

Quality Stabilization of Formulation Process by Using Mahalanobis Taguchi (MT) Method and Applications to Continuous Drug Production

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A paradigm shift in manufacturing processes has been proceeding mainly in formulation processes in the pharmaceutical industry. Pharmaceutical manufacturing, in which product quality is ensured under the control of good manufacturing practice (GMP), is facing the challenge of poor productivity compared with other industries. Thus, pharmaceutical manufacturers are making efforts to increase productivity while maintaining high product quality by transforming their production from batch to continuous processes. For this purpose, technology that ensures ideal continuous production while maintaining quality is required. This paper introduces a case example of a quality stabilization approach by using the Mahalanobis Taguchi (MT) method, and describes technical strategies necessary for constructing a continuous drug production system.

INTRODUCTION

A pharmaceutical process in manufacturing of pharmaceutical products is a batch process that combines stand-alone pharmaceutical machines as unit processes. Process-to-process transfer is mainly performed manually and sample inspection is carried out in each process, so production efficiency is extremely low. Meanwhile, in other manufacturing industries with continuous processes, such as oil refinery, production efficiency has been increased to the limits by optimizing operation by combining full-automation and advanced control. The U.S. Food and Drug Administration (FDA) which has been concerned about the lower efficiency of pharmaceutical product manufacturing compared to that of other manufacturing industries has been recommending to the pharmaceutical companies to introduce the continuous process to pharmaceutical manufacturing since several years ago as a challenge to be taken on by pharmaceutical companies. An in-process real-time monitoring and control

technology is required to implement a continuous process, and the technology matches the Quality by Design (QbD) concept⁽¹⁾ and Process Analytical Technology (PAT) initiative⁽²⁾ recommended by the FDA.

The QbD concept is an approach to ensure the quality in the process at the design phase of the manufacturing process, and the PAT initiative is FDA's initiative to promote the introduction of a system that measures, analyzes, and controls the critical attributes of manufacturing processes in real time.

Since 2004, when the FDA launched the PAT initiative, Yokogawa has developed an on-line near infra-red (NIR) analyzer for powder that directly measures the quality in pharmaceutical processes and studied a process quality monitoring system using the statistical model of process data. In addition, Yokogawa has committed itself to the development of a system to stabilize the quality that is necessary for continuous pharmaceutical processes by applying the product quality stabilization service using the Mahalanobis Taguchi (MT) method to the pharmaceutical process.

This paper describes first a specific method to identify factors that have an influence on the quality by presenting a case example in which the quality of a pharmaceutical process was improved. Deterioration of quality in the process can be prevented and the quality can be stabilized by identifying the influencing factors and monitoring and controlling them. This paper describes then how to design the control system of a pharmaceutical process using a process model. This approach is based on the QbD concept recommended by the FDA,

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and aims to design the optimal control system by defining the relationship between parameters related to the quality. The paper describes finally the concept of a pharmaceutical product continuous production system that Yokogawa aims to implement based on a quality stabilization technology and a control system design approach for pharmaceutical processes.

CHALLENGES OF QUALITY STABILIZATION IN PHARMACEUTICAL PRODUCT MANUFACTURING

The QbD concept that ensures the pharmaceutical product quality in manufacturing processes using a systematical method basically requires the understanding of products and processes as well as the process control, and the following attributes and parameters must be controlled.

- Quality Target Product Profile (QTPP): A summary of quality attributes that must be achieved to assure the required product quality
- Critical Quality Attribute (CQA): Attribute that must be maintained within the appropriate limits, range, and distribution to assure the required product quality.
- Critical Process Parameter (CPP): Process parameter whose changes have an influence on the critical quality attributes

In addition to the above, Critical Material Attribute (CMA) is defined as a material attribute that has an influence on the critical quality attributes.

We asked a question to a person working with a pharmaceutical company: "What is the most important challenge for the quality in pharmaceutical product processes?" The answer was: "Even if you use materials with the same specifications and manufacture products according to the specified manufacturing instructions, the quality of the final products may vary and it is difficult to identify the cause."

