selection of APIs can be based on several different risk issues:

- APIs known to be widely used in generic, blockbuster medicines;

- APIs with OOS results obtained on previous batches or on associated finished products;
- APIs that are prone to counterfeiting;
- APIs that may have known genotoxic or other high risk impurities;
- APIs that are the subject of a new or updated Ph. Eur. monograph;
- APIs that are associated with problematic polymorphic forms.
- In addition, APIs may be selected for surveillance when their related finished products are being tested, or when an inspection is taking place at the API manufacturer;
- APIs may also be chosen for surveillance as a result of issues identified during assessment, pharmaceutical monitoring, inspections, pharmacovigilance monitoring or supply chain issues;
- APIs associated with production processes where the starting material in those processes are very "late-stage" materials.

b) Type of surveillance programmes:

Different approaches may be used when designing an API surveillance programme. These may include routine analysis type and authenticity-related testing programmes:

Routine analysis type programmes

Control of the compliance status/quality of the API samples:

- Control of APIs according to a Ph. Eur. monograph;
- Control of APIs against the MAH's test methods;
- Control of APIs using test methods and screening methods developed by OMCLs themselves (in order to verify a specific parameter for example).

Authenticity-related testing programmes

This includes the determination of the authenticity of the API samples, using for example "Fingerprinting" techniques. In addition, samples of the same API from different sources may be tested to determine differences in their impurity profiles.

In each of the above programmes, a number of different APIs used by one finished product manufacturer may be tested. Also, chemometrics may be used to assess the test results obtained on APIs.

c) Testing parameters:

The testing parameters will of course be dependent on the type of surveillance that is performed. But two different approaches can be applied:

Analytical approach

In Routine analysis type programmes, the main parameters usually applied will be identity, assay, related substances, residual solvents, and water content.

However, alternative or additional and more specific techniques may be applied, especially when determining the authenticity of a sample. These may include:

- For identification tests, Raman or NIR spectrometry;
- For characterisation tests, (e.g. confirmation of structure, information regarding potential isomerism, identification of polymorphic forms, information on particle size, etc.): NMR, X-ray diffraction, mass spectroscopy, thermal analysis, etc.;
- For determination of purity (e.g. impurities, trace metals): HPLC/MS, GC/MS, ICP/MS, etc.

Also, these testing methods should be considered to facilitate the detection of falsified or low quality APIs.

Documentation approach

In addition to analytical testing, several other checks can be considered as test attributes that can be designed into API surveillance programmes. These may include:

- Checks on API drum labels during inspections at manufacturers, bulk manufacturers, wholesalers/distributors, etc., can give valuable information about the supply chain;
- Reviewing documents for signs of falsification or inconsistencies (such as Certificates of Analysis (CoA);
- Reviewing any Certificates of Suitability of the European Pharmacopeia (CEP) to determine whether they are valid;
- Reviewing the date and results of the last regulatory audit performed at the API manufacturer.

d) Sampling design:

The sampling of APIs may be performed at a number of different locations in the supply chain, such as at the API manufacturer, at any wholesalers/distributors involved, at the intermediate and finished product manufacturers, etc. When sampling an API, specific pre-determined batches may be sampled, or a list of batches produced in the last year can be obtained and samples can be taken from those batches, etc. The batch of an API which was used in a particular finished product batch can also be targeted for sampling.

Consideration should be given to sampling APIs manufactured in 3rd countries at those manufacturers and at any related wholesalers/distributors, as well as within the EEA. If it is difficult to be certain that an API batch is intended for the European market, then it may be necessary to collect samples at the bulk product manufacturer or later in the production of the finished medicinal product.

In some countries, there can be difficulties in securing the right to perform the sampling but it is recommended here that efforts should be made to overcome any such issues.

The logistics of sampling also need to be considered, such as the need for secure sampling containers and bags, and the resolution of any customs issues or import/export license issues when crossing borders with samples.

In addition, all sampling should be performed with care in relation to moisture ingress and temperature effects. Appropriately sealed containers and temperature data loggers may be required.

4. API SURVEILLANCE WORK-SHARING AND COMMUNICATION ACROSS THE OMCL NETWORK

Work-sharing in relation to API surveillance programmes across the OMCL Network on MRP/DCP products as well as on National products may be effectively used in many cases:

- to avoid duplicate testing;
- to share samples and test results using existing communication tools (e.g. the Extranet, the MRP/DCP Database etc.);
- to coordinate material sampling activities by Inspectorates so that samples may be obtained during foreign inspections;
- to facilitate performing proactive surveillance work on APIs from new sources when shortages in an API has led to significant drug product shortages (as in the case with heparin and also isoniazid, for treatment of TB);
- to share reference substances (as in the case of heparin);
- to make use of fingerprinting resources in some countries.

5. RECOMMENDED STRATEGIES FOR THE FUTURE

Short-term actions to be undertaken:

- All OMCLs should have API surveillance work as a formal part of their annual work programmes.
- A variety of different surveillance programme designs should be used in the Network in accordance with the concepts presented above, such as testing for compliance checking, testing for authenticity purposes, etc. As part of this, one MSS study focussed entirely on API testing should be developed annually, and different study designs can be explored as these studies progress.
- OMCLs should discuss and implement sampling strategies with their related Inspectorates so that the different sampling strategies discussed in this paper can be considered and adopted, where feasible. In this regard, increased efforts should be made to ensure that APIs are sampled both within the outside of the EEA, at API manufacturers, wholesalers/distributors, intermediate medicinal product manufacturers, and finished medicinal product manufacturers. This will help ensure that APIs are sampled at various important points of the supply chain.
- Appropriate sampling bags and containers should be obtained and used when sampling APIs to ensure that the quality and traceability of the API during transit and storage are not compromised.

- A survey should be performed across the OMCL Network to collect data on the current level and methods of API surveillance that are currently in place. This will allow the Network to form a benchmark as to where it is in this area, and it may bring new ideas forward for designing API surveillance programmes.

- Establish a close collaboration with the Inspectors' Working group at EMA (IWG) to better link planned inspections with potential OMCL surveillance activities.

- Develop a communication platform (e.g. a modified version of the MRP/DCP database) to better share the results from all API testing work.

- Increase the focus on promoting analytical research and related activities within the OMCL Network, as well as with external groups such as universities with specific analytical expertise, to ensure the ability to detect and characterise substances that may be difficult to detect or characterise during routine analysis work.

- Encourage (poster) presentations at key meetings of the OMCL Network to share knowledge and encourage research into new technologies, chemometrics, fingerprinting, etc.

Longer-term actions to be undertaken:

- An optimised risk assessment (RA) tool for the selection of APIs for surveillance testing should be developed following the outcomes of the HMA WGPT pilot programme.

- Define centres of expertise (if needed) beforehand for analytical test methods that are not usually part of routine surveillance work, Set up a coordinated and risk-based testing plan for APIs within the Network.