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Aide-Memoire for GMDP inspectors on the Sampling of APIs and Medicinal Products during Inspections

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Aide-Memoire for GMDP inspectors on the Sampling of APIs and Medicinal Products during Inspections

Introduction

The sampling and subsequent testing of APIs and medicinal products is an important element of the EEA regulatory network's activities for ensuring the quality of medicines on the EEA marketplace and beyond. This paper focusses on the logistics and practical arrangements for sampling activities during GMP inspections, and it sets out points for GMP inspectors to consider.

Sampling activities should ideally reflect the nature and purpose of the testing (or other surveillance work, such as product labelling checks) that is planned by the relevant OMCL on the product or material of concern. It is important, therefore, that there are close links and communication systems between the Inspectorate and the OMCL in this regard, to facilitate the periodic sharing of testing/surveillance plans between the OMCL and its competent authority.

It is also important to recognise that Inspectors may wish to sample APIs or medicinal products for testing that are not yet included in their OMCL's annual testing plan, and this should be possible.

This paper addresses API sampling and medicinal product sampling separately, as there are specific challenges and considerations associated with each. It also addresses the sampling of APIs and medicinal products in third countries. It also provides key points to note about the sampling of centralised products for testing via the ad-hoc testing programme that is in place in the OMCL Network. Some elements described in one of the 4 parts of this document (e.g. ad-hoc sampling in Part 4; sampling in third countries in Part 3; etc.) might also apply to other sampling operations.

In addition to the national testing programmes operated by the individual OMCLs across the EEA, the *OMCL Network* operates a number of additional surveillance programmes, and these are useful for the Inspector to know about. Some of these include:

- **The MSS programme** – this is where medicinal products (and sometimes their corresponding APIs) are sampled from the local markets by a number of OMCLs or their Inspectorates and are tested in those OMCLs in accordance with a common testing protocol.
- **The MRP/DCP programme** – this is where an OMCL tests an MRP or DCP product from its own market (and sometimes from other EEA markets also), and the test results are made available to OMCLs and regulators in the EEA via an OMCL Network database. This programme is designed to avoid unnecessary duplicative testing on MRPs and DCP products by different OMCLs. APIs are sometimes also tested via this programme.
- **The CAP testing programme** – this is where centralised products are tested in accordance with a sampling and testing plan developed in conjunction with, and funded by, the EMA. This programme extents to branded and generic CAP products, as well as Biosimilars.
- **API Fingerprint Analysis** – this is where certain APIs that have known chemical 'fingerprints' are testing using test methods capable of detecting those fingerprints. The test results are sometimes subjected to chemometrics analysis in an effort to detect hidden quality issues or even potential falsifications.
- **OCABR programme for vaccines, blood and plasma-derived medicinal products** – this is not a classical market surveillance programme of the Network. It is where batches of authorised products are subjected to *Official Control Authority Batch Release* testing (or documentation review) by OMCLs before they are placed onto the market. This is in accordance with Article 114 of Directive 2001/83/EC (human legislation) and Article 128 of Regulation (EU) 2019/6 (veterinary legislation).

Part 1: API Sampling

When considering obtaining API samples for OMCL testing, it is useful for the Inspectors to familiarise themselves with the different kinds of API testing that may be in place at their OMCL (or at other OMCLs in the EEA network).

Types of surveillance testing that may be performed on APIs:

There are a number of different types of surveillance testing approaches that may be in place, and it is useful for GMP inspectors to know about which approaches its OMCL may use.

- APIs may be tested against the requirements of the relevant Ph. Eur. (or other pharmacopoeial) monographs that may be in place. Here, the test methods specified and specifications in the monograph would be used by the OMCL.
- Supplementary testing may be performed in accordance with any relevant CEPs (Certificates of Suitability to the Monographs of the European Pharmacopoeia) that many be in place.
- APIs may be tested in accordance with the specifications and test methods described in the relevant marketing authorisation – here, the company's API test methods and specifications would be used by the OMCL.
- APIs may be tested using test methods developed in-house by the OMCL. These may be screening test methods for potentially harmful impurities or contaminants that may be present in API samples, including compounds present at trace levels (e.g. nitrosamines).
- A GMP inspector may wish for an API to be tested for specific parameters in response to an issue seen during an inspection, such as a deviation involving cross-contamination. The batch in question may have been reprocessed or reworked by the manufacturer, and the inspector may wish to have the quality of the resulting reprocessed or reworked API checked by the OMCL. Another example is in relation to low bioburden APIs intended for use in the manufacture of sterile medicinal products. The Inspector may wish to have the API microbiologically tested to check its bioburden level. A third example is where an Inspector finds deficiencies with a company analytical test method, or with its method validation, and wishes an OMCL to run that test method to evaluate its fitness for use.
- API test results (e.g. assay, impurities) may be analysed using chemometric techniques, which can involve pattern recognition methods (e.g. see Ph. Eur. 5.21., *Chemometric methods applied to analytical data*). Sometimes, a number of API samples from different sources will be tested, and chemometrics techniques (e.g. Principal Component Analysis) can help differentiate the samples by manufacturer and may also help determine sample authenticity. Such testing can also help with the detection of quality issues that may not have been detected via compendial or other testing. Sometimes, chemometrics techniques assist with 'fingerprint' analysis of APIs, where the API exhibits a particular impurity or residual solvent profile when tested.

