Bacterial endotoxins Ph. Eur. policy for substances for pharmaceutical use

(Approved by the Ph. Eur. Commission at its 149th Session, June 2014)

1. Reasons for requirements for testing 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 Ph. Eur.

Substances to be used in parenteral preparations must comply with the BET, whatever their origin, since:

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

It is to be noted that the ICH Guideline Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products provides the following recommendation under section 4.1 Drug Substance Specification: “Pharmacopoeial tests (e.g., endotoxin detection) should be performed on the drug substance, where appropriate.”

2. Requirements for bacterial endotoxins in the Ph. Eur.

The Ph. Eur. provides requirements for testing for bacterial endotoxins as follows.

The general monograph Substances for pharmaceutical use (2034) and individual monographs on substances for pharmaceutical use require compliance with the BET when substances are used in the manufacture of parenteral preparations. 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 or, where justified and authorised, the test for pyrogens.

3. Problem statement

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

- With regard to the limits to be applied for the test, individual monographs provide limits whereas general chapter 5.1.10 provides a way to calculate the endotoxin limit:

1 Exceptions: implants and gels for injection
values of $K$ to be used for the calculation of the endotoxin depend on the route of administration and are given in the general chapter (Table 5.1.10.1). There are other ways to establish limits, for example based on process capability, patient population or specific requirements of the competent authority. These are not clearly stated in the Ph. Eur. This might result in apparent contradictions between the different BET requirements.

4. **New policy on the way to prescribe the BET in the Ph. Eur.**

With consideration to the above, the Ph. Eur. 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 *Substances for pharmaceutical use (2034)* apply.

A test is included only where a specific method has to be described, for example if a specific sample preparation has to be used or if a specific method has to be applied.

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

- **Existing monographs**

BET specifications are kept in individual monographs for substances for pharmaceutical use. Existing limits remain in individual monographs to maintain the use of well-established limits.

In order for the policy to be applied, the following changes are proposed to existing Ph. Eur. texts.

- **General chapter 5.1.10** is expanded with further considerations regarding the setting up 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 Ph. Eur. users**

It is up to the user of the Ph. Eur. to determine whether compliance to BET is needed or not for a given substance. Where a test is included in the monograph with no specific limit, it is up to the user to set the limit for the substance, based on the following considerations: use of the substance (route of administration, patient population); calculation according to the formula given in general chapter 5.1.10; process capability; or any other considerations raised by the competent authority.