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Predictive Dissolution Models for Real-Time Release Testing: Development and Implementation – Workshop Summary Report

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ABSTRACT

To date, few examples of dissolution models for real-time release testing (RTRT) have been approved for commercial drug products or published in literature. Thus, a structured approach has not been established by which a novice to the field could design, develop, validate, and implement an RTRT dissolution model. Moreover, with scant examples available, there has not been a body of work by which to learn of general regulatory expectations for such models. To address these gaps and to encourage conversation between regulatory and industrial experts on these topics, a virtual (web-based) workshop entitled "Predictive Dissolution Models for Real-Time Release Testing: Development and Implementation" was held November 11–12, 2021. This article summarizes key points from the podium presentations, panel discussions, and breakout sessions focusing on (1) the current best practices to establish predictive model specifications; (2) designing models to predict the "safe space" of a release test and creating models utilizing process analytical technology (PAT); and (3) exploring the strategy of compliant regulatory submissions, including model validation and post-approval lifecycle management. Industrial case studies were presented showcasing attempted approaches to and successful implementations of RTRT of dissolution for drug product manufacturing.

KEYWORDS: Drug dissolution, in vitro dissolution, real-time release testing (RTRT), modeling and simulation (M&S), process control, process analytical technology (PAT)

BACKGROUND

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Workshop on Predictive Dissolution Models for Real-Time Release Testing: Development and Implementation was held on November 11–12, 2021, virtually using the WebEx video conferencing platform (*1*). Recordings of all podium talks and panel discussions have been made available by the IQ Consortium (*2*).

The workshop was attended by 256 scientists representing 85 organizations from the pharmaceutical industry and academia as well as regulatory and standards agencies. Figure 1 shows the distribution of workshop registrants by organization type and by experience with dissolution real-time release testing (RTRT), based on their answers to the questionnaire provided electronically during registration. Of the registrants, 86% represented the pharmaceutical industry; additionally, of the 8% who identified as "other," most represented vendors to the pharmaceutical industry (e.g., equipment or software manufacturers, pharmaceutical testing laboratories). Less

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than a quarter of registrants self-identified as having had prior experience with dissolution RTRT.

The goal of this workshop was threefold. First, teaching sessions were intended to educate the attendees about the principles of dissolution RTRT, the selection and development of models, and their lifecycle and management. Second, industrial examples and regulatory perspectives were provided to demonstrate the application of the theory into practice. Third, panel discussions and Q&A sessions enabled communication with regulatory attendees and speakers, beginning the process of harmonizing the expectations around the regulatory requirements for dissolution models for RTRT. Overall, the event was designed to enable the industrial attendees to return to their respective companies with the ability to develop and implement predictive dissolution models (PDMs) for RTRT, with the expectation that regulatory authorities are beginning to follow the same consistent set of principles. Table 1 summarizes the key points of talks presented at the workshop.

OVERVIEW OF IN VITRO PDM DEVELOPMENT FOR DRUG PRODUCT RELEASE

The first speaker of the symposium was Tessa M. Carducci, PhD (Merck & Co., Inc., Rahway, NJ, USA) (*3*). Her talk was entitled "Development of an In vitro Predictive Dissolution Model for Drug Product Release – Overview and Impact," which provided a fitting kickoff to the 2-day symposium. She began by providing definitions from relevant regulations and a previous white paper on the topic, drivers for use of modeling and surrogate testing in the pharmaceutical industry, and a map to level set on the present topic in the broader realm of predictive technologies (Fig. 2) (*4–11*). PDM is one aspect of a larger RTRT control strategy that has benefits including lead time gains, inventory reduction, which equates to financial savings, and enhanced safety and compliance. Specifically, the addition of a predictive dissolution model to an RTRT strategy can extend business drivers of RTRT to low solubility products (Biopharmaceutics Classification System [BCS] class II/IV), avoidance of traditional dissolution testing, and lead to enhanced mechanistic understanding of the product's dissolution.

Dr. Carducci presented an end-to-end strategy for development of a PDM of a drug product. Understanding the dissolution mechanism is important for identifying the factors that influence the dissolution performance. A design of experiments (DoE) is performed to vary dissolution predictors, and the resulting dissolution data are collected. An empirical or hybrid model can be constructed in two steps: 1) curve fitting the dissolution profiles, followed by 2) regression of the curve fit parameters in step one against the predictors and/or near-infrared (NIR) data. The model predictions vs. measured dissolution results are then assessed. Routine and periodic verification will trigger future model updates and revalidation if needed.

The next part of her talk focused on a case study for development of a PDM. Through early stage DoEs, tablet disintegration was found to be the rate limiting step for dissolution, so parameters like hardness are impactful on the dissolution process. Dr. Carducci noted that first-principles modeling can aid in determination of the dissolution mechanism and identification of key inputs to model; although, there can be secondary effects from process parameters that are only able to be included in a multivariate model. She also emphasized that understanding the dissolution process is critical to the modeling strategy as well as method selection and specification strategy. The quality control (QC) method must be justified (i.e., discriminating) and robust because the model is built using data as generated by this method. Potential factors that affect dissolution were identified using a fishbone framework and investigated through

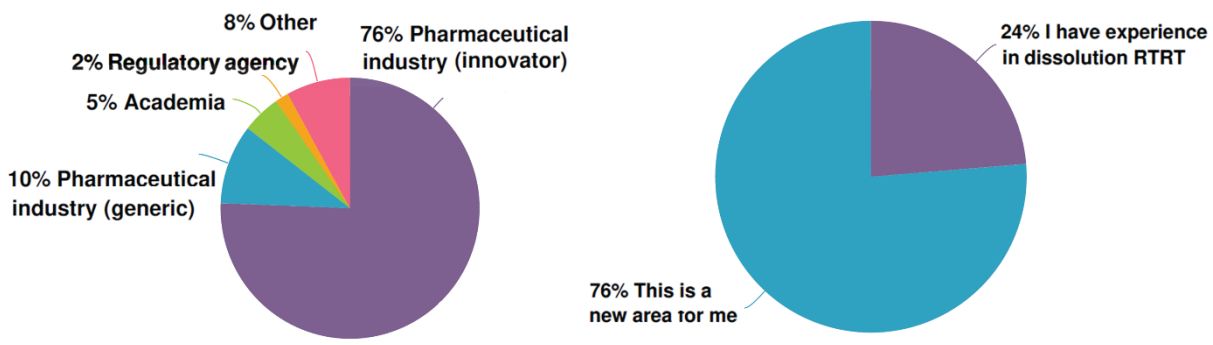

Figure 1. Distribution of workshop registrants based on self-identification on a registration questionnaire, by organization type (left) and by previous experience with dissolution real-time release testing (RTRT) (right).