Where APIs may be sampled from:

The sampling of APIs may be performed at several different locations in the supply chain, such as at following:

- API manufacturers
- API distributors
- Sites that relabel and sell APIs
- Medicinal product manufacturers

Selecting APIs for OMCL Testing:

The Inspector's OMCL will have a testing plan in place for the year and this may specify a number of APIs that it wants to test. The Inspector may wish to have additional APIs tested by the OMCL, based on inspection activity.

The selection of APIs for surveillance testing can be based on various risk factors:

- APIs produced by manufacturers with a history of poor GMP compliance.
- APIs produced in countries or regions with a history of poor GMP compliance.
- APIs known to be widely used in generic and/or blockbuster medicines, whereby any quality issue with the APIs could impact large numbers of patients.

- 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 new or updated European Pharmacopoeia (Ph. Eur.) or other compendial monographs.
- APIs that are associated with problematic polymorphic forms.
- APIs from newly registered manufacturers.
- APIs may be selected for surveillance testing when the related finished products are also being tested.
- APIs may be selected for surveillance testing 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 route of synthesis or the manufacturing method that is used, or where the Assessor has a concern relating to the company's analytical test methods or their validation).
- APIs for which the 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 started to be applied in the API manufacturing process.
- APIs that are available in various grades, such as different particle size grades, different grades of purity, where a mix-up could have negative consequences for the patient or for the performance of the medicinal product.
- APIs may be selected based on the risk assessments performed by Quality Assessors when they are assessing new MRP and DCP marketing authorisation applications. The Assessors currently risk-assess all such products using a pre-marketing risk assessment approach developed under the auspices of the HMA, and they make test recommendations in relation to the medicinal product and its related API. The risk scores and the test recommendations for the product and its API are held in a database operated by the EDQM for the OMCL Network; this is called the 'MRP/DCP/API OMCL Network Database'. The Inspector's OMCL will be able to assist the Inspector in accessing this database. Inspectors are encouraged to use that database as a trigger for API sampling.

<u>Selecting the API batches to sample:</u>
When an Inspector decides to obtain API samples during an inspection or during a sampling visit, they need to decide which actual batches should be sampled. A random selection may be performed from the stock that is available at the site in question, or it can be useful to apply a risk-based approach to such decision making, whereby specific risk signals are used to determine the batches to be sampled.

When sampling an API, specific batches may be selected that are considered more at risk of having quality problems than other batches. The following are some useful points in this regard:

- Certain batches may have been associated with serious GMP deviations or complex change controls, and these can be useful to sample.
- Certain API batches may have been associated with laboratory out-of-specification or out-of-trend investigations, and they may be at risk of being sub-standard in quality.
- Certain API batches may be at risk of having unacceptable levels of contaminants or cross-contaminants as a result of poor manufacturing controls. One example might be the first API batch produced after equipment cleaning, or the first batch at the start of a production campaign. Another example could 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 batch.
- Certain API batches may be at risk of having unacceptable levels of known or unknown impurities, as a result of process-related change controls that may not have been impact-assessed well by the manufacturer.

- Certain API batches may be at risk of having unacceptable levels of optical enantiomers, as a result of poor or highly complex process controls that are intended to separate the enantiomers from one another during production.

Note: The testing that is then performed on the APIs should generally reflect the risks that triggered the sampling.

The inspector may wish to select the actual drums or containers in a batch that they wish the samples to be taken from. This usually involves going to the warehouse (or to the reserve sample storage location) to make those selections.

When to perform the API sampling during a GMP inspection:
It is useful to leave the sampling of APIs until relatively late in an inspection, as by then the Inspector will have had time to consider which APIs and API batches should be sampled based on risk considerations. For example, if the inspector decides to select particular API batches based on risk signals such as deviations, change controls and laboratory investigations, they will need time to review those issues before deciding which APIs and which specific batches to sample.