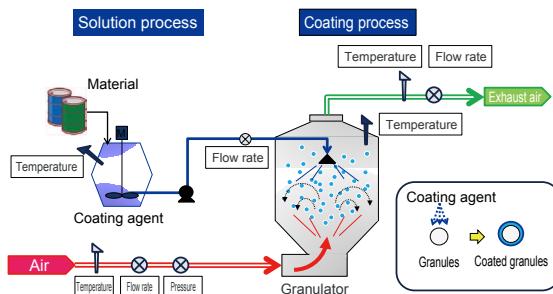


Figure 1 Target process

The target process of a challenge (Figure 1) is a process in which coating material is sprayed while granules are agitated with a granulator to coat the surface of the granules. In this process, the dissolution rate (of a drug), which is a critical quality attribute (CQA), is adjusted by the coating thickness. The thickness can be adjusted by changing the spray speed of the coating material. When the dissolution rate of the granules is maintained within the target dissolution rate range while the coating spray speed is constant, the lot is defined as a normal lot, and when the dissolution rate does not fit into the target range if the spray speed is not changed, the lot is defined as a manual intervention lot (Figure 2).

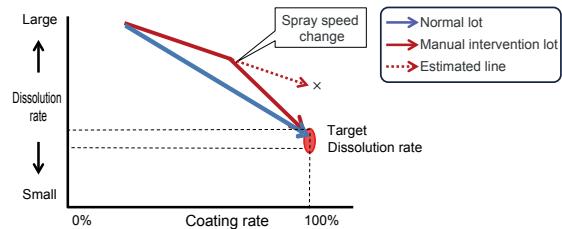


Figure 2 Dissolution rate change and spray speed change image

The Quality Stabilization Service provided by Yokogawa begins with understanding the actual process, the target quality, the critical factors that have an influence on the quality, and how the critical factors are controlled in order to solve the challenge. Figure 3 shows the relationship between the target dissolution rate (CQA), material composition (CMA), and process parameters (CPP) in this case.

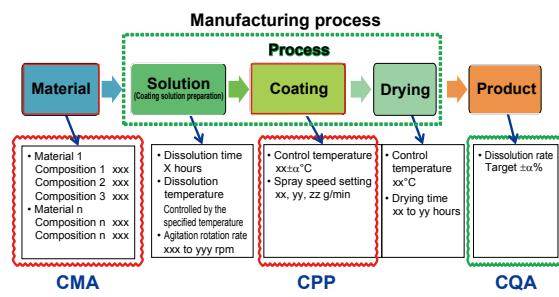


Figure 3 Relationship between CQA, CMA, and CPP

We made the following two hypotheses to analyze the manufacturing data.

[Hypothesis 1] Normal lot and manual intervention lot can be distinguished from the material composition data.

[Hypothesis 2] Dissolution rate can be estimated from the material composition data and process parameters.

The following describes the analysis results based on those hypotheses.

ANALYSIS RESULTS BY QUALITY STABILIZATION SERVICE

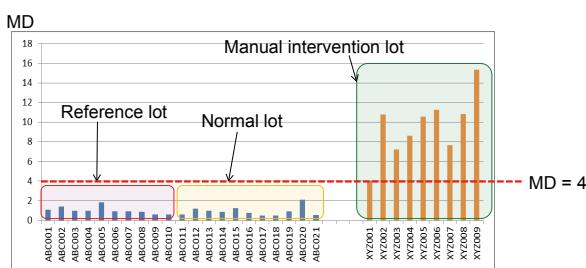
Distinguishing Normal Lot and Manual Intervention Lot by Material Composition Data

The coating material is made of 12 types of materials and there is a total of 81 composition items. The Quality Stabilization Service took an approach of extracting material compositions that were determined to have a significant influence on the elution from all material compositions. We made a risk assessment in cooperation with multiple members from the manufacturing, quality control, R&D, and other departments of the user company. Only material compositions that were determined to have a significant influence on the elution were extracted by the assessment. This time around, only materials with an influence level of 7 or more (7 types of materials and 38 compositions) were extracted (Figure 4).

