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In Vitro Performance Tests for Continuous Manufacturing: The Impact on the Current Compendial Framework from the Viewpoint of the USP New Advancements in Product Performance Testing Expert Panel

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ABSTRACT

As continuous manufacturing (CM) evolves from an emerging to widely adopted technology by industry in drug product manufacturing, the compendial framework in product performance testing is also being evaluated for its applicability in CM. As such, the CM Working Group of the New Advancements in Product Performance Testing (NAPPT) Expert Panel was convened in 2019 to review the current standard for product performance testing, identify gaps in its applicability to CM, and recommend the development of new standards to support the adoption of advancing technologies industry-wide. This *Stimuli* article discusses the challenges and limitations of the current performance testing by dissolution for CM applications. It also presents recommendations on alternatives or surrogate methods, including in/at-line process analytical technology methods, with a decision tree to support users in identifying an option that is fit for their process. The Expert Panel seeks stakeholder feedback on the recommendations presented in this *Stimuli* article, and requests additional comments on the perceived challenges and limitations of performance testing.

INTRODUCTION

Continuous Manufacturing (CM) is considered one of the most important innovations to modernize the pharmaceutical industry (*1*). Unlike conventional batch processes, which comprise a series of disconnected unit operations, the CM process includes a single integrated process train end-to-end. Starting material is continuously fed into the train, while the finished product gets continuously harvested from the train. Since the first successful application of CM to commercial manufacturing of Orkambi by Vertex in 2015, seven CM products from four different companies have been approved for the market (*2*), with many more in the clinical stage.

Some of the key benefits of CM over batch process include reduced manufacturing footprint, elimination of process scale-up between development and commercial manufacturing, flexible supply with the production duration adjusted according to demand, reduced equipment downtime, and eliminated process intermediate transfer. As a result, up to 50% reduction in manufacturing cost has been demonstrated (*3*). In addition, process control parameters could be varied over pre-defined time intervals during a single development

process to quickly and efficiently execute design of experiment (DOE) to explore the process design space. This agile DOE and real-time process monitoring by process analytical technology (PAT), which is typically an integral part of CM, allows the generation of rich process insights that significantly improves process robustness and final product quality.

However, the continuous nature of CM also poses some unique challenges from both regulatory and technical perspectives, such as batch definition, process validation, and advanced process and product quality control strategies. In this article, the CM Working Group of the New Advancements in Product Performance Testing (NAPPT) Expert Panel discusses some specific challenges around product performance testing and some possible solutions.

CURRENT REGULATORY AND COMPENDIAL FRAMEWORK FOR PERFORMANCE TESTING

Conventional methods for ensuring final drug product quality in standard batch manufacturing such as those in pharmacopeia (United States or any other pharmacopeia) are reliable. Monograph tests, analytical procedures, and acceptance criteria for testing oral drug products are divided into two categories: general product quality attributes and drug product performance tests. Drug product performance tests are designed to assess in vitro drug release from dosage forms (e.g., Dissolution <711> (*4*) and Drug Release <724> (*5*).

The regulatory requirement for the quality of the product in CM remains the same as in conventional batch processing. The drug product performance, which is typically measured with dissolution, is a specific quality attribute that links to bioavailability and bioequivalence studies (*2*). Therefore, the dissolution method should be meaningful, able to characterize the quality of the drug product and capable of distinguishing significant changes in the formulation or manufacturing process that might affect the in vivo performance, and should be sensitive to any changes in product integrity during its shelf life.

Dissolution can also link product quality to in vivo performance through in vivo-in vitro correlations and relationships (IVIVC/IVIVR). This correlation enables the use of dissolution data as a tool for evaluating any post-approval changes to the formulation or manufacturing process, as well as for the development and approval of generic products. It is used as an effective tool to waive in vivo bioequivalence (BE) clinical study requirements, per Scale Up and Post Approval Changes (SUPAC) guidance (see also *In Vitro and In Vivo Evaluation of Oral Dosage Forms* <1088> (*6*) and *Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution* <1090> (*7*)).

The biopharmaceutics classification system (BCS) is commonly applied as a framework for risk assessment when determining the approach for product performance assurance (*7*). For highly soluble drugs, dissolution testing can be replaced by disintegration testing if it is shown that the active pharmaceutical ingredient is highly soluble, the formulation is rapidly releasing (*8*), and a relationship between dissolution and disintegration is established.

