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Aide Memoire: How to identify a falsified Monoclonal Antibody (mAb)/Ab containing Fusion Protein (AbFP)?

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Aide Memoire: How to identify a falsified Monoclonal Antibody (mAb) / Ab containing Fusion Protein (AbFP)?

Position Paper for the OMCL Network

Introduction

In recent years the use of biologicals in the treatment of (often serious) illnesses has significantly increased which is reflected in the augmented demand for testing CAP biologicals in the CAP Sampling & Testing Programme. Together with this development, a worldwide increase of falsifications and thefts of biologicals has been reported which greatly affects the European market. In particular mAb preparations which are considered as high-price products have been subject of falsification, for instance in connection with stolen vials which later have been reintroduced into the legal supply chain (e.g. via parallel trading).

With regards to falsification cases of mAbs, OMCLs have been confronted not only with the request to deliver analytical evidence of the falsification, but also to establish to which extent the active pharmaceutical ingredient (API) was still present and remained active in the confiscated material. As new cases can be expected to emerge in the future, the need to prepare the OMCL Network for the testing of suspected falsified or stolen mAbs and/or AbFPs has been identified. Testing could be limited to physico-chemical parameters, but could also include the performance of bioassay, as deemed necessary depending on the request. In certain cases, non-API related quality attributes that could have an impact on the safety of a suspected falsified product may also need to be investigated (e.g. microbiological contamination).

Taking into consideration this new challenge, an OMCL group (OMCL mAb Testing Group) was put in place in December 2018. One of the tasks assigned to the group was elaborating a general protocol for testing suspected falsified mAbs / AbFPs. This test protocol is described below. Note that all steps explained for mAbs in the text apply also to AbFPs.

Test protocol

The OMCL, in agreement with the stakeholder(s), defines the testing strategy and workflow according to the request and the case.

In cases where falsification is suspected, it is important to keep the testing as simple and quick as possible. Many falsified medicines have been identified by visual examination of the package / vial / label. Pictures of the packages for centrally authorised products are stored by the EMA. Depending on the case it may be enough

i) to perform a qualitative identity test using a genuine product as a comparator, or

ii) to estimate the content in comparison to the genuine product, while in some cases

iii) an exact quantitation of the API, or

iv) analysis of impurities and safety related quality attributes is needed.

With respect to stolen mAbs, determination of the potency may also be of importance since in these cases, the transport and storage temperature / conditions are not known.

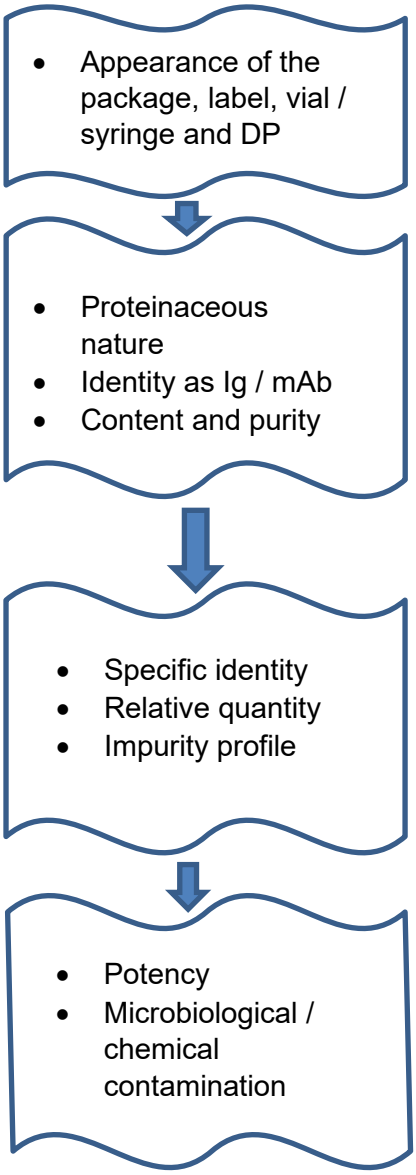
A genuine product obtained from a reliable source should be used as a comparator. The marketing authorisation holder / manufacturer or a wholesaler / distributor could be contacted to obtain the comparator and further detailed information on the product. In addition to the comparator, when feasible, pharmacopoeial or international standards for the biotherapeutic in question may be used to verify the performance of the methods and/or calibrated bioassays. It should be noted that pharmacopoeial or international standards are currently only available for a limited number of mAbs and AbFPs.

