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SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines, Pharmacovigilance and Committees Division

Questions and answers on the exemption from batch controls carried out on ATMPs imported into the European Union from a third country

1. What are the obligations of the Qualified Person (QP) regarding testing of batches for ATMPs imported into EU?

In the case of an authorised ATMP imported from a third country, the QP has to ensure that each batch has been manufactured in accordance with Good Manuafacturing Practice and that the quality is in accordance with the terms of the marketing authorisation. Imported ATMP batches have to be re-tested upon importation into the EU, as required by Article 51(1)(b) of Directive 2001/83/EC.

Article 51(2) of Directive 2001/83/EC, makes provision for the Qualified Person certifying the imported batch to rely on controls conducted in a third country (batch release testing in accordance with the terms of the marketing authorisation) where the product has been manufactured and tested in a country having a relevant mutual recognition agreement (or equivalent arrangements) (MRA) with the EU.

The possibility to rely on controls conducted outside of the EU (where no relevant MRA on GMP is in place) is exceptional and cannot be applied beyond the specific scenarios described in the GMP Guideline for ATMPs.

2. In which cases can the exemption from EU batch re-testing for imported ATMPs be granted?

The exemption from re-testing batches upon import into the EU for ATMPs may only be granted where the conditions laid down in paragraph 11.17 of the EU GMP guideline for ATMPs[1] are met, specifically:

1) limited amount of material available;

Or

2) short shelf-life;

[1] Eudralex Volume 4 Good manufacturing practice "Guideline on Good manufacturing practice specific to Advanced Therapy Medicinal Products", at paragraph 11.17

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And

3) the testing in the third country should be conducted in GMP-certified facilities.

This exceptional exemption is primarily foreseen for imported patient-specific ATMPs (e.g. autologous product).

Technical difficulties in the transfer of analytical methods from third countries to the EU cannot be used as a basis to accept an exemption from re-testing of batches imported into the EU.

Requests for an exemption from batch re-testing in the EU for an imported ATMP should be supported by a justification and, where applicable, scientific data to substantiate the claim made (please refer to Question 3 below). The request and corresponding justification will be assessed by the CAT/CHMP during the evaluation of the marketing authorisation procedure.

As the EU GMP guideline for ATMPs requires that "*in such cases, the testing in the third country should be conducted in GMP-certified facilities (in the case of authorised ATMPs)*", a GMP pre-approval inspection is expected to be triggered unless a valid GMP certificate is available from an inspection carried out by an EEA competent authority, on the same or similar category of testing.

Applicants intending to rely on paragraph 11.17 of the GMP for ATMPs Guidelines to request an exemption from re-testing of batches imported into the EU are strongly advised to proactively consult with EMA early in product development.

3. Which data should be submitted in the marketing authorisation application to the EMA in order to justify the exemption from batch re-testing in the EU of imported ATMPs?

To substantiate the request, the applicant/MAH should provide at least the following data in the initial marketing authorisation application:

- total batch size and number of units required for batch release testing;
- available stability data and proposed shelf life;
- analytical sampling plan;
- a GMP certificate issued by an EEA Competent Authority relevant to the particular category of testing at the facility located in the third country.

Changes to the particulars of the marketing authorisation, for instance upscaling of batch size, may annul the exemption granted if the ATMP no longer meets the criteria set out in the EU GMP guideline for ATMPs. In such cases, batch release testing would be required to be conducted in the EU, in accordance with Article 51(1)(b) of Directive 2001/83/EC.

4. What are the obligations of the Qualified Person for the batch release of imported batches exempted from re-testing in the EU?

The general obligations of the QP as laid down into the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products[2] are not waived for imported ATMPs subject to exemption from re-testing in the EU as regards to the requirements for performing the batch release. However, only in case of a granted exemption, the EU QP certifying the imported batch may rely on quality control testing in accordance with the terms of the marketing authorisation performed in a third country. The EU QP should have access to additional manufacturer documents (e.g. raw analytical data), as needed, in order to certify the imported batches.

[2] Eudralex Volume 4 Good manufacturing practice "Guideline on Good manufacturing practice specific to Advanced Therapy Medicinal Products"