Control Strategies and Change Control Concepts at Each Stage of Chromatography Lifecycle (Change Control in Chromatography Lifecycle) 〈*G1-5-181*〉

Analytical methods (analytical procedures) for pharmaceuticals must be set to provide test results suitable for their purpose, which must be considered throughout the lifecycle of analytical procedures, from design to development, qualification and continuous verification. In the field of drug development, particularly in the fields of manufacturing control and quality control, the effort of systematic quality assurance by quality risk assessment is implemented throughout the lifecycle (General Information "Basic Concept of Quality Risk Management" 〈*G0-2-170*〉). Effort to apply similar approaches to control strategy at each stage of the life cycle of analytical procedures are described.[1)-4)]

Various chromatographic systems are widely used for the analysis of pharmaceuticals, their components and impurities. Under these circumstances, a guide for changing analytical conditions was presented in the internationally harmonized test methods using chromatography (Chromatography <*2.00*>). However, there are various causes and timings for changing analysis conditions, and the positions of these factors in the overall lifecycle should be considered when change control of analytical condition is designed. Therefore, this general information describes the outline of the methodology for establishing control strategy at each stage of a chromatography lifecycle, aiming at the efficient control of analytical procedures, including changes of analytical methods. The methodology described below does not intend to newly add or mitigate regulatory requirements, but can be apprehended as the systematic documentation of the work that has been performed in laboratories. In addition, the concept of change control described in this General Information can be used as a reference for quality tests of pharmaceuticals in public testing institutions.

1. Analytical procedures that give test results suitable for the purpose of the test

Before designing and developing an analytical procedure, the purpose and goal (target profile) for the development of the analytical procedure are provisionally set and finalized in the latter stage of the development. When chromatography is used for quantitative analysis of active ingredients, etc., an analyte must be quantified with an accuracy and a precision within a certain range including the labeled amount in the presence of impurities or excipients. In addition, quantitative tests for impurities must be able to quantify impurities with an accuracy and a precision in the presence of various components presented in a sample within a range from the reporting threshold[5)] to the specification limit. As stated in section 5, for example, an analytical procedure may be changed or an analytical procedure itself may become unnecessary due to changes in impurity profiles, etc., however, the target profile of this analytical procedure can be the indicator whether the analytical performance characteristics are appropriate over the lifecycle. Here, the analytical performance characteristics are mainly characteristics evaluated by the "validation characteristics" described in General Information "Validation of Analytical Procedures" 〈*G1-1-130*〉. (In the test methods prescribed in the Japanese Pharmacopoeia, specifications and acceptance criteria in the monographs can be a target profile.)

2. Design and development of the draft procedure of chromatography

When the target profile of an analytical procedure is proposed, the draft of the analytical procedure is designed based on this profile, and the analytical procedure is established. In the process of the establishment, the implementation of risk assessment deepens the understanding of sources of variability in a series of analytical operations including analytical systems and their effect on reported values. Sources of variability are investigated using a method such as a characteristic diagram (Ishikawa diagram), and the root causes are identified and eliminated. At that time, the justification of various relevant validation characteristics proposed in the target profile, such as accuracy and precision, as well as specificity and linearity that affect the accuracy and precision, is confirmed. By a series of the confirmation of the justification, the target profile of the analytical procedure is reflected in key analytical performance characteristic[1)], and at the same time, it is possible to identify sources of variability and modify the analytical method from the results of those experiments. In addition, design of experiments (DOE), etc. can be used to clarify the relationship among the sources of variability and to study the degree of the variation that can occur when the analytical procedure is conducted under different conditions. Then, the sources of variability to be controlled and the acceptable ranges are clarified, and the analytical procedure is optimized.

Establish a control strategy based on the results of risk assessment. Control items may also include, for example, temperature, stability of sample solution, and number of replicates as well as the requirements of system suitability as described below.

System suitability testing is set as an appropriate check test to evaluate the effect of the sources of variability remaining in the analytical procedure that cannot be controlled as variable sources of variability(e.g., pH of mobile phase and column size) (General Information "System

Suitability"〈*G1-2-181*〉). Therefore, system suitability testing should be considered as a minimum control method during the qualification stage of analytical performance described below. System suitability testing should be set to focus on the analytical performance characteristics that can be affected and to ensure that the testing is considered to meet the requirements of the target profile. For system suitability testing, for example, resolution and a symmetry factor are set.

3. Preparatory stage for qualification

A control strategy for an analytical method is proposed by the clarification of the sources of variability and accumulated knowledge, and the analytical performance is ready to be qualified.

When a test method is already prescribed in the Japanese Pharmacopoeia, based on the test method, it is necessary to understand and examine beforehand to what extent additional sources of variability exist in the laboratory where the acutual analysis is conducted and to what extent advance information has been already obtained. Additional sources of variability include, for example, samples, reagents, facilities, instruments, and the number of replicates that can occur with those variations. When applying a test method prescribed in the Japanese Pharmacopoeia, in many cases analysts do not have the knowledge and understanding obtained during the development of the analytical method. Therefore, the analysts should be aware of the potential risks due to additional sources of variability and should ensure that the above risks are appropriately reduced by the qualification of the analytical performance, etc. (Column information available on the Pharmaceuticals and Medical Devices Agency website may be useful as advance information.)

4. Qualification of analytical procedure performance

The purpose of qualification is to confirm that an analytical procedure used routinely in a laboratory constantly meets a target profile. For qualification testing, a protocol is prepared and the test is performed according to the procedure manual and appropriate control. As the result of the test, for example, when the variation of the reported values may exceed the requirements in the target profile, examine whether the control strategy is optimized for the laboratory, identify the sources of variability, and the control strategy of the analytical method may be improved or revised.