The actual API material that may be available to sample:
Not all of the APIs of interest to the Inspector (or the OMCL) may be available in the manufacturers warehouse at the time of the inspection/sampling visit. Often only a small inventory of different APIs may be present. For this reason, consideration may be given to obtaining samples from the company's retained reserve samples of the APIs/batches in question, but care should be taken not to deplete those supplies in case there is a need for future testing by the company to support complaints or other investigations.

The Inspector should request a list of API batches in the warehouse at the time of the sampling activity; this can be useful, and the oldest batch in stock for a particular API may be identified and sampled.

Performing the actual sampling:
API sampling should be performed with care; moisture ingress, temperature effects and contamination risks need to be considered. Appropriately sampling tools, sealed containers and labels will be required, and temperature data loggers may be needed during transportation.

It may be appropriate for the Inspector not to perform the actual physical sampling of the material themselves, but instead to witness a trained staff member from the company doing the sampling.

Inspectors should generally not perform the actual physical sampling of the API material themselves. This is because the sampling activity usually involves opening drums and other containers of powders or liquids and inserting sampling thieves into the material to extract the samples. This gives rise to potential contamination and cross-contamination risks, and the Inspector would need to undergo training on the sampling process, and this can consume valuable time during an inspection. In addition, there will be gowning requirements to adhere to in order to enter a sampling/weigh-booth or other such area to perform sampling, and again there may be training involved in this. It is usually preferable for the Inspector to ask the company to perform the sampling and to witness that activity.

It is important to recognise that API sampling can take several hours from start to finish, and the inspector should make provision for that in their inspection plan, if he or she does want to witness the sampling in full. And if more than one API is to be sampled, this may significantly extend the total time needed to organise and obtain the samples, and it will often not be possible for all of that to be done in one day.

API sampling can take considerable time because:

- The containers of the API material of interest may need to be brought from a warehouse location to the sampling location, which may be a sampling/weigh-booth in another part of the facility.
- The sampling/weigh-booth may need to be cleaned (or re-cleaned) before the material in question can be brought into it. (And if more than one API is to be sampled, the booth will need to be recleaned between each material.)
- The sampling will need to be performed, and the samples packaged and labelled.

- The sampling/weigh-booth will need to be cleaned again at the end of sampling.

It may be preferrable, and more practical, for the Inspector to simply witness some of the sampling activity and leave the rest up to the company. This will take much less time.

Quantities needed:
The Inspector will need to advise the company how much of each API is required to be sampled. This will depend on the tests that will be carried out by the OMCL, and whether the OMCL may need additional quantities of a batch in the event that a suspected OOS test result is obtained. It is useful for the Inspector to ask the company to advise on how much material would be needed to perform the tests of interest on one occasion, and then to consult with the OMCL to determine if more than that quantity should be obtained.

Reference standards and other materials for use by the OMCL
There may be reference standards and other materials needed to run some of the test methods by the OMCL which may not be commercially available. If this is the case, the Inspector may need to obtain these from the company at the time the API samples are obtained. The Inspector may need to consult with the OMCL about this.

Packaging of the API samples:
The company will usually advise on the nature of the packaging that the samples should go into. This should be equivalent to, or more protective than, the packaging used to package the API for commercial sale. (See point 11.72 in Part II of the EU GMP Guide.)

Transportation and delivery of the API samples to the OMCL:
As many APIs will be powders, or in some cases liquids, it is usually preferable to have the company organise the delivery of the samples to the OMCL directly, instead of the Inspector taking physical possession of the samples. The inspector may wish to ensure that the packages in which the samples are packaged at the end of sampling are tamper evident. If the Inspector's agency has an Enforcement group, that group will usually have sealable and tamper-proof evidence bags that may be used to put the samples into at the end of the sampling activity. Information about the storage conditions of the provided material and Safety Data Sheets need to be provided together with the sample and any other essential material needed for the analysis. If the testing is to be performed according to an on-site SOP, the respective document will also need to be provided.

Part 2: Medicinal Product Sampling

When considering obtaining medicinal product samples for OMCL testing, it is useful for the Inspector to familiarise themselves with the different types of surveillance testing that may be in place at their OMCL (or at other OMCLs in the EEA network).

Types of surveillance testing that may be performed on medicinal products:
There are a number of different types of testing approaches that may be in place, and it is useful for GMP inspectors to know about which approaches their OMCL may use.

