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. Under which circumstances can out-of-specification (OOS) batches of authorised cell/tissue based advanced therapy medicinal products (ATMPs) be administered?

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 authority that should be informed when a patient in the EU has been administered an OOS batch is the Supervisory Authority (Competent Authority responsible for granting the manufacturing authorisation to the site manufacturing or importing the medicinal product within the European Union).

Following the supply of the product at the request of the treating physician, it is expected that the manufacturer/importer/MAH informs the Supervisory Authority within 48 hours.

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

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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.

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

In addition to informing the Supervisory Authority when a patient has been administered an OOS batch, the manufacturer/importer/MAH should provide a periodic review of the OOS batches that have been administered according to Section 11.5 of the Guidelines on GMP for ATMPs to the EMA (as the body responsible for the scientific evaluation and oversight of ATMPs that have been granted a marketing authorisation).

This periodic review should be submitted by the MAH as a Quality Defect report[2] every 6 months and should include an overview of the OOS batches compared to batches released according to specifications during the previous 6 months, with the objective of verifying the consistency of the existing process, the appropriateness of current specifications, to highlight any trends and to identify potential product and process improvements.

EMA will provide this periodic review to the CAT Rapporteur of the authorised product. If a trend is detected, additional information might be requested and/or the need for regulatory actions will be considered.

4. 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.

5. 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