Even when applying a test method prescribed in the Japanese Pharmacopoeia, different control strategies are required for different laboratories and instruments. For qualification in the laboratory where a test method prescribed in the Japanese Pharmacopoeia is performed, the process of the quality risk management of the analytical method should be considered to meet the intended target profiles of specifications and acceptance criteria in each monograph.

In the qualification when applying test methods prescribed in the Japanese Pharmacopoeia, it is not essential to perform the verification of the validity of validation characteristics again to the same extent when establishing the analytical procedures, however, it is necessary to confirm the qualification using appropriate validation characteristics listed in General Information "Validation of Analytical Procedures"〈*G1-1-130*〉. The content of the implementation should consider the type of analytical procedures, related instruments, etc. In addition, consideration should be given to factors derived from test samples. For example, when applying a test method prescribed in the Japanese Pharmacopoeia, impurities that may differ depending on a drug substance or drug product can affect the "specificity" of the test method. When resolution is set in the system suitability testing, confirm the effect by the resolution, and if the specificity is reduced, examine the effect on the test result. If the analytical performance deteriorates, it will be necessary to examine the analytical conditions. In addition, since different excipients in drug products may affect interference with a substance to be analyzed (specificity), detection (detection limit), recovery (accuracy) and variation in quantitative values (precision), perform the qualification using system suitability testing and appropriate validation characteristics described in General Information "Validation of Analytical Procedures"〈*G1-1-130*〉.

5. Continuous verification of Analytical Methods

1) Routine monitoring: At this stage, data on the performance of analytical procedures, such as analytical results, suitability for system suitability, deviations from specifications and specific trends, are collected and analyzed. If nonconformity to the system suitability, deviation from the specification, or a specific trend becomes clear, it is necessary to examine the cause and take corrective and preventive measures.

2) Change of analytical procedures: As with the manufacture of pharmaceuticals, analytical procedures may be changed for the activity of continual improvement and for analysis in different environments. When newly applying a test method prescribed in the Japanese Pharmacopoeia, it may be necessary to change the procedure according to the current equipment or columns. Furthermore, it is expected that an analytical method will need to be changed as the result of routine monitoring described in 1). Depending on the extent of the change, the contents and amount of work for evaluating the effect of the change on the test results vary. Examples of possible changes are shown below.

① When an analytical procedure is changed within the acceptable range of the procedure evaluated at the time of the development of the analytical procedure, it is

necessary to evaluate the effect on a case-by-case basis and confirm that the changed procedure always meets the target profile. (However, this does not apply when such acceptable range has not been examined at the time of the development of the analytical method.) Even if the change of each condition is within the acceptable range, when multiple conditions are changed, it may be necessary to take similar measures as the following ②.

② When an analytical procedure is changed beyond the acceptable range of variability of the procedure evaluated at the time of the development of the analytical method, risk assessment is required. In addition, if the acceptable range of changes has not been examined by quality risk management at the time of the development of the analytical method, risk assessment is required when changing the analytical conditions. When conducting risk assessment, consider which analytical performance characteristics (validation characteristics) can be affected by the change. Then, qualification is performed to confirm that the analytical performance does not deviate from the target profile (refer to 4). Specifically, verify using validation characteristics that may be affected by the change among validation characteristics listed in General Information "Validation of Analytical Procedures" 〈*G1-1-130*〉. When validation characteristics that may be affected by a change are set as one item of system suitability testing, the validation characteristics may be verified by using the system suitability testing. Further, when changing a column size and the composition of a mobile phase in chromatography, verify analytical performance appropriately, referring to "Adjustment of Chromatographic Conditions" in Chromatography <*2.00*>.

③ When a laboratory is changed or a test method prescribed in the Japanese Pharmacopoeia is newly applied, the analytical performance characteristics may be affected by the change in analytical instruments, analysts, reagents, etc., so perform risk assessment and appropriate qualification (refer to 3 and 4). On the other hand, when updating analytical equipment or columns or replacing analysts in a same laboratory, at least perform system suitability testing with the changed analytical system to confirm that the same results are obtained before and after the change.

④ When changing to a new analytical procedure or technology, qualification must be performed during the development of the new analytical procedure(refer to 2, 3 and 4) to demonstrate that the new procedure meets the target profile.

⑤ When a change that affects a target profile (e.g., changes in specifications, changes to methods for determining the amount of a new analyte, such as impurities that were not considered in the original target profile) is required, it may be necessary to review the current analytical procedure and qualification to update the target profile and assess whether the analytical procedure meets the requirements of the new target profile (refer to 1, 2, 3 and 4).

The extent of work to confirm whether a change in an analytical method gives a test result suitable for the purpose depends on ① risk associated with the change, ② knowledge obtained about the analytical procedure, and ③ control strategies. Whatever changes are made, perform more or less risk assessment to ensure that the changed analytical procedure provides the results that meet the purpose of the test method (i.e., within the range specified in the target profile).

6. References

1) G.P. Martin, et al., Pharmacopeial Forum 39 (5), 2013
2) Proposed New USP General Chapter: The Analytical Procedure Lifecycle <1220>, Pharmacopeial Forum 43 (1), 2017
3) K.L. Barnett, et al., Pharmacopeial Forum 42 (5), 2016
4) E. Kovacs, et al., Pharmacopeial Forum 42 (5), 2016
5) ICH: Guideline for Q3A (R2), Impurities in New Drug Substances.