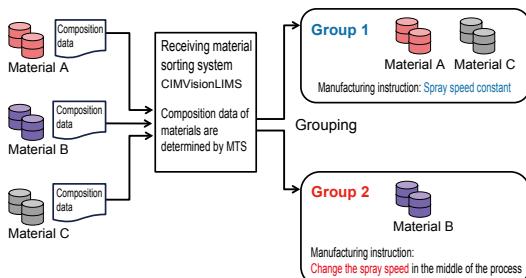
All material compositions (12 types / 81 compositions)			Critical material compositions (7 types / 38 compositions)		
Material name	Composition name	Influence level	Material name	Composition name	Influence level
Material 1	Composition 1	8	Material 1	Composition 1	8
	Composition 2	5		Composition 3	7
	Composition 3	7			
Material 2	Composition 1	3	Material 2	Composition 2	10
	Composition 2	10		Composition 3	9
	Composition 3	9		Composition 4	8
	Composition 4	8			
	Composition 5	4			
Material 1 ₂			Material 1 ₂		
Composition 1			Composition 1		
Composition 2			Composition 3		
Composition 3			Composition 3		

Figure 4 Risk assessment results

A comparison and analysis using the MT method was made to determine the differences between the normal and manual intervention lots using the extracted material composition data as the input data. It was found that the normal and manual intervention lots can be distinguished by a clustering around Mahalanobis distance (MD) values between some values of the material composition data (Figure 5).

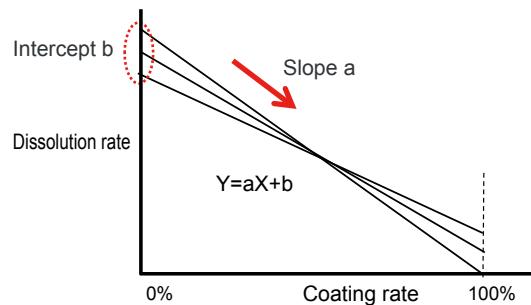
**Figure 5** Distinguishing analysis results using MD values

Usually, a sampling test is carried out for the material composition data when materials are received. The sampling data is accumulated in the laboratory information management system (LIMS). Therefore, the material composition conditions can be understood in advance using a receiving material sorting system that can be implemented by incorporating the logic of the MT method used in the analysis in Figure 5 into CIMVisionLIMS provided by the Yokogawa Solution Service. As a result, when using a material that requires the spray speed to be changed, preparation for changing the speed can be made in advance and thus production efficiency can be improved (Figure 6).

**Figure 6** Proposal to improve production efficiency using LIMS data

Dissolution rate Estimation Using Material Composition Data and Process Parameters

The following describes the analysis method and results in hypothesis 2. The purpose of this analysis is to estimate the dissolution rate, in other words, the quality, and identify factors that have an influence on the variations in the dissolution rate. We used two types of analysis methods. One is to estimate the dissolution rate itself and the other is to estimate the slope and intercept of a regression line that indicates the elution tendency (Figure 7). A regression line indicates the relationship between coating rate (X) and dissolution rate (Y): $Y=aX+b$, and the values to be estimated are slope (a) and intercept (b).

**Figure 7** Slope and intercept of regression line indicating elution tendency

The analysis results show that the estimation of the dissolution rate itself was not as accurate as expected and the estimation of the slope and intercept of the regression line tends to be more accurate. It is possible to estimate that variations in the dissolution rate due to influences other than those of the material composition data and process parameters can be reduced by regression and thus accuracy can be increased.

We analyzed the slope and intercept of the regression line that indicates the dissolution rate from the material composition data and process parameters by analyzing the lots using the same materials to identify factors that have an influence on the variations in the dissolution rate. In addition to the analysis results of the slope and intercept, influencing factors for the slope and intercept were output in order of the values. Figure 8 shows the analysis results. The spray air quantity is at the top of the list of significant influencing factors. It can be concluded from this that not only the material composition but also a process parameter (spray air quantity) have an influence on the elution tendency.

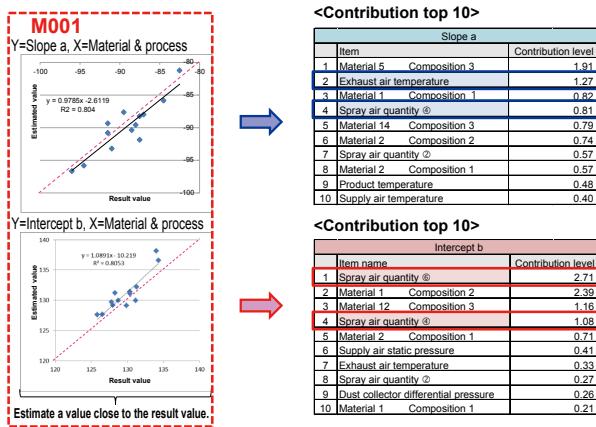


Figure 8 Analysis results excluding level of influence on variations in specific materials

As a result of the analysis this time around, it was found that a spray speed guidance or automatic setting can be implemented by estimating the dissolution rate based on the material composition and process data. As a benefit of this analysis, we could build a system to stabilize (improve) the quality and reduce the manufacturing lead time. Figure 9 shows an automated quality stabilization system in pharmaceutical processes proposed by Yokogawa.

