

# OMCL Network of the Council of Europe GENERAL DOCUMENT

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### API Surveillance: Position Paper for OMCLs

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## **API SURVEILLANCE IN PUBLIC HEALTH PROTECTION – BENEFITS AND PRACTICALITIES**

### **POSITION PAPER FOR OMCLs**

#### **1. SCOPE**

This position paper discusses some of the general risk issues with APIs and the strategic importance of risk-based API surveillance for the protection of public and animal health. Its purpose is to provide useful discussion points for OMCLs on the manner in which risk-based 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 that this paper will be of use to OMCLs and their associated inspectors who may be involved in designing surveillance programs and in performing material sampling. OMCLs are strongly encouraged to carry out surveillance testing on APIs, and to discuss the contents of this paper with their inspector colleagues, because cooperative work in this area is especially important, given the challenges that may arise when attempting to obtain samples of APIs for testing.

#### **2. INTRODUCTION**

##### *General risk issues with APIs*

The worldwide threat of falsified or substandard 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. In Europe, infiltration of falsified or substandard medicines into the legal supply chain is also increasing. 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.

Apart from falsification issues, significant GMP non-compliance issues continue to be identified via inspection activities at certain API manufacturing sites (including in the supply chain of APIs), and these have the potential to pose a threat to the quality of the related medicinal products and the safety of patients.

##### *Need for API surveillance*

Medicines manufacturers have a responsibility to ensure that the APIs they use are of the required quality before formulation of the finished medicinal products. Several systems have been set up to safeguard the quality and safety of medicinal products; however criminal groups have on occasion by-passed these systems, and independent surveillance activities continue to be important to detect such instances. The aforementioned GMP non-compliance issues that are identified every year at API sites

also indicate the value in the independent surveillance testing of APIs. In addition, certain important tests are often only carried out on APIs – they are usually not performed on the finished medicinal products. These include impurity tests, which are designed to detect the presence and levels of potentially harmful impurities and related substances, as well as API-specific tests such as particle size, optical rotation, residue on ignition, and others. Thus, there is a definite need for surveillance testing of APIs in order to determine their quality with respect to these attributes, and to contribute towards the protection of public and animal health by detecting sub-standard APIs.

The main EU medicines directive, No. 2001/83/EC, has been updated in recent years and many of its recent provisions in relation to falsified medicines and active substances came into effect starting in 2013. These helped strengthen the EU systems that are in place to prevent falsified and substandard APIs and medicinal products infiltrating the legal supply chain. The changes included strengthened the requirements for medicinal products for human use that relate to controls and inspections, record-keeping for wholesale distributors, on-line sale to the public, and the introduction of an obligation to put safety features on the outer packaging of certain medicinal products. They also included new requirements over imported APIs together with a clear legal basis to inspect API sites both within the EEA and in 3<sup>rd</sup> countries. The HMA in its “EU Medicines Agencies Network Strategy to 2020 - Heads of Medicines Agencies (HMA) Multi-annual Work Plan” document indicated that the quality and the safety of APIs should be ensured by supporting and encouraging the use of work-sharing mechanism.

The OMCL Network can support and contribute to these initiatives by increasing the amount and type of surveillance work that is performed on APIs. There are also opportunities for increased and more coordinated and transparent approaches to API surveillance across the OMCL Network and their associated inspectorates.

The importance of API surveillance has also been acknowledged by the OMCL Network. The OMCL Network Counterfeit paper (titled “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. An OMCL Working Group dedicated to surveillance activities on APIs was established in 2011. The key task of that Working Group is to develop strategies and programmes for the OMCL Network that will lead to increased levels of risk-based API surveillance testing across the network. This will support the efforts of the European Health Authorities in ensuring the quality and safety of APIs on the European market into the future.

Several other initiatives have also been undertaken by the OMCL Network in this area. For example, the surveillance programme that is dedicated to Centrally Authorised Products (CAP) was expanded to include APIs. Market surveillance studies involving fingerprinted APIs have also been set up under the auspices of the API Working Group. Furthermore, APIs are now also tested as part of surveys on generic medicinal products, and the database supporting the MRP/DCP surveillance programme has been modified to capture surveillance activities on APIs. This allows the sharing of surveillance plans and test results on APIs between OMCLs and member states - each OMCL can now upload its proposed national controls on APIs and their results from such testing. This helps not only to ensure effective communication between the OMCLs and with their stakeholders, it helps reduce duplicative testing.