- Medicinal products may be tested in accordance with the specifications and test methods described in the relevant marketing authorisation – here, the company's shelf-life test methods and specifications would be used by the OMCL.
- Medicinal products may be tested against the requirements of the relevant Ph. Eur. (or other pharmacopoeial) monographs that may be in place. Here, the test methods and specifications specified in the monograph would be used by the OMCL.
- Medicinal products may be tested using test methods developed in-house by the OMCL, such as for identity, assay/potency, impurities, etc. Some of these may be screening test methods designed to detect and quantify specific active substances in the samples.
- A GMP inspector may wish for a medicinal product to be tested for specific parameters in response to an issue seen during an inspection, such as a deviation involving a product mix-up issue, or a cold-chain failure. Another example may relate to observing poor cleaning controls at the site, which may trigger the Inspector to sample a number of medicinal products for microbiological testing. The Inspector may find

deficiencies with a company's analytical test method, or its method validation, and may wish an OMCL to run that method to evaluate its fitness for use.

Where medicinal products may be sampled from:
The sampling of medicinal product may be performed at several different locations in the supply chain, such as at following:

- Medicinal product manufacturers (bulk and finished product)
- Medicinal product wholesalers
- Pharmacies and hospitals
- Veterinary clinics
- Retailers of various kinds (e.g. supermarkets).

Selecting medicinal products for OMCL Testing:
The Inspector's OMCL will have a testing plan in place for the year and this will specify a number of medicinal products that it wants to test. The Inspector may wish to have additional medicinal products tested by the OMCL, based on their inspection activity.

The medicinal products selected for surveillance testing can be based on various risk factors:

- Medicinal products produced by manufacturers with a history of poor GMP compliance.
- Medicinal products produced in countries or regions with a history of poor GMP compliance.
- Medicinal products which are blockbuster medicines, whereby any quality issues could impact large numbers of patients.
- Medicinal products with OOS results obtained during previous OMCL testing.
- Medicinal products that are prone to falsification.
- Medicinal products that may have known genotoxic or other high-risk impurities.
- Medicinal products that are the subject of new or updated European Pharmacopoeia (Ph. Eur.) or other compendial monographs.
- Medicinal products from newly registered manufacturers.
- Medicinal products may be selected for surveillance testing when the related APIs are also being tested.
- Medicinal products may be selected for surveillance testing as a result of issues identified during dossier assessment, (e.g. where the Assessor has a concern with regard to the stability of the product, or where the Assessor has a concern relating to the company's analytical test methods or their validation).
- Medicinal products may be selected based on the risk assessments performed by Quality Assessors when they are assessing new MRP and DCP marketing authorisation applications. The Assessors currently risk-assess all such products using a pre-marketing risk assessment approach developed under the auspices of the HMA, and they make test recommendations in relation to the medicinal product (and its related API). The risk scores and the test recommendations for the product (and its API) are held in a database operated by the EDQM for the OMCL Network; this is called the 'MRP/DCP/API Testing Database' of the OMCL Network, and the Inspector's OMCL will be able to assist the Inspector in accessing it. Inspectors are encouraged to use that database as a trigger for medicinal products sampling.

Selecting the medicinal product batches to sample:
When an Inspector decides to obtain medicinal product samples during an inspection or during a sampling visit, they need to decide which actual batches should be sampled. A random selection may be performed from the stock that is available at the site in question, or it can be useful to apply a risk-based approach to such decision making, whereby specific risk signals are used to determine the batches to be sampled.

When sampling a medicinal product, specific batches may be selected that are considered more at risk of having quality problems than other batches. The following are some useful points in this regard.

- Certain medicinal product batches may have been associated with serious GMP deviations or complex change controls, and these can be useful to sample.
- Certain medicinal product batches may have been associated with laboratory out-of-specification or out-of-trend investigations, and they may be at risk of being sub-standard in quality.
- Certain medicinal product batches may be at risk of having unacceptable levels of contaminants or cross-contaminants as a result of poor equipment cleaning controls. The first medicinal product batch produced on equipment after equipment cleaning can be useful to sample.
- Certain medicinal product batches may be at risk of having quality issues (e.g. a poor dissolution profile) as a result of manufacturing or supplier issues (e.g. an inadequate qualification of the supplier of an important excipient used to control the release profile of the product).

Note: The testing that is then performed on the medicinal products should generally reflect the risks that triggered the sampling, if any.

The inspector may wish to select the actual packs in a batch that is being sampled. This usually involves going to the company warehouse (or to the reference sample storage location) to make those selections.

When to perform the medicinal product sampling during a GMP inspection:
It is useful to leave the sampling until relatively late in an inspection, as by then the Inspector will have had time to consider which medicinal products and batches should be sampled based on risk considerations. For example, if the inspector decides to select particular batches based on risk signals such as deviations, change controls and laboratory investigations, they will need time to review those issues before deciding which medicinal products and batches to sample.