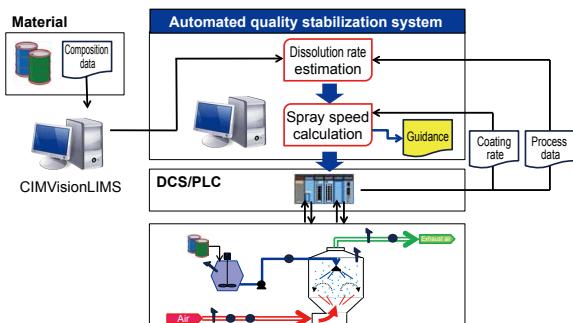


Figure 9 Proposal of automated quality stabilization system

PRODUCTION CONTROL SYSTEM FOR CONTINUOUS PROCESS PRODUCTION

The following describes an approach to using process models to design a pharmaceutical process control system that enables the implementation of QbD-based production control. To implement such a control system, it is necessary to measure, analyze, and control the data related to the target product quality seamlessly and in real time using the system described above.

The following describes first how to build a QbD-based production control system, then manufacturing plants (batch, real-time release testing, continuous process, and continuous devices) in phases towards a continuous process production, and finally how to build and operate a production control system for the entire continuous process.

QbD-based Production Control System

The following describes the concept of how to control product quality. The quality target product profile (QTPP) is defined as a collection of multiple critical quality attributes (CQAs). Accordingly, QTPP is defined as a vector of critical quality attributes.

$$QTPP = (CQA1, CQA2, CQA3, \dots) \quad (1)$$

CQAs are controlled in association with critical material attributes (CMAs) and critical process parameters (CPPs) in unit processes. The relationship between specific quality parameters is established according to an experimental design method, etc. and is usually represented by a fishbone diagram as shown in Figure 10.

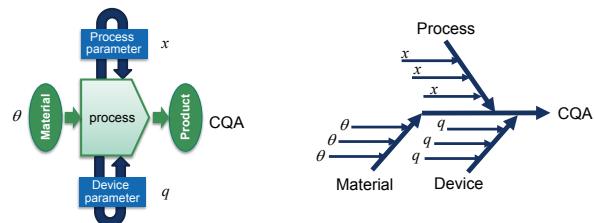


Figure 10 Unit process and fishbone diagram

A unit process is described as a dynamic system using process attributes and device attributes as shown below, and the design problem of a supervisory control system is generally formulated as an optimization problem as follows.

$$\text{Objective function: } y = g(\theta, x)$$

$$\text{Process attribute: } \dot{\theta} = f_{process}(\theta, x)$$

θ : Material attribute vector

x : Process parameter vector

$$\text{Device attribute: } \dot{\theta} = f_{device}(\theta, q)$$

θ : Material attribute vector

q : Device parameter vector

Derive process parameters $X^{\text{target}}(t)$ that minimize the above objective function and design a supervisory control system that equalizes each parameter to $X^{\text{target}}(t)$.

In general, the objective function is defined as follows.

$$\text{Objective function: } y = \min_x \int (CQA^{\text{target}} - CQA) dt \quad (2)$$

Derive process parameters $X^{\text{target}}(t)$ that minimize the accumulated error values of the target product's critical quality attribute CQA^{target} and perform control to track the time changes of the derived process parameter. Furthermore, CQA is defined as a multiple regression equation of multiple critical material attributes (CMAs) selected from the material attribute variable θ as a critical factor as shown in the formula (3).

$$h(CQA, CMA1, CMA2, CMA3, \dots) = 0 \quad (3)$$

Set the upper and lower limits for CMA in each process as shown in the formulas below so CMA meets the CQA_{target} and perform operation so CMA falls between the upper and lower limit values.