The protocol and workflow below are intended to provide guidance in designing the experimental approach for identifying a falsified mAb. The chosen sequence should be tailored to the particular scenario depending on the amount of material, purpose, request, or previous findings. The selected test methods should be fit for purpose. Several Ph. Eur. texts relevant for the testing of mAbs are available. In cases, where bioassays may be required, it is expected that longer time frames may be needed for the delivery of solid test results.

	Protocol	**Obtain information on**
A	Inspect the package, vial / syringe, label, leaflet and appearance of the drug product (DP) visually. Photograph and document the observations. Contact MAH to identify a possible falsified batch number, when necessary.	– Intactness / authenticity of the package / vial / syringe – appearance of the DP
B	Experimental analysis of the API and API-related impurities in the DP	
1	Depending on the product presentation, knowledge, scenario, etc. consider one of the following steps: reconstitute (for lyophilised products), use directly, concentrate or dilute in a suitable diluent. Aim at concentrations 0.1 - 10.0 mg/ml and proceed to analysis. When possible, treat the test sample and comparator in parallel.	
2	Verify the presence of protein (e.g. SDS-PAGE or total protein analysis (e.g. Ph. Eur. 2.5.33, Method 1)).	– protein presence – total protein content
3	Electrophoresis (gel format or CE)	
3.1	Serum protein electrophoresis – SPE (gel or CE format)	– identification of immunoglobulin / immunoglobulin class
3.2	SDS-PAGE or CE-SDS (in reducing and non-reducing conditions)	– identification of immunoglobulin structure – MW distribution compared to comparator – purity compared to comparator
3.3	Charge variant composition by ion exchange chromatography, IEF, cIEF, icIEF or CZE	– identity based on charge heterogeneity pattern compared to comparator – purity compared to comparator

	Protocol	**Obtain information on**
4	SEC	– identity compared to comparator – purity (HMW variants and fragments) based on area normalisation – content relative to comparator may be assessed exactly based on area calculations
5	Peptide mapping with an option to sequence the variable region peptides distinguishing the mAb / AbFP from other similar molecules (combined with UV or MS detection)	– identity based on peptide map compared to comparator – identity based on amino acid sequence
6	Potency assay (usually cell-based bioassay is preferred)	– identity based on activity – potency relative to comparator and/or public biological standards when available
C	Experimental analysis of the non-API related impurities in the DP e.g. microbiological analysis, toxins, heavy metals	– impact on safety

WORKFLOW



- Outer package: appearance and batch numbers
- PIL and label: label position, material, font of the text, font and color of batch numbers
- Container: Integrity of the vial / syringe: does it feel 'normal' to open the cap? Is the septum intact?

- Is it a protein?
- What is the rough / exact amount (e.g. total protein) of protein?
- Is it a monoclonal antibody / immunoglobulin (e.g. SPE)?
- What is the MW (e.g. SDS-PAGE)?

- What is the pI?
- Does the charge variant pattern (electropherogram from cIEF or CZE) correspond to that of the comparator?
- Does the main peak area (e.g. SEC) correspond to that of the comparator?
- Are there oligomers, aggregates, fragments (e.g. SEC)?
- Does the peptide map correspond to that of the comparator? Are the sequences specific?

- Does the potency correspond to that of the comparator?
- Are there non-API related contaminants present which can have an impact on safety?