Table 1. Overview of workshop presentations and key teaching points.

Presenter (Company)	Title of Presentation	Key Teaching Points
Tessa Carducci (Merck & Co., Inc., Rahway, NJ, USA)	Development of an In vitro Predictive Dissolution Model for Drug Product Release – Overview and Impact	PDM is one aspect of a larger RTRT strategy with benefits to cost, assurance of safety, and compliance. Understanding the dissolution mechanism is important for identifying the factors that influence the dissolution performance, and first-principles modeling can guide that understanding, but some process parameters can only be included in a multivariate model. In CM, a continuous-study DoE for model calibration can save time and reduce material use.
Nikolay Zaborenko (Eli Lilly & Co.)	RTRT PDM Model Selection and Development	Development of PDMs for RTRT is very flexible, based on first principles, empirical models, or a hybrid, incorporating or excluding spectroscopic PAT, or predicting adherence to a dissolution safe space based on RTRT of other CQAs. A PLS model of dissolution vs. process and material variables can elucidate CPPs/CMAs, leading to a PDM. This should be validated by a DoE around critical variables to demonstrate the model's predictive capability and the ability to detect outliers.
James Drennen (Duquesne University)	Prediction of Dissolution Profiles from Process Parameters, Formulation, and Spectroscopic Measurements	Individual drug characteristics will determine which parameters are critical to guide DoE building, which must provide adequate dissolution variability for model training. A hierarchical modeling approach for PDM development can provide understanding of how certain variables affect dissolution through linkage between their variation and the effect on different parameters of the PDM. Spectroscopic PAT can capture individual tablet differences and incorporate it into prediction of dissolution behavior.
Alexander Ryckaert (Ghent University)	Fast and Non-destructive PAT-based Dissolution Assay for Immediate Release Tablets	A BCS class II (poorly soluble) drug product dissolution performance can be rate-limited by disintegration in certain cases. Therefore, it is possible to establish disintegration as a surrogate for dissolution performance of a poorly soluble drug. A NIR spectroscopic model can predict disintegration (and by extension dissolution) of such a drug product across a range of API particle sizes and tablet compression profiles.
Haritha Mandula (FDA)	Dissolution RTRT: Summary of Regulatory Requirements and Expectations	A PDM for RTRT is a high-impact model on the condition that it can predict outliers in behavior across variation of all parameters that could possibly vary in drug product manufacturing. Thus, model development should consider variations in all such parameters through a dedicated DoE to demonstrate understanding of CPPs/CMAs and model validation. It is expected that a discriminating, in vivo relevant dissolution method would be established as early as possible in development, and the PDM would be capable of predicting performance against this method across all time points. It is recommended that sampling is equally spaced, statistically justified for dissolution prediction and sufficient to detect the dissolution variability of the batch for the production duration.
Matthew Walworth (Eli Lilly and Co.)	Data Selection and Generation for PDM and RTRT Development	The initial stage of model training is establishing technical feasibility, which should be completed as soon as possible in process development. Once PDM technical feasibility has been established, a more robust data set should be acquired. Samples should be representative of the commercial manufacturing process. The entire design space should be represented in the samples using a statistically relevant sampling method (such as factorial sampling); the training data set should have designed sources of variability and statistical probability. Samples specifically designed to fail should be created to confirm that the model can identify a failing sample. In production, data should be continually collected to support continued use or justify the need for a model update.
Sandra Suarez-Sharp (Simulations Plus)	From QC Dissolution Method to RTRT Dissolution Model	A dissolution method must be fit for purpose, with PBPK modeling used to establish its in vivo relevance. A successful model is built upon identification and inclusion of all relevant failure modes in the dissolution method and their interactions. A clinically relevant dissolution method should be established as early as possible in drug product development to enable determining which variables are critical to meaningful dissolution performance.
Melanie Dumarey (AstraZeneca)	Predictive Modeling for RTRT of Dissolution: Quality Considerations	PDMs for RTRT require detailed description in the CTD, including justification for the selected model parameters based on dedicated DoE and/or first principles analysis. Models must be validated with a data set not included in model calibration, including non-compliant batches. The validity range of the model should be defined, as well as diagnostics implemented to prevent invalid model predictions. Long-term validity of a model is ensured by the implementation of a lifecycle management plan, monitoring common and special cause variation over time, and triggering model updates as needed.
Sara Manteiga (Vertex)	Putting it All Together: PDM RTRT in Action – Case Study 1	PDM was accepted for RTRT of a CM product. Segmented sampling (12 segments per batch) is used for dissolution prediction, consistent with USP <711> stage 2 testing. Each PAT input method was validated per ICH Q2(R1). The model was challenged against 25 CM batches with variations spanning the manufacturing range of process parameters and material attributes. Model maintenance includes assessing model performance through routine parallel testing, after changes to materials/ instruments/ process, and observation of trends (including model diagnostics). PDM was demonstrated to detect non-conforming batches.
Stan Altan and Sarah Nielsen (Janssen)	Putting it All Together: PDM RTRT in Action – Case Study 2	A PDM was used for batch RTRT of a fluid-bed granulated BCS class IV product. CPPs had been identified from prior manufacturing designs, and PDM was developed via a comprehensive DoE, using process parameters and tablet content measured by NIR as inputs. Model provided "health check" of current batches against historical standard.

BCS: Biopharmaceutics Classification System; CM: continuous manufacturing; CMA: critical material attribute; CPP: critical process parameter; CQA: critical quality attribute; CTD: common technical document; DoE: Design of Experiments; IV: intravenous; NIR: near infrared; PAT: process analytical technology; PBPK: physiologically based pharmacokinetics; PDM: predictive dissolution modeling; PLS: partial least squares; QC: quality control; RTRT: real-time release testing.