$$h(CMA_{Mixing}^{target}, CMA_{Granulation}^{target}, CMA_{Tableting}^{target}, CMA_{Material}^{target}) = 0$$

$$CMA_{Mixing}^{target} \in [\theta_{Mixing}^{min}, \theta_{Mixing}^{max}]$$

$$CMA_{Granulation}^{target} \in [\theta_{Granulation}^{min}, \theta_{Granulation}^{max}]$$

$$CMA_{Tableting}^{target} \in [\theta_{Tableting}^{min}, \theta_{Tableting}^{max}]$$

$$CMA_{Material}^{target} \in [\theta_{Material}^{min}, \theta_{Material}^{max}]$$

A solid pharmaceutical process is made up by connecting unit processes such as mixing, granulation, tableting, and coating processes, and the relationship between specific quality parameters can be visualized by a fishbone diagram as shown in Figure 11.

It is important to measure, analyze, and control those factors (CPP, CMA, and CQA) throughout the entire process seamlessly and in real time in order to ensure that products with the target quality are produced.

Each unit process (mixing, granulation, tableting, and coating) is described as a dynamic system using process attributes and device attributes as follows, and in general, the design of the control system for each unit process is formulated as an optimization problem of each process. A process parameter of each process that minimizes the objective function of each process (X^{target}) is derived and a supervisory control system is designed to equalize each parameter to $X^{target}(t)$.

In general, the objective function of each unit process is defined as in the formula (4).

$$\text{Objective function: } y = \min_x \int (CMA^{target} - CMA) dt \quad (4)$$

Process parameters $X^{target}(t)$ that minimizes the accumulated error values of the target critical quality attribute of the intermediate is derived.

Each unit process is controlled by a control system designed by the above method, and the quality target product profile (QTPP) is evaluated by multiple product CQAs as shown in Figure 12.

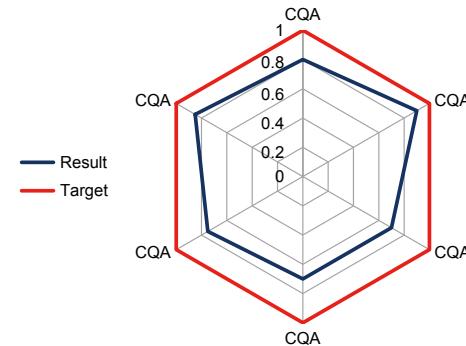


Figure 12 Target quality profile display

Production Control System for Continuous Process Production

Figure 13 shows a conceptual diagram of a production control system for a production system for a continuous pharmaceutical process. Figure 14 shows its operation lifecycle. In Figure 14, control is performed while each unit process is monitored in real time, and an upper-level supervisory control function controls the entire process. Figure 14 shows how mixing, granulation, tableting, and coating processes are started in a sequence and products are produced after the entire process is up and running.