Given these and other important initiatives, OMCLs are strongly encouraged to ensure that API surveillance testing is part of their annual work activities and, in this regard, they are encouraged to devote a defined proportion of their annual work programmes to the testing of APIs.

### 3. POTENTIAL DESIGNS FOR API SURVEILLANCE PROGRAMS

Different designs for API surveillance programs may be used, relating to: a) the selection of the APIs, b) the type of surveillance work to be performed, 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 and /or blockbuster medicines;
- APIs with OOS results obtained on previous batches or on associated finished products;
- APIs that are prone to falsification;
- APIs that may have known genotoxic or other high risk impurities;
- APIs that are the subject of a new or updated Ph. Eur. monographs;
- APIs that are associated with problematic polymorphic forms;
- APIs that are at risk of having contaminants or cross-contaminants as a result of poor manufacturing controls. An example here would be the first API batch produced after cleaning of equipment or the first batch at the start of a production campaign. Another example might relate to the use of recovered solvents in the API manufacturing process, where the solvent recovery and purification process may not be fit for purpose and the solvent may lead to contaminants in the API;
- APIs that are used at the finished dosage form manufacturing site covering the entire supply chain of the API;
- APIs at finished dosage form manufacturing site after a regulatory variation of the dossier related to API sources;
- 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 dossier assessment, (e.g. where the assessor has a concern with regard to the potential presence of harmful impurities or related substances as a result of the process chemistry or the manufacturing method that is used);
- APIs may also be chosen for surveillance as a result of issues identified during pharmaceutical monitoring, inspections, pharmacovigilance monitoring or regulation of the supply chain;
- APIs for which their starting materials involved in the API manufacturing processes are very “late-stage” materials, meaning that the main structural elements of the API molecule or moiety are already in place by the time GMP starts to be applied in the API manufacturing process.
- APIs that are available in various grades, such as different particle size profiles, different levels of purity, as well as APIs that are destined for use in different kinds of products besides medicines, etc. (This presents potential risk of mix-up during material management activities and during medicinal product production.)

### b) Type of surveillance work to be performed:

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

#### *Routine analysis type programs*

These are designed to determine the compliance status and the quality of the API samples. They can involve:

- The control of APIs according to a Ph. Eur. monograph;
- The control of APIs against the MAH's (Marketing Authorisation Holder) test methods;
- The control of APIs using test methods developed by OMCLs themselves (in order to verify a specific parameter, for example). This might involve using OMCL screening test methods for potentially harmful impurities or contaminants that may be present in API samples, including compounds present at trace levels.)

#### *Authenticity-related testing programs*

These are designed to help determine the authenticity of the API samples, which may be from different sources. They may use, for example, "Fingerprinting" techniques where a comparison of impurity profiles is performed between the sample under test and a sample whose authenticity is known.

In each of the above programs, a number of different APIs (batches or sources) used by one finished product manufacturer may also be tested. Also, chemometric techniques provide a useful means of evaluating test data on APIs of different sources.

### c) Testing parameters:

The testing parameters will of course be dependent on the type of surveillance that is performed, but in general two different approaches can be applied:

#### *Analytical approach*

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

However, alternative or additional and more specific techniques may be applied, especially when the analysis is intended to help determine the authenticity of a sample. These may include:

- For identification/authenticity tests, IR, 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 spectrometry, thermal analysis, particle size testing, etc.;
- For determination of purity (e.g. related substances, elemental impurities, genotoxic impurities): HPLC/MS, GC/MS, ICP/MS, etc.

The above 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 programs or when sampling for surveillance testing is being performed during GMP inspections. These may include:

- Checks on API drum labels during inspections at API manufacturers, medicinal product manufacturers, API distributors, etc., can give valuable information about the supply chain;
- Reviewing documents related to the API samples for signs of falsification or inconsistencies (such as Certificates of Analysis (CoA), Delivery Notes, Invoices);
- Reviewing any Certificates of Suitability of the European Pharmacopoeia (CEP) to determine whether they are valid;
- Reviewing the date and results of the last regulatory inspection performed at the API manufacturer.
- Reviewing information regarding any reference standard materials that may be obtained from the manufacturer for the purposes of API surveillance testing at the OMCL, i.e. whether the labelling of the standards is in line with any certificates of analysis for those standards, whether there are any unusual aspects to the appearance or labelling / packaging of the standards that may be important, how the standards were qualified by the manufacturer, if applicable. (Note that some of these checks can pertain more to GMP inspection than to surveillance work and the OMCL should work with its Inspectorate in relation to those checks.)