The actual medicinal product material that may be available to sample:
Not all of the medicinal products and batches of interest to the Inspector (or the OMCL) may be available in the manufacturer's warehouse at the time of the inspection/sampling visit. Often only a small inventory of different medicinal products may be present. For this reason, consideration may be given to obtaining samples from the company's retained reference samples of the batches in question, but care should be taken not to deplete those supplies in case there is a need for future testing by the company to support quality defect or other investigations.

The Inspector should request the list of medicinal product batches in the warehouse at the time of the sampling activity; this can be useful, and the oldest batch in stock for a particular medicinal product may be identified and sampled.

Performing the actual sampling:
Medicinal product sampling is usually much less time-consuming than API sampling. It many simply involve going to the company's warehouse and picking packs from the medicinal product batches of interest. Or the Inspector may simply witness the sampling activity by company staff.

Quantities needed:
The Inspector will need to advise the company how much of each medicinal product is required to be sampled. This will depend on the tests that will be carried out by the OMCL, and whether the OMCL may need additional quantities of a batch in the event that a suspected OOS test result is obtained. It is useful for the Inspector to ask the company to advise on how much material (or how many packs) would be needed to perform the tests of interest on one occasion, and then to consult with the OMCL to determine if more than that quantity should be obtained.

Reference standards and other materials for use by the OMCL:
There may be reference standards and other materials needed to run some of the test methods by the OMCL may not be commercially available. If this is the case, the Inspector may need to obtain these from the company at the time the medicinal product samples are obtained. The Inspector may need to consult with the OMCL about this.

Part 3: Sampling APIs and Medicinal Products in Third Countries

Consideration should be given to sampling APIs and medicinal products manufactured in third countries when performing inspections at those sites. In some countries, there can be difficulties in securing the right to perform the sampling, but this is not always the case. If the Inspector is interested in obtaining samples during a third country inspection, they should discuss this (and the logistics of the sampling) with the inspectee in advance of the inspection.

There may be customs issues or import/export licence issues to resolve when obtaining samples in third countries. These issues should also be discussed with the inspectee in advance of the inspection.

Note: The inspector may wish to only select samples from API batches which are intended for supply to the EEA, or which are intended to be used in the manufacture of medicinal products that will be placed on the EEA market. With regard to sampling medicinal products, the Inspector may wish to only select samples from batches which are intended for supply to the EEA.

The following are some key points when obtaining samples during third country inspections:

- The sampling of APIs should be performed by trained company staff, as per the company's own sampling procedure, on request of, and witnessed by, the inspector.
- Each container within which the API samples are put should be appropriately labelled by or for the persons who performed the sampling. The labelling of each container should be checked for accuracy by the inspector.
- Two samples of each API material may be taken. One may be offered to the company, and one shipped to destination laboratory or inspectorate.
- If it is a local customs requirement to provide a sample of each API material being taken out of the country to a customs official, such samples for customs should be taken and made available to them.
- A receipt for the samples taken should be provided by the inspector.
- The samples of APIs and medicinal products should be made ready for shipment by packing them into a suitable container. This should be performed by company staff in the presence of the inspector. The package should be tamper-evident, and it may need to contain temperature data loggers, depending on the required storage conditions of the APIs or medicinal products inside. There should be assurance that the storage conditions required for the samples (e.g. cold chain) can be met by the shipping arrangements that are made. The inspector should bring tamper evident bags or containers with them to the inspection.
- Ideally, the overall package should be shipped from the company to the destination on the day the packaging occurred, or before the end of the inspection.

Part 4: Ad-hoc CAP Testing Programme – key points to note

In case sampling is to be done within the framework of the Ad-hoc CAP Testing Programme, liaison with EDQM staff will become necessary. As the testing OMCL will normally not be selected at the stage of the sampling operation, the EDQM will act as the receiving addressee for the samples and any accompanying essential materials and documentation needed for the testing. These items will be forwarded by the EDQM to a suitable testing OMCL. The EMA will also be informed about the sampling and testing operations.

Note: The EDQM needs to be pre-informed about the arrival of the samples. The inspector should therefore provide sufficient background information and information about the scope of the testing request to the EDQM, or this information can be passed to the EDQM by the Inspector's OMCL.

In case information about the necessary amount of sample to obtain for the testing is not available, as a general rough-and-ready rule, 5 g of API samples or 100 dosage form units (e.g. for tablets) or 5 bottles (e.g. for liquid multi-dosage forms) of medicinal product samples should be sufficient.