EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines, Pharmacovigilance and Committees Division

Questions and answers on the use of out-of-specification batches of authorised cell/tissue-based advanced therapy medicinal products

1. What is the pathway for the exceptional administration of out-of-specification (OOS) batches of a cell/tissue based advanced therapy medicinal products (ATMPs) that have been granted a marketing authorisation?

In the exceptional circumstances set out in Section 11.5 of the Guidelines on GMP for ATMPs[1], the administration of a cell/tissue-based ATMP that does not comply with the specifications set out in the marketing authorisation may be considered to avoid an immediate significant hazard to the patient. The supply of an OOS batch can only occur when the conditions laid down in Section 11.5 of the above-mentioned Guidelines are met, in particular that the manufacturer provides an evaluation of the risks to the treating physician and that the supply of the batch is requested by the treating physician after having considered the specific condition of the patient and the evaluation of the risks provided by the manufacturer.

The manufacturer of the OOS batch should always be at the centre of the investigation of the root causes leading to the OOS result and of the evaluation of the risks. In cases where the manufacturer, importer and marketing authorisation holder (MAH) are different legal entities, there should be a written agreement between the parties which lays down the respective roles including also with regard to the communication with the treating physician and competent authorities.

2. Who should be notified and when?

When an OOS batch of a cell/tissue-based ATMP that has been granted a marketing authorisation is detected, the priority for the MAH/manufacturer/importer should be to immediately inform the treating physician and to conduct an evaluation of risks.

The competent authorities that should be informed when a patient has been administered an OOS batch are the Supervisory Authority (Competent Authority responsible for granting the manufacturing authorisation to the site manufacturing or importing the medicinal product within the European Union) and EMA (as the body responsible for the scientific evaluation and oversight of ATMPs that have been granted a marketing authorisation).

The manufacturer/importer/MAH should inform the Supervisory Authority and EMA whenever an OOS batch has been supplied for administration to a patient in the EU. Following the supply of the product

[1] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf

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at the request of the treating physician, it is expected that the manufacturer/importer/MAH informs at the same time the Supervisory Authority and EMA within 48 hours.

3. How should the manufacturer/importer/MAH notify the EMA of the OOS batch(es)?

The manufacturer/importer/MAH should notify EMA of any OOS batch(es) by submitting a Quality Defect report[2]. The risk evaluation should be attached, including the results of the batch analysis .

EMA will inform the CAT Rapporteur of the authorised product of each OOS.If a trend is detected, the need for regulatory actions will be considered.

4. Are National Competent Authorities involved?

ATMPs are centrally authorised products and, once authorised, fall under the oversight of EMA and the Supervisory Authority for the importing into the EU/manufacturing site.

The manufacturer/importer/MAH should contact the National Authority of the treating site(s) to check if they have to be informed. Where required, the information should be provided to National Competent Authorities at the same time as the submission to the supervisory authority and EMA (see question 2).

5. Are there any other obligations or expectations that the manufacturer/importer and MAH have to follow in case of an OOS batch of a cell/tissue based ATMP that has been granted a marketing authorisation?

The obligations of the manufacturer/importer are not waived. Although it is acknowledged that the QP cannot certify the OOS batch, he/she has to ensure that the verifications on the batch have been performed. It follows that the import into the EU of OOS batches should follow standard import procedures.

Additionally, the manufacturing/importing site should - as a minimum - keep records of all details concerning the manufacture, testing, transport and storage of the product, the request of the treating physician and the analysis of the risks provided by the MAH / manufacturer. The records on the investigation of the OOS result(s) and associated risk assessment in relation to the potential impact on product quality should also be available.

The obligations of the MAH are also not waived. Therefore, pharmacovigilance reporting obligations or specific additional obligations to follow-up patients treated with the ATMP *(e.g*. registry) continue to apply in respect of OOS batches.

6. What information should be provided to the patient?

The patient should be informed about the OOS ATMP the patient is going to receive. The information that shall be provided to the patient is governed by national legislation of the treating site.

The information to patients should be provided in lay language.

It is stressed that document(s) designed to inform patients can neither transfer any responsibilities to the patient nor discharge the responsibilities of the MAH or the manufacturer.

[2] https://www.ema.europa.eu/en/documents/template-form/defective-product-report_en.pdf