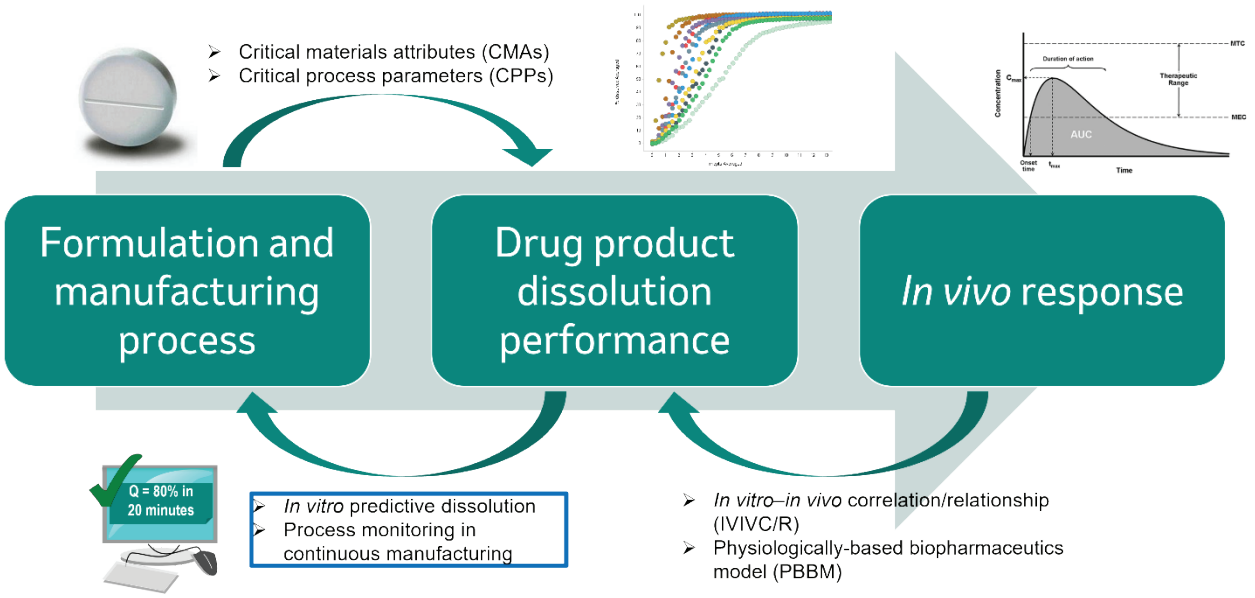

Figure 2. Types of dissolution modeling in the realm of predictive technology.

DoE or one-factor-at-a-time experiments. She stressed the importance of performing a raw materials risk assessment to ensure either that material attributes are not critical to the dissolution performance of the product or that they are captured in the model if they are critical. After building mechanistic dissolution understanding, the dissolution-critical parameters/attributes should be confirmed and model training set finalized. Spotfire was used to aggregate the large amount of dissolution and process parameter data to facilitate modeling iterations.

The strategy for selecting the model was performed in two stages: 1) exploratory analysis involving regression of dissolution predictors (X-block) and a variety of individual dissolution time points (Y-block) to better understand the X-Y relationship; and 2) iterative development towards the final model using dissolution profile fit coefficient regression as the Y-block (*12*). At this stage, parameters that do not significantly impact dissolution performance or those that are encompassed by other parameters were excluded from the X-block with appropriate justification. Model rank and condition number were evaluated for empirical models and mechanistic/hybrid models based on a Noyes-Whitney framework. The Gompertz model explained the dissolution profiles best, especially at the approach of the plateau region (*13*, *14*). Also, no advantage was identified to using "high resolution" dissolution data using fiber optic versus "low resolution" or traditional discrete time point dissolution sampling. Furthermore, traditional sampling is seen as preferable for model maintenance in supply. Future steps include model validation and implementation.

Alternate modeling approaches including spectrum-based (or process analytical technology [PAT]) modeling were also discussed, and a case study of a first-principles modeling approach to support a particle size distribution (PSD) specification was presented. Then, the topic shifted to how PDM can play a role in continuous manufacturing (CM). If executed as a continuous study, the main DoE used for the model calibration set would use significantly less material and require a much shorter manufacturing duration. To realize the full benefits of CM of low-solubility drug products, Dr. Carducci opined that development of a PDM to enable a full RTRT strategy is imperative. In closing, Dr. Carducci summarized lessons learned for PDM through her work and through external networks and mentioned some interesting topics for future research and development.

MODEL SELECTION AND DEVELOPMENT

Nikolay Zaborenko, PhD (Eli Lilly & Co., USA; Chair of the organizing committee) presented his perspective on the selection and development of PDMs for RTRT (*15*). An overview of first-principles and empirical approaches to predicting in vitro dissolution for product release testing, as previously presented and published in an industry white paper and reviews, described the difference between mechanistic and empirical modeling approaches, including chemometric modeling (*9*, *16*, *17*). The aim of PDM for RTRT was stated as predicting a quantitative value of the level of drug released at a specific time point, as is done traditionally with a physical dissolution test. A PDM can achieve this either by predicting the entire dissolution profile (mathematically describing the profile

curve) or by directly predicting release at one or more time points (typically via statistical modeling). Both the speaker and subsequent discussions established that regulatory reviews do not find it sufficient to only predict qualitatively whether the unit or batch passes or fails its dissolution specification, even when operating in a process safe space. Indeed, the regulatory expectation for a PDM is that it predicts a full dissolution profile, either as a mathematical function or as a series of time points, and not just a single time point value. However, it is acceptable for validation to be performed only on the specification time point.

Dr. Zaborenko provided a framework for building models based solely on critical material attributes and critical process parameters (CMAs/CPPs), as well as for building models that incorporate PAT, e.g., spectroscopic measurements, providing literature examples of both methodologies (*18*–*21*). It was emphasized, both through the talk and in subsequent panel discussions including the FDA speaker Dr. Haritha Mandula, that spectroscopic PAT is not a requirement for successful implementation of dissolution RTRT. A sufficiently robust PDM can be developed and validated using only CMAs/CPPs and inline or at-line measurements of certain critical quality attributes (CQAs), such as, e.g., tablet weight, hardness, or solid fraction. Either methodology requires demonstrated understanding of dissolution dependence on process and material variables including which variables are critical to dissolution performance and examples of significant variation of process and material parameters, including variations performed at final production scale.

One type of PDM for RTRT presented was partial least squares (PLS) regression, which uses singular value decomposition to extract predictive component variables through covariance of independent (X block) and dependent (Y block) variables (*22*). An advancement of the method, O2-PLS, which separates correlated variation in X and Y variables from structured noise in X and in Y, has been used previously for PDM (*16*, *23*). Another approach discussed was the use of artificial neural networks (ANN), an error-minimizing technique that adjusts weights of variables based on a learning set to generate a black-box predictive algorithm, with literature examples of their use in pharmaceutical PDM (*24*–*26*). The strength of ANN lies in its ability to solve nonlinear or multi-response systems and to use historical data generated without reliance on a rules-based DoE; however, it requires very large amounts of data to train.