Limitations of Current Dissolution Performance Test

While dissolution testing has been widely used in the pharmaceutical industry for formulation development, batch-to-batch quality assurance, product stability and release, and regulatory acceptance of bioequivalence and biowaiver, several limitations associated with the test have also been identified. These limitations can be divided into 3 aspects. The first is related to the test operation. Dissolution testing is time consuming. A normal test run, not including finish detection and data processing, can take up to 1 h for immediate release dosage forms, 3 h for controlled release dosage forms, and much longer for extended-release dosage forms. The test relies on relatively large equipment in a laboratory setting, is not suitable for in-line operation, and can be very challenging for at-line operation. It is a destructive test, and generates a large quantity of aqueous waste, which has an adverse environmental impact.

The second aspect is related to the variability of the test. Dissolution testing can exhibit greater variability than other testing methods for product quality assessment, such as for assay and content uniformity. While some of these potential sources of variance can be reduced or controlled by optimizing the method, they can potentially be reduced even further by substituting PAT data-based dissolution modeling prediction, as will be discussed for use in CM product release.

The third aspect is the biorelevance of the testing. Dissolution testing conditions defined in the pharmacopeia are very different from an in vivo environment, including the volume, media, and mechanisms of agitation. Many dissolution methods developed using compendia! equipment as a quality control tool for manufacturing may not lead to data that can be correlated to in vivo performance. In recent years, significant efforts have been made to develop biorelevant dissolution methods and set clinically relevant specifications (*9*).

Current dissolution testing has other limitations when being considered for use with CM (*10*), which will be discussed in the section below.

ANALYTICAL CHALLENGES OF CONVENTIONAL DISSOLUTION TESTING IN A CONTINUOUS PROCESS

Performance testing of CM batches can be done by off-line traditional dissolution testing per USP <711> or per *Ph. Eur.* 2.9.3 via physical sampling. As CM is still a relatively new technology in drug manufacturing, there hasn't been any well-established documented procedure or guidance defining dissolution testing strategies, specifically in sampling and testing frequency. ICH Q13 (*11*), which is currently in step 3 under public consultation and expected to be officially adopted by the end of 2022, provides guidelines in sampling strategies for process monitoring and control, but it excludes sampling for release testing, especially in the context of physical sampling for offiine testing. This is a unique challenge that CM sponsors face when justifying the testing strategy against expectations from health authorities. For a traditional batch process, dissolution sampling and testing for batch release is typically done post-production, and is achieved by testing a composite sample following well defined and established sampling requirements per USP <711> or *Ph. Eur.* 2.9.3.

However, for a continuous process, the production is defined by time, and the concept of a "composite sample" is quite different from a traditional batch process. There is no well-defined guideline on composite sampling for a CM process, and there may be different expectations from health authorities of different regions. For a sponsor that submits globally, the most complex and conservative sampling procedure usually prevails. The complex sampling procedure may not be an issue through data sampling using in-line measurement if real-time release testing (RTRT) is employed; however, it can be burdensome if sampling is done through physical sampling followed by traditional offline testing. For stratified composite sampling throughout the continuous process, one has to carefully design the sampling probe and sampling point and may need to introduce additional sampling diverter valves in order to not disturb the material flow.

Compared to batch processes, the amount of sampling required by health authorities for a continuous process is generally significantly higher. In one example of a marketing application for a film-coated tablet product, a sampling request of up to 12% of the coating runs was made, which translated to hundreds of tablets for offline dissolution testing. From a practical and economical perspective, the additional and complex sampling throughout the process adds significant resource use and cost to the production. Testing of the composite sample collected through a continuous process for dissolution also faces unique challenges compared to a batch process. Because of the complex sampling design, the number of samples to be tested for dissolution may not be able to follow the staged testing and/or acceptance criteria defined in USP <711>.

The different expectations and requirements from different health authorities create additional challenges for the sponsor to manage a product globally. As there is no harmonized approach across regions, the sponsor would have to manage the dissolution release testing in multiple ways, each specifically tailored to meet different health authorities' requests, as some still follow the pharmacopeia, while others have very specific requirements for sampling and testing.

In this same example above, after rounds of open discussions with the health authority, the final agreed-upon sampling and testing strategy was to sample the process through 12 pre-defined segments, with traceability, and the USP <711> stage 2 criteria were applied for 12 tablets. The agreed-upon sampling and testing plan was based on significant development data and statistical analysis. This sampling and testing strategy, along with the application of USP stage 2 criteria, has subsequently been accepted by multiple major regions.

CM, by design, employs significantly more in-line measurement via PAT, resulting in significantly more process data than a typical batch process. Sampling frequency for a continuous process should take a risk-based approach, and should be determined based on development stage, product and process knowledge (i.e., through quality by design), and fit for the intended use of the data (e.g., making local process-stage vs batch-level quality statements). Once the process is validated for routine commercial production, the role of the physical sample measurements should change from being the primary indicator of quality to solely confirming quality, because quality is ensured by maintaining a state of control with the process parameters within acceptable ranges (*12*). With the amount of in-process monitoring and control implemented in the continuous process, the sampling for release testing should be simplified and harmonized.

