# European Pharmacopoeia policy on bacterial endotoxins in substances for pharmaceutical use

*Approved by the European Pharmacopoeia Commission at its 149th Session, June 2014*

## 1. Reasons for requirement of compliance with the test for bacterial endotoxins

Bacterial endotoxins are contaminants from gram-negative bacteria and are the most common cause of pyrogenicity in pharmaceutical products. Any preparation administered parenterally should be sterile and comply with the test for bacterial endotoxins (BET) as described in the European Pharmacopoeia.

Substances to be used in parenteral preparations should comply with the test for bacterial endotoxins, whatever their origin, since:

- contamination by bacterial endotoxins can take place prior to or during the manufacturing process;
- bacterial endotoxins cannot always be easily removed by the manufacturing process;
- the detection of bacterial endotoxins should be carried out as early as possible in the manufacturing process.

However, if the manufacturing process for the parenteral preparation includes a further appropriate procedure for the removal of bacterial endotoxins, compliance with BET is not required.

## 2. Requirements for bacterial endotoxins in the European Pharmacopoeia

The European Pharmacopoeia currently provides the following requirements for compliance with the test for bacterial endotoxins.

The general monograph *Substances for pharmaceutical use (2034)* requires compliance with BET for substances offered as a bacterial endotoxin-free grade, while individual monographs on substances for pharmaceutical use require compliance with BET when substances are used in the preparation of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. The monographs refer to general chapters *2.6.14. Bacterial endotoxins* and *5.1.10. Guidelines for using the test for bacterial endotoxins*.

According to the general monograph *Parenteral preparations (0520)*, pharmaceutical preparations to be used parenterally have to comply with the test for bacterial endotoxins[1].

## 3. Problem statement

- During elaboration of monographs, it is not always known if the substance is to be used for the production of a parenteral preparation and therefore, it is not known whether compliance with BET is needed or not.

1 Exceptions: Implants and gels for injection

- With regard to the limits to be applied for the test, individual monographs include actual values, whereas general chapter *5.1.10* provides a means of calculating the endotoxin limit: the values of *K* to be used for this calculation depend on the route of administration and are given in the chapter (Table 5.1.10-1). There are other ways to establish limits, for example based on process capability, patient population or a specific requirement of the competent authority. These are not clearly stated in the European Pharmacopoeia and may result in apparent contradictions between the different BET requirements.

## 4. New policy on prescribing BET in the European Pharmacopoeia

In consideration of the above, the European Pharmacopoeia Commission recommends the following approach to bacterial endotoxins.

- **Elaboration of new individual monographs**

A test for bacterial endotoxins is not included in new monographs for substances for pharmaceutical use. The requirements of the general monograph S*ubstances for pharmaceutical use (2034)* apply.

Such requirements are only included when, for example, a specific sample preparation has to be used or a specific method has to be applied.

If a test is included in the monograph, no limit is given.

- **Existing monographs**

The test for bacterial endotoxins is kept in individual monographs for substances for pharmaceutical use. Existing limits remain in these monographs to maintain the use of well-established limits.

In order to apply this policy, the following changes[2] are made to existing European Pharmacopoeia texts:

- **general chapter *5.1.10*** is expanded with further considerations regarding the setting of limits;
- **general monograph *Substances for pharmaceutical use (2034)*** is slightly reworded in order to take the above policy into consideration.

## 5. Consequences of the new BET policy for European Pharmacopoeia users: control strategy

New monographs on substances for pharmaceutical use no longer include a test for bacterial endotoxins (with possible exceptions); this aspect will now be covered by the general monograph *Substances for pharmaceutical use (2034)*. In other words, it is the manufacturer's responsibility to decide whether or not the requirements for bacterial endotoxins have to be applied, and if so, to calculate the corresponding limits based on the following considerations: use of the substance (route of administration, patient population), calculation according to the formula given in chapter *5.1.10*, process capability, or any other considerations raised by the competent authority.

2 The present policy will be applied as soon as the two revised texts under public enquiry, in Pharmeuropa 26.4 and 27.2 respectively, have been implemented in the European Pharmacopoeia.

Moreover, as specified in the monograph on *Parenteral preparations (0520)*, these requirements apply to the finished product. To ensure that a preparation complies with the requirements, the manufacturer may therefore use substances that comply with the test for bacterial endotoxins and/or demonstrate that the process includes an appropriate procedure for the removal of bacterial endotoxins. This decision is part of an overall control strategy that the manufacturer establishes for a preparation, as is the decision on whether or not it is necessary to perform the test for bacterial endotoxins at the level of the substance, in accordance with the General notices – Demonstration of compliance with the Pharmacopoeia: "*An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process*."