To incorporate spectroscopic PAT, principal component analysis (PCA) was briefly described. PCA is the statistical approach to processing large amounts of correlated data (e.g., dissolution vs. time, absorption vs. wavelength). It allows for predictive modeling that maximizes the variance of projected data with fewer dimensions by producing latent variables (principal components) that combine aspects of individual X variables. Its use in pharmaceutical development has been well documented (*22*, *23*, *27*). The use of PAT generally requires preprocessing of spectral data, with various approaches commonly used (*28*). For PDM application, PCA typically delivers one or several summary values of a spectrum for use as input into the PDM.

The need to quantitatively evaluate model performance was discussed. In general, for prediction of any single value (e.g., dissolution at a given time point), this includes absolute and relative standard errors of prediction (SEP) and the R^2 value (goodness of fit, or level of correlation between predicted and actual values). For PCA models, one should evaluate Hotelling's T^2 (the model's ability to detect outliers) and the residuals Q^2(Y) and R^2(Y), or the "scores" of the model's abilities to predict novel samples and account for variation in the model inputs, respectively. For prediction of an overall profile, one can also evaluate f_1 and f_2, the difference and similarity factors, although there is a great deal of debate and discussion as to the applicability of these factors and the situations in which they are relevant, as well as alternative methods of comparing dissolution profiles (*29*–*31*).

Finally, a series of case studies were presented, highlighting the different approaches to establishing a PDM for RTRT. An example was presented of establishing a PDM using only spectroscopic data to correlate with dissolution, in this case using an ANN for the analysis and prediction (*26*). Subsequently, a converse example was shown of a PDM for an immediate-release (IR) tablet made via continuous direct compression (CDC). The model was based on process parameters and material attributes (without the use of spectroscopic data), as illustrated in Figure 3. Dissolution profiles were measured for coated and uncoated tablets across multiple tablet strengths with variations in formula (composition), active pharmaceutical ingredient (API), filler excipient particle sizes, and in CDC and coating process parameters. A PCA analysis established a 4-PC model to predict dissolution at the investigated time points (addition of a fifth PC did not show improvement in R^2 or Q^2 over the 4-PC model). The 45-minute time point had been selected as the specification (Q) time point, and the model showed reasonable correlation between predicted and

measured values (in this case, R^2 of 0.55) with adequate absolute and relative SEP. A PLS analysis showed that the biggest contribution to variation in dissolution stemmed from variations in filler and disintegrant levels in the composition (as well as from differences in performance across tablet strengths). To validate the model, tablets were made with large changes to filler and disintegrant levels from the target formula. The 4-PC PDM was able to predict the release (%LC of API) of these tablet batches at the proposed specification point with sufficient accuracy (with the exception of one outlier, the predicted value for any individual test was within 6% of observed value).

Another example of a dissolution surrogate model without the use of spectroscopic data was presented. In this example, a PDM was built to predict performance within an established clinical safe space (i.e., performance ensuring bioequivalent [BE] maximum plasma concentration, C_{max}) (*19*). An in vivo-in vitro correlation (IVIVC) was established between C_{max} and dissolution. Additionally, CQAs of tablet hardness and thickness were able to predict the %LC dissolved at the specification time point. Thus, the IVIVC enabled rapid at-line measurement of non-destructive CQAs to establish if the tablets were within the clinical safe space.

Lastly, a case study was presented exemplifying a process safe space, with assay and content uniformity (CU) RTRT and control that ensured operation within a safe space for those CQAs (*17*). The example demonstrated the use of final blend NIR in a CDC tablet process for RTRT of assay and CU, rejecting nonconforming drug product. Dissolution measurement at specification time point was shown to consistently reproduce the drug product assay across wide variation of process parameters and material attributes, behavior typical of (but not exclusive to) BCS class I drug products. An argument was made that the assay model can be extended to use for PDM against this dissolution specification. The overall ability to reject nonconforming drug product thus ensures RTRT and safe-space operation for CU, assay, and dissolution.

PDM DEVELOPMENT VIA PAT AND CPPS/CMAS

In the first of two academic talks, Professor James K. Drennen, III, PhD (Duquesne University, USA) presented "Prediction of Dissolution Profiles from Process Parameters, Formulation, and Spectroscopic Measurements" (*32*). He discussed the academic state of the art based on his and his colleagues' work as well as that of other researchers in the field (*21*, *33–35*).