The conversion from a batch process to a continuous process could also present challenges in performance testing, especially for a well established product. Can the

same sampling and testing strategy be applied from batch to continuous, or is a completely new set of strategies required, or somewhere in between? This remains a point of uncertainty with regard to requirements from global regulatory bodies.

POSSIBLE ALTERNATIVES OR SURROGATES TO CONVENTIONAL PERFORMANCE TESTING

As mentioned in the previous section, most standard compendia! performance tests are not compatible with the requirements of CM. Suitable performance tests in a CM environment should be real or at least near-real-time, and optimally nondestructive. There are two principal approaches to collecting the required results. The first is on- or at-line tests, such as at-line disintegration test for highly soluble drugs. The second is leveraging data from one or more of the many measurements gathered in the data rich environment associated with CM to create a preferable nondestructive surrogate test. This approach may rely on predictive modeling to convert collected data into the surrogate performance test results. By establishing a relationship/correlation between dissolution and other methods or process parameters, the documented control of this/these parameter(s) during manufacturing will allow for elimination of the requirement for conventional dissolution tests.

As is often the case with analysis of solid oral dosage forms, the nature of the performance tests required to validate product quality correlate to the BCS Classification of the product, and in particular, the solubility. This does not change in a CM environment. Therefore, the recommendations for possible alternative measurement techniques are divided into those for highly soluble and poorly soluble drugs.

Highly Soluble Drugs (BCS Class 1 and 3)

As is also the case in batch manufacturing, one possible approach to testing BCS Class 1 and 3 drugs is to use conventional disintegration testing as a surrogate for the dissolution test (*13*, *14*). To better harmonize the time scale of disintegration testing with CM, one can possibly switch to at-line testing. The advantages of this approach are that it is based on existing, well-defined testing methodologies and that for a product being converted from a batch process to CM, the protocol can be transferred intact. The main disadvantage of this approach is that because disintegration is a destructive test, there is no option for 100% monitoring. Also, while brief, disintegration testing is not real-time, eliminating the possibility of true continuous monitoring.

The alternative method would be a Quality by Design (QbD) approach based on the use of predictive modeling. These models may be based on a single parameter or a combination of measurements. An example of the first approach is to substitute a near-infrared (NIR) spectroscopic measurement for the disintegration test. This virtually eliminates the limits on both the number of units sampled and the time between samples. If required, NIR data can be supplemented or replaced in the model by the addition of particle characterization data on the active pharmaceutical ingredient (API) and excipients, dosage form hardness data, coating thickness data, etc.

BCS Class 2 and 4

For BCS Class 2 and 4 drugs, the available alternative method to conventional dissolution is a QbD approach based on the use of predictive modeling. Again, with sufficient validation, these models may be based on a single parameter or a combination of measurements, with the latter probably being more appropriate for these products. As is common in such modeling (for example, see Reference 10 and all the citations included therein) the required measured inputs for the model will need to account for ongoing variations in characteristics of all the constituent materials, the manufacturing process (wet or dry granulation, hot-melt extrusion, spray-dried dispersion, etc.), and any other process that may affect the final product. These parameters may be part of the existing set of PAT measurements that are already included as part of the rest of the CM control strategy or may require additional readings and sensors to comprise a sufficient set.

Limitations of Alternative or Surrogate Methods

The application of surrogate dissolution testing is a new and rapidly evolving field. Because of this, there are relatively few examples of approved products using surrogate dissolution testing. For predictive modeling, the inputs needed to predict product performance may vary widely depending on the type of process used, and the properties of the drug substance and drug product formulation. This makes it challenging to define standards for surrogate testing. Any standard would need to be flexible enough to encompass both emerging technology and the variety of inputs and models that may be leveraged to predict dissolution performance.

For CM processes, the number of samples needed to demonstrate adequate control and consistent performance is larger than typically required for a batch process. Currently, there is no guidance on approaches to select the appropriate sampling frequency. The larger number of samples can limit the application of on- or

at-line testing. While at-line disintegration testing is commonly applied in a manufacturing setting, the higher frequency of testing needed to assure performance may introduce additional challenges such as the need for additional operator training, waste handling, and long test times relative to the required sampling frequency. These issues are magnified for at-line dissolution testing, which requires larger volumes of medium and spectroscopic or chromatographic analysis endpoints.

The larger number of samples for a typical CM process also leads to uncertainty on how to apply the current USP acceptance criteria for dissolution, which is based on low "n" sampling. A statistical approach may be used to determine the probability of passing each stage based on the larger number of results or predictions from a continuous run. This approach has not yet been standardized.

