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Principles of Sterility Test and Mycoplasma Test

Matters related to the principles of sterility test and mycoplasma test are frequently brought up in Pharmaceutical Affairs Consultation on R&D Strategy (or Regulatory Science Strategy Consultation [R&D]) and need to be addressed before the start of clinical trials. In this document, the matters common to all types of products are organized, and the resultant principles are presented in a format of questions and answers. Please refer to this document where necessary.

It should be noted that the principles provided below are examples of strategies acceptable at the present time, and other strategies may become acceptable in the future as science and technology advance. Where appropriate, QA practices will be added as well. Furthermore, as the Act was amended in November last year, cabinet orders, ministerial orders, and notifications related to the regulations on regenerative medical products are supposed to be issued in the future. Any applicant should pay close attention to the trends in the related standards and guidelines, and if any question arises in the development of a specific product, the Pharmaceutical Affairs Consultation on R&D Strategy should be utilized.

Question 1 Unlike general drugs, some cell/tissue processed products are manufactured in a process where the manufacturable volume of the final product is limited. After the amount to be administered (applied) to a patient is set aside, the remaining amount that may be used in quality testing as a sample would be limited. In such cases, is it acceptable to omit the sterility test and mycoplasma test with the final product by using a portion of the manufacturing intermediate, etc. as the test sample?

Answer The sterility test and mycoplasma test with the final product may be omitted if the following requirements are met: (a) all operations throughout the process from cell culture to formulation are appropriately controlled by advanced aseptic processing techniques; (b) sterility test and mycoplasma test are performed in a middle step; (c) a system is established to robustly ensure that the subsequent steps are not contaminated; and thereby (d) results of the sterility tests, etc. in the middle step and the process control results ruling out contamination in all steps lead to the conclusion that the final product conforms to the specifications.

Question 2 Because the sterility test and mycoplasma test take a long time to provide results, the tests with the final product would provide results only after its administration to the subject. Even in such cases, should the tests be performed?

Answer Even if the results from the sterility test and mycoplasma test with the final product are obtained only after administration (application), the tests should be performed. In this case, the subject should be appropriately informed that documented results ruling out contamination in the final product are not available at the time of administration and

would be available only after the administration. If the test result is positive, appropriate treatment should be promptly provided to the subject in cooperation with the study site. In addition, prior measures should be taken on the subject in view of potential onset of infectious diseases before obtainment of the test result. Furthermore, if rapid sterility test is additionally performed to obtain the result before administration to the subject, the detectability should be checked to adequately understand limitations of the relevant rapid test.

Question 3 For cell/tissue processed products, the sample amount available for stability testing is limited because of the limited manufacturing volume, potentially precluding sterility test from being performed multiple times during the storage period. In such cases, is it acceptable to perform integrity test of the containers such as vials once confirmed to be sterile and substitute the obtained results for sterility test results at subsequent sampling points in the stability testing?

Answer Yes. However, it is desirable to perform sterility test at the final sampling point. For integrity tests of containers, no recommended methods are available currently, and thus justification of choice of the test method is required with data from evaluation for the validity and robustness of the test method in view of the attributes of the container.

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