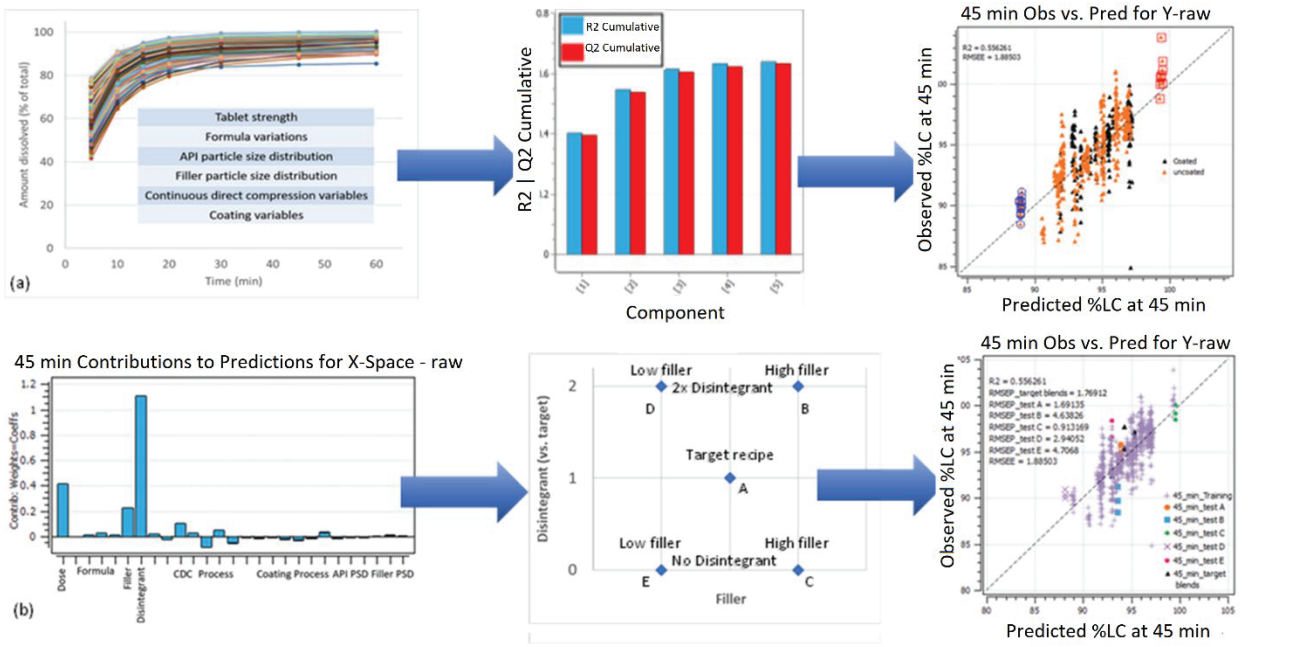

Figure 3. PDM for RTRT based on process parameters and material attributes.
(a) Model development (left to right): Measurement of dissolution of drug products with variations in process and material variables, PC analysis to establish a 5-PC PDM for release levels at specified time points, predicted vs. observed API %LC dissolved at 45-minute time point for training set (including coated and uncoated tablets).
(b) Model validation (left to right): Partial least squares analysis to establish CPP/CMAs for release at 45 minutes, creation of a validation set DoE of tablets with large declination in CMAs, predicted vs. observed API %LC dissolved at 45-minute time point for validation set (plotted against the training set data).
API: active pharmaceutical ingredient; CPP: critical process parameter; CMA: critical material attribute; DoE: Design of Experiments; PC: principal component; PDM: predictive dissolution modeling; RTRT: real-time release testing; %LC, percent label claim.

The talk focused on a series of components necessary for overall model building, including: 1) building a DoE based on individual drug characteristics for acceptable dissolution variability; 2) selecting between global models vs. a hierarchical modeling approach for PDM; 3) training PLS models based on formulation, material, process, and spectroscopic data; and 4) using the models to predict dissolution profiles as direct time points vs. as mathematical functions (e.g., a Weibull curve).

DEVELOPMENT OF PDM USING ONLY PAT

In the second academic session, Alexander Ryckaert, PhD (Ghent University, Belgium) presented a case study where in vitro PDMs were developed for an IR tablet using solely spectroscopic measurement (*36*). The tablets consisted of a hydrophobic API of BCS class II, lactose, microcrystalline cellulose (MCC), a disintegrant, and a lubricant. The predictive models were built using offline collected NIR data, offline collected Raman data, or process/material information with the ultimate goal to enable RTRT in tablet manufacturing. As the API particle size was identified as the CMA and the tablet compression force as the CPP, these variables were used for the experimental design. Compression force was varied at 7 levels (i.e., 2, 4, 6, 8, 10, 12, and 16 kN), resulting in tablets with varying porosity. Although the applied range for compression force was probably beyond the meaningful variation that would be expected during manufacturing, it provided more dissolution variability, which enhances the discriminative power of the predictive models. In addition, four different API batches, each having a different API particle size (i.e., d50 values of 30, 40, 43, and 51 µm), were used for the production of the tablets.

Dissolution profiles were obtained for all tablets using USP apparatus 2. Figure 4 shows the dissolution profiles at the two most extreme compression forces (i.e., 2 and 16 kN) for the four different API batches. It was observed that tablets compressed at lower compression force resulted in a faster release because the higher porosity promoted liquid penetration through the pores in the tablets more easily. According to Maclean et al., this is due to the combination of the poorly soluble MCC and the slowly dissolving lactose, making the effect of porosity dominant (*37*). The fastest dissolution rate was observed for tablets made with the smallest API particle size, whereas the slowest dissolution rate was observed for those with the largest API particle size. Although this is a logical finding due to the surface area-to-volume ratio, it does show that API batch-to-batch variability can clearly influence the dissolution rate.

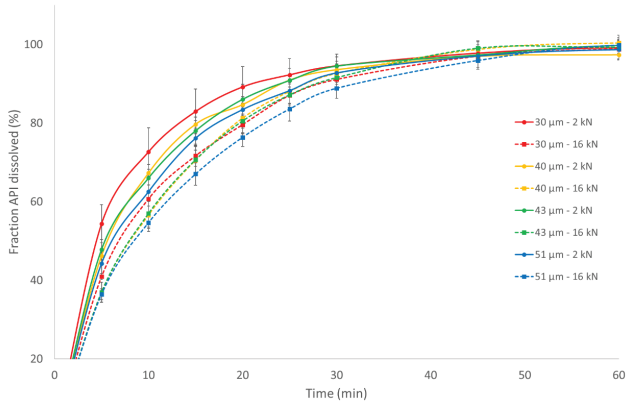

Figure 4. Dissolution profiles of tablets compressed with the lowest (solid line) and the highest (dotted line) compression force for the API batches with differing particle size. API: active pharmaceutical ingredient.

The Weibull model was fitted to all dissolution profiles; and Weibull scale and shape parameters were determined (see the "Data Selection and Generation" summary below for detailed review of the Weibull function). Furthermore, traditional linear PLS regression and non-linear kernel ridge regression (kRR) modelling techniques were applied to predict these parameters from the NIR spectra, Raman spectra, or the process/material information (i.e., compression force and API particle size) of the tablets. The models were evaluated by cross-validation where a test set consisting of 10% of the data was left out of the model. Weibull scale and shape parameters were subsequently predicted and used to reconstruct the dissolution profiles. Figure 5 shows a representative example where the dissolution profiles predicted with kRR for Raman, NIR, process/material information with PLS for Raman (as results were similar for NIR), and their corresponding measured profile are plotted. KRR outperformed PLS when spectroscopic data were used as the reconstructed profiles, with kRR for both NIR and Raman being very similar to the measured profile. This is probably due to kRR being able to model the non-linearity between compression force/API particle size and the dissolution profile. Using only information of the applied process parameters and material attributes resulted in a poor fit with an R^2 value for both the Weibull a and b parameter below 0.4, indicating that the limited amount of information was not sufficient to build a good model. Two concerns about kRR modelling were mentioned during the workshop. The first concern was kRR sensitivity to the scale of the input; however, this was avoided by applying standard-scaling of the features beforehand. The second concern was the risk of overfitting. The study was not yet completed at the time of writing, so this still has to be evaluated by using an independent validation set that falls within the operation space of the calibration

model. In addition, similarity between the measured and predicted profiles has also to be tested, and a more in-depth statistical analysis has to be performed to evaluate the model performances.