For predictive dissolution modeling, there is also uncertainty around how much of the profile needs to be predicted to assure adequate control of product performance. While traditional acceptance criteria may only require testing a single time point in the dissolution profile, the ability to predict the entire profile may provide additional assurance of product performance. This, however, has potential to increase the complexity of model development and validation, as well as setting acceptance criteria.

Finally, surrogate performance testing still relies on the existence of a reference dissolution method to act as the surrogate for in vivo product performance. Therefore, the in vivo relevance of the surrogate model can be no better than the in vivo relevance of the reference method. As advances continue in the field of predictive absorption modeling, consideration should be made for the ability to predict absorption directly without the need for the intermediate dissolution prediction.

RECOMMENDATIONS AND CONCLUSIONS

The challenges and limitations of performance testing in a CM process under the current compendial framework are discussed, with alternative surrogates and approaches recommended. To potentially utilize alternative methods to dissolution testing for solid oral dosage forms and enabling RTRT, it is recommended first to clearly examine the dissolution mechanism and understand the risks and factors impacting the dissolution performance of the dosage form. This dissolution mechanism is not only dependent on the solubility and form and particle morphology of the drug but might also depend on the manufacturing process and formulation properties (i.e., excipient selection and properties).

The dissolution mechanism and risk assessment should be used as a guide for selection of the possible surrogate test or dissolution model or if replacing dissolution as a release test is not appropriate. In addition, the overall biopharmaceutic risk for potential dissolution changes on bio performance should be considered when selecting a potential surrogate measure. The decision tree in Figure 1 can be used as starting point for selection of possible alternative methods as RTRT for dissolution.

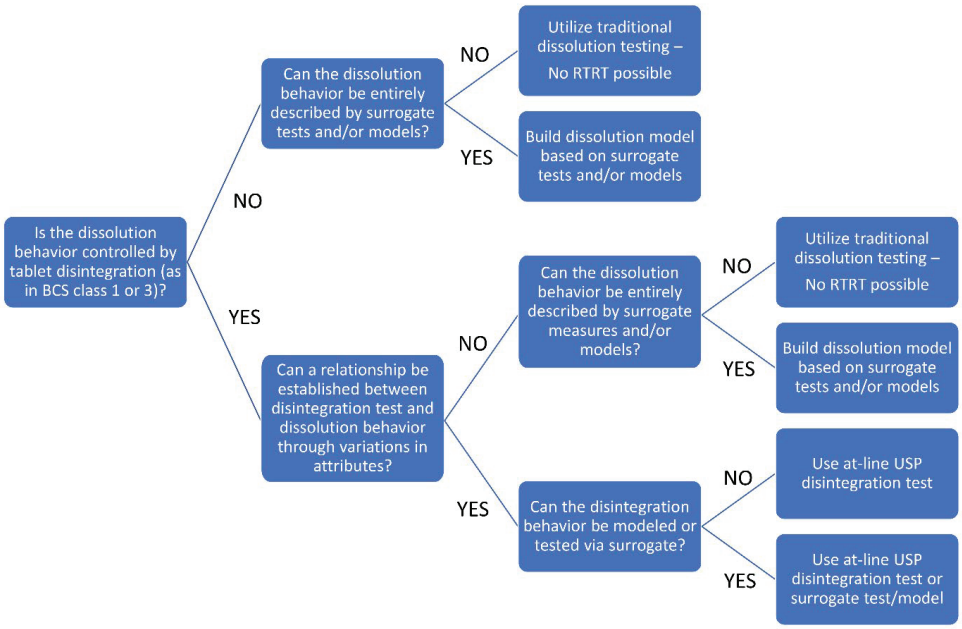

Figure 1. Decision tree for determining if a real-time release alternative or surrogate method to dissolution can be implemented in the continuous manufacturing process for a drug product.

As discussed, sampling for release testing in CM is another challenge that currently doesn't have clear guidance. A risk-based sampling strategy is recommended. Development stage-based sampling may be considered. A harmonized approach on sampling strategy for product performance release testing that is acceptable globally is highly desired. Therefore, this USP Expert Panel recommends that a new standard or addendum to an existing standard be developed that covers the topics of sampling frequency, acceptance criteria application, and bridging the compendia! reference method with the surrogate method.

CONFLICT OF INTEREST

Expert Panel members may have conflicts of interest; the following named author of this article declared a conflict of interest: Carrie A. Coutant is an employee of Eli Lilly and Company.

DISCLAIMER

This article reflects the views of the author and should not be construed to represent the FDA's views or policies.

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