Parametric Release for Moist Heated Pharmaceutical Products in Japan

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1. Introduction

Referring to International Standards on sterilization and sterility assurance of health care products, prepared by the ISO/TC198, parametric release (PR) or dosimetric release is applied to medical devices, but not to pharmaceutical products in Japan (Table 1). Everybody knows that sterility testing is meaningless for terminally sterilized products, but sterility testing is still carried out on terminally sterilized pharmaceutical products in many countries. In Japan, we have investigated the introduction of PR for terminally sterilized pharmaceutical products from a scientific viewpoint for the past two years. As a result, the legal requirements for acceptance of PR for moist heated pharmaceutical products have been put in place. So, I’d now like to describe the current status of PR for terminally sterilized pharmaceutical products in Japan.

2. Definition of PR

The Japanese Pharmacopoeia (JP) has a chapter entitled “Sterility Assurance of Terminally Sterilized Pharmaceutical Products.” This chapter shows the requirements necessary for the PR. In this chapter, the definition of the PR is “A release procedure based on an evaluation of the production records and critical parameters of the sterilization process based on the results of validation, in lieu of release based on testing results of the final products (Table 2).”

On the other hand, the ISO definition is “Declaration that a product is sterile, based on the records demonstrating that the process parameters were delivered within specified tolerances (Table 3).” The original definition included the deleted phrase “rather than on the basis of sample testing or biological indicator result.” The meaning of the deleted phrase is essentially included in the shorter definition. PR is a system such that the physical parameters of the process cycle are controlled within specified tolerances and all specified biological parameters for the cycle are met. Sterility testing is not required to confirm acceptability of the cycle.

3. Global Movement towards PR

This slide shows global movement towards PR (Table 4). General Notices of the three pharmacopoeias (EP, USP, JP) and the ICH/Q6A Guideline, USP<1222> draft or the JP chapter <Sterility Assurance of Terminally Sterilized Pharmaceutical Products> describe PR, but the acceptance criteria for the PR are not clearly indicated in these official compendiums. So, pharmaceutical industries have not been able to introduce PR.

However, in 1996, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) introduced the alternative sterilizing condition of F0>8 in the Note for Guidance on Manufacture of the Finished Dosage Form (Table 5). This appears to establish the minimum sterilizing cycle applicable to pharmaceutical products.

In the JP, General Notices for preparation of injections, ophthalmic solution and ointments say that “Unless otherwise specified, these pharmaceutical preparations must meet the requirements of the Sterility Test (Table 6).” So, sterility testing was mandatory for any kind of sterile preparation.

However, last year, the concept of PR was introduced in the General Notice of the revised JP (Table 7). Article 6 of the General Notices says that “When a high level of sterility assurance is maintained consistently, based on the records derived from validation studies of the manufacturing process and the in-process controls, the sterility test usually required for the release of the product may be omitted.” Different from the USP or EP, the JP is a legally authorized publication under the Pharmaceutical Affairs Law. So, in Japan, there is now no legal bar to the introduction of PR for terminally sterilized products. The only problem is, what are the minimum acceptable requirements for PR.

Article 6 of the General Notices is not targeted at only terminally sterilized pharmaceutical products, but also covers aseptically produced ones (Table 8). For terminal sterilization, it is not difficult to demonstrate SAL<10^-6.
but in the case of aseptic processing, there is no way to demonstrate SAL<10⁻⁶ in terms of processing parameters. So, it is impossible to permit PR. But, in future, it may be possible to accept PR for them. So, in the preparation of article 6, we did not specify PR only for terminally sterilized products.

4. Current Sterilization of Pharmaceutical Products in Japan

Next, I would like to introduce current sterilization of pharmaceutical products in Japan. Two years ago, I conducted a questionnaire survey on the sterilization of pharmaceutical products among pharmaceutical industries in Japan. Most of the pharmaceutical companies that were producing moist heated drugs responded to the questionnaire. I would like to show you some of the results.

The Pharmaceutical Affairs Law is the basic law covering production of health care products such as drugs, quasi-drugs, medical devices, and cosmetics. This law places no limitation on the sterilizing methods for health care products. For new sterilizing methods, licensing authorities review the application, taking into consideration of changes in the safety, effectiveness and quality of the product after the sterilization. If there is no problem, the authorities will give manufacturing approval to the applicant through the local governor where the applicant’s plant is located. Sterilizing methods used in pharmaceutical industries are shown on Table 9. Autoclaving is the most widely used method for pharmaceutical products, but microwave or pulsed-light sterilization is also used.

