What does the removal of the rabbit pyrogen test (RPT) from the European Pharmacopoeia mean for CEP holders?

Answer:

The European Pharmacopoeia Commission has removed the Rabbit Pyrogen Test (RPT) from all European Pharmacopoeia monographs and introduced a new risk-based approach to pyrogenicity testing through general chapter *5.1.13. Pyrogenicity*. Based on the principles outlined in the general chapter, CEP holders should select an appropriate *in vitro* method, such as the monocyte activation test (MAT) or, where justified, a bacterial endotoxins test (BET). No comparison with the RPT is envisaged.

CEPs for sterile substances or CEPs carrying subtitles related to parenteral use account for the control of pyrogens. In other situations, the implementation of an *in vitro* control strategy for pyrogens is not considered sufficient to support a “pyrogen-free” or “endotoxin-free” claim on a CEP, and such claims will not be accepted. If the monograph on the substance covered by the CEP prescribes a limit for bacterial endotoxins, no subtitle is needed (unless specified in the labelling section).

An update of the CEP dossier to remove or substitute the RPT typically requires the submission of an application for a minor revision. If the risk assessment concludes that a suitable method is already approved in the dossier and allows appropriate control in the absence of the RPT, the addition of a replacement method may not be required. This is the case for instance, when a BET is already in place for the control of pyrogenicity. If the risk assessment concludes that the test in place (e.g. BET) is not adequate to control pyrogens, then the MAT should be implemented.

If a BET had already been approved as the sole control for pyrogens,it is not necessary to revise the dossier.

Applications for new CEPs or revisions of existing CEPs for substances where a control strategy for pyrogens is deemed necessary should include the following:

- a summary of the relevant risk assessment;
- the corresponding limit in the substance specification, unless a limit is already provided in the relevant monograph. Limits should be set in accordance with general chapter *1.10* (if a BET is selected) or *2.6.30* (if a MAT is selected);
- clear reference in section 3.2.S.4.1 to the method used (BET *6.14* method A/B/C/D/E/F/G or 2.6.32 – until this chapter is officially suppressed on 01/01/2027 – or MAT *2.6.30* method 1 or 2);
- if the MAT is selected, the analytical procedure should be described in section 3.2.S.4.2 and the study of the suitability of the method (i.e. test for interfering factors) should be provided in section 3.2.S.4.3.

Compendial methods, whether the BET or MAT, will not be appended to the CEP.