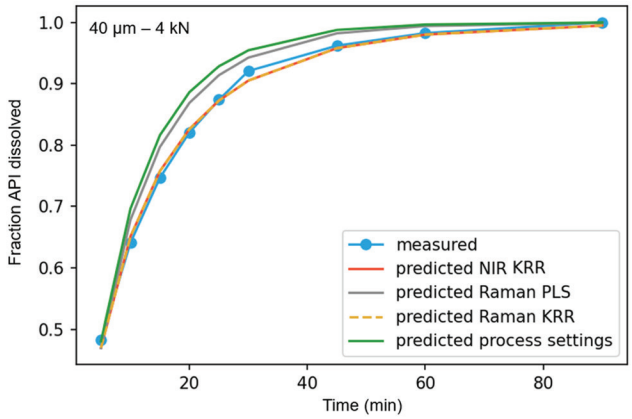

Figure 5. Representative example of the predicted and measured dissolution profiles for a tablet with an API particle size of 40 µm compressed with 4 kN. API: active pharmaceutical ingredient; KRR: kernel ridge regression; NIR: near infrared; PLS; partial least squares.

REGULATORY REQUIREMENTS AND EXPECTATIONS

In the final podium presentation of the first day of the workshop, Haritha Mandula, PhD (United States Food and Drug Administration [FDA]) presented her views on the regulatory requirements and expectations for dissolution RTRT (*38*). In her presentation, Dr. Mandula provided detailed definitions of RTRT and its components, lifecycle, considerations, and requirements for implementation and regulatory submission, and two case studies of regulatory approval of dissolution RTRT as a surrogate for traditional testing.

Dr. Mandula began her talk with an overarching definition of RTRT as the ability to evaluate and ensure the quality of in-process and/or final product based on a valid combination of measured material attributes and process data (*4*). Figure 6 shows an example of RTRT within a continuous process, wherein input materials are continuously received into the system with continuous blending, continuous granulation, continuous compression, and continuous film coating followed by parallel at-line and inline assays. The measurements generated from these assays are input into the dissolution model to generate a dissolution rate, which could be further used for real-time dissolution testing. Examples of RTRT approaches involving dissolution include fast at-line measurements like disintegration in lieu of dissolution. Dissolution models serve as a surrogate for traditional time-consuming measurements like release tests are usually multivariate high-impact models and typically relate process parameters and/or material attributes to dissolution.

Methodology

A dissolution method for traditional QC dissolution testing is typically developed in a lab based on critical material, process, and manufacturing variables, as well as design space (Fig. 7). Sometimes, these methods incorporate clinical relevance and such a method is highly desirable. During CM, product quality is also monitored by NIR measurements. These measurements are incorporated into PCA, and a final dissolution model based on multiple linear regression is developed. The observed and predicted data are compared to verify the model. Once the model is developed, model validation is performed using a different independent set of validation batches that were not included as part of the model development.

Model Development Regulatory Considerations

Several recommendations for dissolution model development were made. 1) An RTRT model should be developed based on a dedicated DoE study. For DoE studies, detailed formulation and process parameters for each studied development run/batch, as well as dissolution profile data (including the mean, individual vessel data, and CV% for each test), should be provided. 2) A detailed description of the dissolution RTRT model and justification for the selection of the model and its inputs should be provided. 3) All model calibration and validation activities and results should be provided. The RTRT model should be able to predict the entire dissolution-time profile instead of dissolution at one time point and predict non-conforming batches (batches that fail dissolution). 4) Dissolution profile data for model calibration and validation including individual vessel data as well as the mean and CV% should be provided. 5) A detailed sampling plan of RTRT for batch release should be provided. The sampling locations should be equally spaced and statistically justified for dissolution prediction. The sampling plan should be sufficient to detect the dissolution variability of the batch for the production duration. 6) If physiologically based pharmacokinetics (PBPK) modeling and simulation is used to support the proposed manufacturing design space, then the complete study report is to be submitted.

Model Validation Regulatory Considerations

Consideration for models serving as surrogates for release tests involve development of a robust calibration model. This can be accomplished by use of an appropriate reference method that would include variations in raw materials and would cover the entire design space.

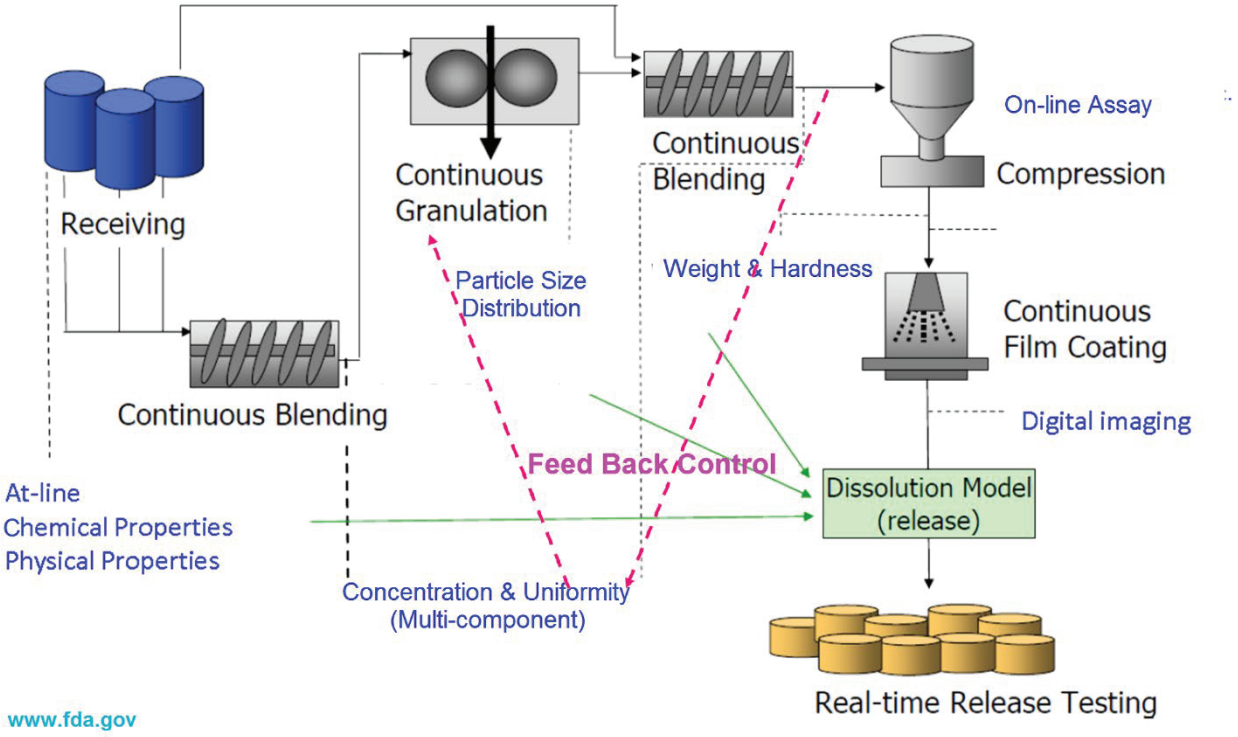

Figure 6. Example of real-time release testing within a continuous process, wherein input materials are continuously received into the system with continuous blending, granulation, compression, and film coating followed by parallel at-line and inline assays.