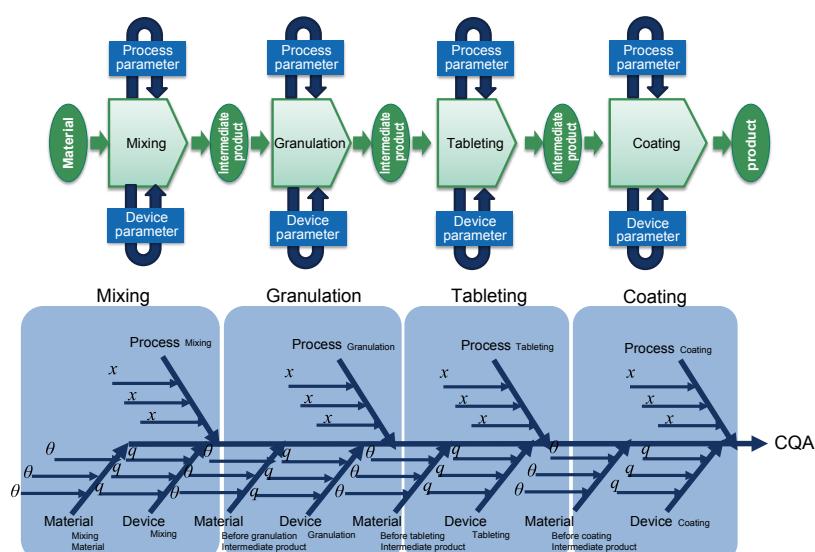


Figure 11 Entire process and fishbone diagram

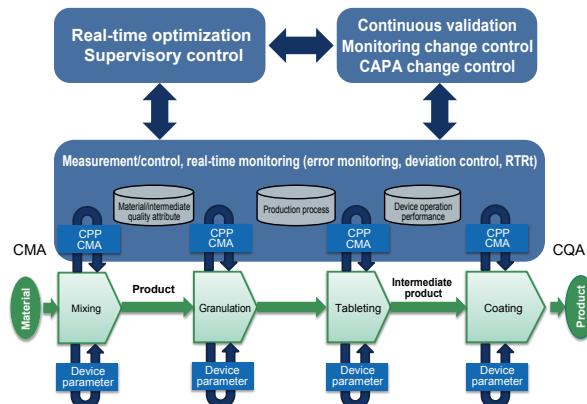


Figure 13 Production control system conceptual diagram

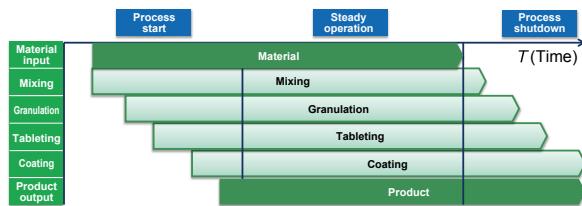


Figure 14 Continuous process operation lifecycle

The operation lifecycle of a continuous process for a pharmaceutical process is made up of the start, steady operation, and shutdown, and it is necessary to stabilize the quality and increase the production yield of the steady operation. In the case of a continuous process, optimizing the entire process by optimizing each unit process is much more difficult than that in a batch process. The reason is that the process attributes of each process are related to each other and the operational objectives are also diverse.

For example, it is necessary to determine the operational conditions (CPP) and intermediate product's CMA to increase the production yield and stabilize the process for the steady operation at the same time. Usually, it is necessary to derive the CPP and CMA conditions using static attributes of the process as constraints in steady operation and produce products under operational conditions that gain a high production yield in a range that does not deviate from the quality.

It is also necessary to minimize the quantity of good products that meet the required quality level rejected as defective products that do not reach the required quality level and reduce the risk of defective products being passed as good to zero. To do so, it is necessary to determine the control range of CQA based on the knowledge about the process and experimental data obtained in the laboratory.

Today, the pharmaceutical manufacturing industry has started to introduce the Operational Excellence⁽³⁾ initiative

that will improve the operational processes from the process design at laboratories through to the production process, and to design and operate an overall optimized production process. The industry is expected to implement a continuous operation improvement process to ensure that the production process is operated as designed and planned, thus producing the desired pharmaceutical products stably and efficiently as shown in Figure 15.

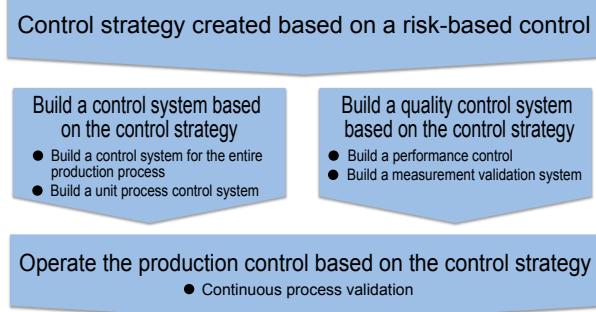


Figure 15 Operation process for design and improvement

CONCLUSION

Continuous process for pharmaceutical process is a paradigm shift that brings about innovation in the manufacturing technology and is also a challenge, for which Yokogawa can make the best use of knowledge and experience acquired from manufacturing sites in diverse industries. The Quality Stabilization Service presented in this paper has not only the pharmaceutical industry's case examples but also many improvement case examples in the chemical industry that mainly uses a continuous process. We believe the use of knowledge and systems acquired in those industries, combined with the control system design concept described above, will enable making a paradigm shift from the batch process to continuous production that can provide products with a stable quality that the FDA expects, and will contribute to building a pharmaceutical process that will produce products with a continuous stable quality.

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