#### 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 API distributors that may be part of the supply chain, at the intermediate and finished product manufacturers, etc. When sampling an API, specific batches may be selected which may be considered more at risk of having quality problems than other batches. These may include API batches which were associated with serious GMP deviations, laboratory investigations, or complex change controls. The list of API batches produced at the API manufacturer within a certain time period can be obtained and samples can be taken from those batches, if available, etc. The oldest API batches in stock may also be sampled. In addition, the batch of an API which was used in a particular finished product batch may also be targeted for sampling.

Consideration should be given to sampling APIs manufactured in 3<sup>rd</sup> 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, temperature effects, and potential routes of contamination. Appropriately sealed containers and temperature data loggers may be required, as well as appropriate sampling tools (e.g. to avoid metallic contamination of the sample when the “Heavy metal” test is to be performed). It may be appropriate for the OMCL staff member not to perform the actual physical sampling of the material themselves, but instead to witness a trained staff member of the company concerned doing the sampling.

Depending on the specific national arrangements, it can be important for the OMCL to agree sampling activities with their respective Inspectorate.

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

Work-sharing in relation to API surveillance programs across the OMCL Network on MRP/DCP products as well as on nationally authorised 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 API/MRP/DCP Database etc.);
- to coordinate material sampling activities by Inspectorates so that samples may be obtained during foreign inspections. See Section 5 below for a practical example of this (Heparin sampling in China);
- to facilitate performing proactive surveillance work on APIs from new sources when shortages in an API have led to significant drug product shortages (as in the case with heparin and also isoniazid);
- to share reference substances (as in the case of heparin);
- to make use of fingerprinting and chemometric resources in some countries.

#### **5. RECOMMENDED STRATEGIES FOR IMPROVED API SURVEILLANCE**

- Where possible, all OMCLs should strongly encourage API surveillance work as a formal part of their annual work programs. OMCLs are encouraged to liaise with their API Inspector colleagues to determine API testing plans and strategies. The inspectors may be in a position to advise their OMCL colleagues about API or medicinal product manufacturing sites that have specific risk issues associated with them (e.g. poor controls in relation to cross contamination seen at the last GMP inspection) and this may help select which sites to sample from and which APIs to select. In addition, the risk assessment approach developed under the auspices of, and approved by, the HMA in November 2017 will likely serve as a useful source for the OMCL Network of risk-based assessor test recommendations for APIs. For example, and as noted above, pharmaceutical assessors may recommend that certain impurity tests be performed to check for the presence of potentially harmful impurities or related substances.)

- A variety of different surveillance program 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 and 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, tools 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.
- Periodic surveys (e.g. every two or three years) should be performed across the OMCL Network to collect data on the extent and type of API surveillance that is occurring. This will allow the Network to periodically review where it is in this area, and it may help bring new ideas forward for improving the design of API surveillance activities.
- Focussed collaborative work with the Inspectors' Working group at EMA (IWG) should continue to link planned API inspections with potential OMCL surveillance activities. The 2011 heparin sampling in China during a GMP inspection demonstrated the benefits of such collaborative work, and the heparin inspections being planned by the EMA in China for 2018 and 2019 present further opportunities to continue such collaborations. However, such work should not only relate to heparin inspections, and the OMCLs are encouraged to discuss other potential API surveillance opportunities with their Inspectorates.
- OMCLs should use the API/MRP/DCP database to better share the results from all API testing work. It is especially important to add information into the database about planned API testing, including the rationale for such, at an early stage, in order to promote and facilitate co-operation.
- 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.

*Other potential actions to be undertaken:*

- Define centres of expertise (if needed) beforehand for analytical test methods that are not usually part of routine surveillance work.

- For such APIs that are produced at a multi-purpose production unit, potential contaminations can be foreseen by knowledge about other possible products and processes at the same site.