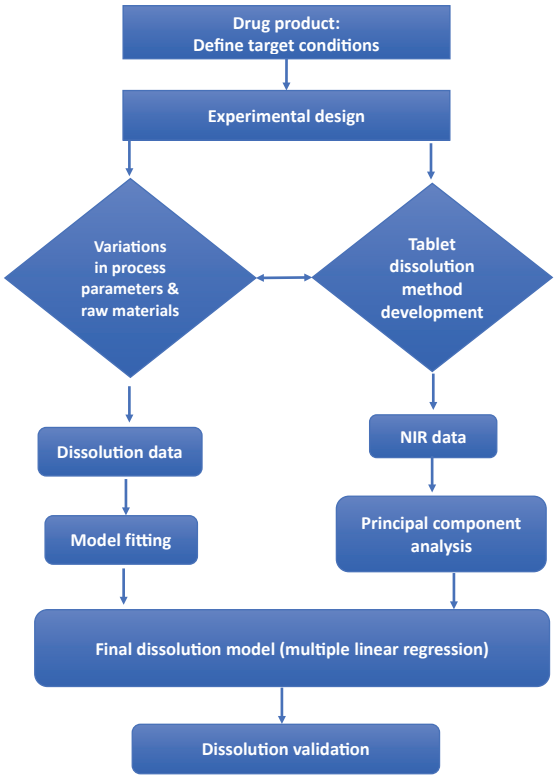

Figure 7. Methodology for traditional quality control dissolution testing based on critical material, process, and manufacturing variables and design space. NIR: near infrared.

Typically, an independent dataset is recommended for validation. The model performance should be demonstrated at a commercial scale. To accomplish this, it is important to understand and work within the model limitations and model assumptions and compare the model results to a reference method for a statistically acceptable number of batches. Some of the general considerations for dissolution models involving RTRT include justification/appropriateness of sample size; approach for data pretreatment; statistical analysis of data showing fit and prediction ability and rationale for selection of model diagnostic criteria; robustness of the model outside the ranges used for calibration/validation; strategy for model suitability throughout drug product life cycle as part of applicant's quality system; and in the case of CM process, and strategy for verification of state of control and potential trending due to random variability; as well as sampling strategy for dissolution testing.

Case Study 1

The first case study was an original new drug application (NDA) wherein a PDM was included as part of an RTRT model. This NDA consisted of two APIs, one belonging to BCS class II (low solubility and high permeability) and the other being BCS class IV (low solubility and low permeability). Owing to the low solubility, both drug substances were provided as amorphous spray dried dispersion (SDD) intermediates for drug product formulation. Biopharmaceutics review focused on dissolution method, acceptance criterion, and alternative approach of dissolution testing as RTRT. Dissolution testing was also used in establishment of manufacturing design space for the fixed dose combination tablet. Acceptance criterion was based on pivotal clinical batches, stability data, tablet to tablet variability from individual pharmacokinetics (PK) of clinical batches, and risk-based assessment of critical parameters to dissolution such as crystalline content and granule particle size. RTRT dissolution testing was based on a PLS model. The in-process material attributes and process parameters measured by PAT in CM were used to calculate a dissolution rate (Z). The dissolution rate is then used to predict the dissolution profile based on a modified Noyes-Whitney equation. The measured final blend API content, average granule particle size, API SDD bulk density, hardness, tablet weight, and thickness were used as input factors in the PLS dissolution rate model. Calibration of the PLS dissolution rate model was performed using reference dissolution methods for core tablets from manufacturing runs spanning design space and manufacturing range with various drug substance, SDD, and excipient lots. Predicted vs. reference sets with R of 0.95 were included for calibration (the absolute differences for percent dissolved between the two methods are < 5%). In addition, root mean square error (RMSE) and root mean square error cross validation (RMSECV) vs. factors plot and factor loadings plot were used to justify latent variables. RTRT dissolution results were consistent with those obtained from regulatory dissolution methods with no more than 5% difference across the 19 continuous Quality by Design (QbD) runs during development and launch setup and three QbD confirmation runs. To further verify if results fall within the calibrated space of the model, non-confirming batches were detected using Hotelling T^2 with not more than (NMT) 23.6 and Q-residual with NMT 35.4 as the criteria. Stratified sampling of 12 segments for each batch was considered. An out-of-specification investigation would be initiated if an RTRT dissolution result does not conform to the specification.

Case study 2

The second case study was a post-approval NDA. At the time of approval of the original NDA, a regular QC dissolution method was approved. Eventually, the applicant chose to include PDM as part of RTRT as a post-approval supplement. The agency reviewed the RTRT dissolution model that was submitted as surrogate of dissolution testing to replace the in vitro analytical dissolution method and as additional in-process control under CM. The dissolution model was not found to be acceptable initially due to the following reasons. The developed model was bivariate that predicts dissolution at 30 min. The proposed model was based on PLS analysis of DoE data based on API concentration and tablet weight and thickness. The study did not include API particle size and their interactions with other critical parameters. During initial dissolution method development, release was thought not to be affected by particle size in the ranges tested. Hence, API particle size was excluded from DoE studies. However, based on previous supplements it was found that particle size (coarse vs. fine API) affects the bioavailability (based on a relative bioavailability [RBA] study), although QC release was not able to capture the differences at Q = 80% of the labelled amount dissolved in 30 minutes. Further, PLS analysis and DoE study were thought to be confounded as approvability ranges were wider than ranges tested. Variable ranges evaluated in the DoE study were narrower than the approved ranges, resulting in dissolution profiles that are likely to fail dissolution comparison, which in turn would lead to variation in in vivo product performance and lack of BE. In addition, approved ranges in PSD would result in drug product batches that are not BE when

comparing the upper/lower bounds. Mitigation strategies involved exploring the model with a dedicated design space including API particle size or revision of dissolution acceptance criterion to Q = 80% of the labelled amount dissolved in 20 minutes along with tightening of three-tier API PSD based on clinical experience. Recommended sampling strategy was to include 10 tablets randomly selected within each of the 16 Quarantine Hoppers (QH) tested. The applicant counter-proposed a sampling plan to align with sampling for at-line NIR testing (for assay and uniformity analysis – collection of ten tablets from each QH prior to each QH being released). The applicant's proposed final plan was acceptable as it aligned with current CM line sampling and analysis workflow along with risk mitigation by tightening of API PSD specification.