Table 10 shows Fo values of a major product at each company. The Fo value is defined as the equivalent sterilization time related to the temperature of 121°C and a z-value of 10°C for a given sterilization process. However, the Fo values shown on this slide were calculated from exposure time after reaching the predetermined temperature for each product. So, the lethal rates of the heating and cooling phases of the cycle are not included in these values. For a long time, the JP recommended the sterilizing condition of 121°C for 20 min. So, many companies are using this sterilizing condition. Some products prepared at Fo<8 were aseptically produced by using sterilizing grade filters, followed by moist-heat sterilization. A media fill run was also carried out periodically for process validation.
Table 11 shows the releasing methods of terminally sterilized products. They were released on the basis of sterility testing or a combination with the BI test.

5. Introduction of PR in Japan

Last year, the ICH/Q6A Guideline on testing procedures and acceptance criteria for new drug substances and new drug products was enforced in Japan (Table 12). This Guideline includes some new concepts such as skip tests, in-process tests, and parametric release. To implement these new concepts in the pharmaceutical industries without problems, we have done feasibility studies on these new concepts for the past three years, and we proposed suitable acceptance criteria for PR for moist-heated pharmaceutical products.

6. Proposal for PR Requirements

We proposed three methods (Table 13). Method 1 is applied to the products to be sterilized at 121°C for more than 15 min. Maximum bioburden is less than 1,000 cfu/container. As method 1 is the most reliable method, we hope that the pharmaceutical industries will prepare for changing their releasing method for their products from sterility testing to PR within a couple of years. Method 2 is based on the alternative method shown in the Guidance of the CPMP of the EMEA. But, maximum bioburden is different from the Fo value for the product. For the time being, Methods 1 and 2 will be given priority in the review of changes in the testing procedures and acceptance criteria of licensed drugs and new approval drugs by the licensing authorities. Method 3 is applicable to products which can be treated at Fo=2 or more. In this case, the product shall be prepared by aseptic processing before undergoing sterilization. We know that careful consideration is necessary for the PR of products treated at Fo<8. In the questionnaire survey, we found that some infusion fluids containing heat-labile substances such as vitamins, amino acids and so on are produced with a combination of aseptic processing and sterilization. So, if the PR is authorized for these products with low Fo values, it will be good news for manufacturers. For several years, Method 3 is likely to be applied only to aseptically produced products. Further investigations on the minimum Fo value, bioburden testing, releasing criteria and so on are needed.
In Japan, it seems that the opinion from industry sources on PR for terminally sterilized products is becoming favorable. Two years ago, the majority opinion was that they could not apply PR even to WFI or saline because the risk is too great compared with release based on sterility testing (Table 14). They also thought that new facilities and new sterilizers would be necessary to introduce PR for their products. Can this really be so? From the questionnaire results, it became clear that they produced their products under controlled sterilizing cycles with full validations as described in the Validation Requirements for Pharmaceutical Products in Japan. The problem is that they have to continue sterility testing while entertaining doubts as to its sensitivity. We must resolve this situation. Recently, several companies are under investigation to introduce the PR for their moist-heated products. This year, a few companies will apply to introduce PR for their terminally sterilized products.

7. Regulation of PR in Japan

This slide shows the flow of the procedures to approve PR for licensed drugs (Table 15). In Japan, we have no experience on the approval of PR. So, for the time being, applications for PR will be reviewed at the central governmental office. Manufacturers must apply to make the necessary changes of the testing procedures and acceptance criteria for licensed drugs to the local governor where the manufacturer's plant is located. From the local governmental office and if necessary from the central governmental office, GMP inspectors go to the applicant's plant. If there is no problem, the Minister will issue approval for PR to the applicant through the local governor.

To promote smooth introduction of PR, we are now preparing Q & A for PR. This slide shows some examples of Q & A (Table 16).

For example, for the question that, if one of the parameters is out of specification, can we do re-sterilization of the product, the answer is yes, you can do it, if you have validation data showing that there is no change in the efficacy, safety and quality of the products after the re-sterilization and if you specified re-sterilizing conditions in your SOP. You must investigate the reason why the parameter was out of specification (Table 17).

8. Conclusions

Considering the higher sterility assurance levels (SAL) of terminally sterilized products, it is undesirable to permit the release of the products based on sterility testing. Regulatory authorities should permit PR for terminally sterilized products if the products are consistently produced with SAL < 10^-6. First of all, regulatory authorities must understand the meaning and importance of PR for terminally sterilized products. Fortunately, our regulatory authorities understand PR well. However, the introduction of PR throughout the pharmaceutical industries will require careful regulatory control. So, we will have to carefully monitor the introduction of PR in Japan for at least several years.