Dr. Mandula's presentation spurred quite a few questions from the audience, leading to further discussion and clarification of the above points in the subsequent interactive question/answer session. The discussion centered on the acceptance of PDM models and the components of successful justification packages that gain regulatory acceptance. In general, Dr. Mandula's perspective was that it is advisable to have a discriminating method early in the development process. She suggested that filing a dissolution method at the IND stage, as an amendment, if necessary, may be helpful because dissolution methods can be approved ahead of the NDA. This presents an opportunity to engage in face-to-face meetings with the health authority ahead of submission, which allows both parties to gain insight into the applicant's dissolution strategy and for the applicant to receive input from the agency.

In response to a query regarding discriminating capability of a PDM method as compared to an in vitro one, Dr. Mandula indicated that they both should serve to address the same risks. Both QC and PDM methods should ensure safety and efficacy, be discriminating and clinically relevant when possible, and if not possible, to ensure adherence to a safe operating space. The PDM method will be subject to scrutiny due to the inherent risks involved with a predictive method. When preparing packages for submission, a risk-based approach should drive experimentation and data set decisions. Sample sets should represent the entirety of a run and be subject to rigorous statistical analysis to inform risk. In terms of sampling strategy, applicants should propose sample plans that adequately capture risk. It is advisable to test the PDM with batches that differ from those used for the model building process. The preferred approach is data from real batches, conforming and non-conforming, as non-conforming batches help to define the operating space of the model. Data based on simulated batches should be avoided for defining process operating space, although simulated batches could be used to supplement model evaluation. Applicants are encouraged to consider the PDM approach for all types of manufacturing processes (e.g., wet granulation, modified-release formulations, etc.).

DATA SELECTION AND GENERATION

The first presentation of the second day of the workshop was given by Matthew J. Walworth, PhD (Eli Lilly & Co., USA), providing the basis and rationale for data selection and generation in service of a PDM for RTRT, exemplified by a case study (*39*). A PDM in support of RTRT of pharmaceutical tablets can enable cost and time savings over standard dissolution methods such as USP <711> (*8*). A PDM must reliably produce accurate predictions to be accepted by regulatory agencies. To successfully build a PDM, high-quality dissolution data (i.e., data obtained using a well-developed reference method) is essential to model training and validation.

Model Training

The initial stage of model training is establishing technical feasibility, which should be completed as soon as possible in process development. Because dissolution is evaluated in early-stage control strategy development, nondestructive analytical techniques such as NIR or Raman could be performed before destructive dissolution in order to establish whether RTRT is feasible. Once PDM technical feasibility has been established, a more robust data set should be acquired. The following factors should be considered: 1) samples are representative of the commercial manufacturing process; 2) the entire design space should be represented in the samples using a statistically relevant sampling method (such as factorial sampling); 3) the training data set should have designed sources of variability and statistical probability; 4) and samples specifically designed to fail should be created to confirm that the model can identify a failing sample.

An SDD-based roller-compacted IR tablet formulation with two commercial dosage strengths and an accelerated commercialization plan was presented as a case study. To create a PDM, a Weibull function (see equation below) can be used to accurately model the dissolution profile.

$$\textit{Fraction of drug released (t)} = A\left(1 - e^{-\left(\frac{t}{\lambda}\right)^{k}}\right)$$

The Weibull function describes the fraction of drug released as a function of time, *t*, where *A* is the potency

factor, λ is a scale factor, and *k* is a shape factor.

Figure 8 shows how varying the *k* and λ factors affects the dissolution profile. In this case study, a PLS model based on NIR predicts *A*. Another PLS model based on NIR, roll force, roll gap, and compression force predicts λ. Finally, a linear relationship was established between the compression force and *k*.

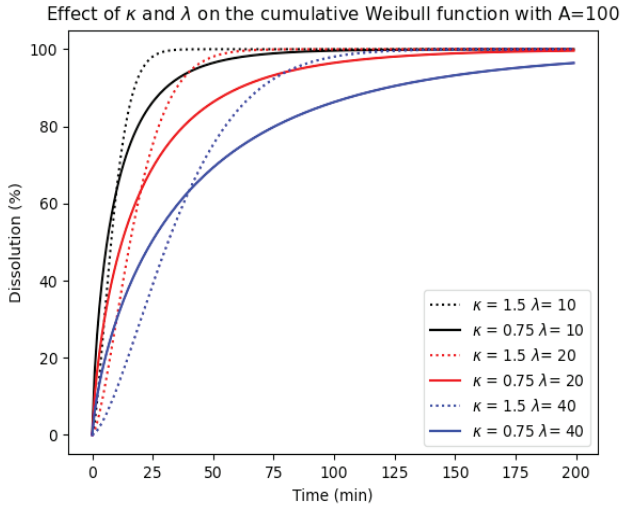

Figure 8. Weibull function profiles.

Model Validation

Training data is critical to model development and model validation. A best-case scenario for model validation involves collecting data from a serial experiment/production of drug product. This data set should include data outside of the operating space (non-conforming material), as well as data that is representative of the entire design space. Special care should be taken to include data that samples the extreme ranges of critical process parameters and common failure modes.

Model Lifecycle

Following model validation and deployment, data should be continually collected to support continued use or justify the need for a model update. After initial deployment for use in supporting GMP activities, a period of heightened monitoring against the reference method (per USP <711>) should be considered (*8*). Additionally, non-conforming material should be prepared to support the continued use of the model. The most common reason for a model update might be an ingredient (API or excipient) supplier change or a change in excipients.

QC METHOD DEVELOPMENT FOR PDM APPLICATION

Sandra Suarez-Sharp, PhD (Simulations Plus, USA) presented her perspective on developing a dissolution release method with the aim of serving as the basis for a PDM (*40*). Dr. Suarez-Sharp's perspective as an expert in the field and previous experience in the FDA afforded a unique opportunity for detailed discussion of this topic.

The implementation of RTRT to drug product development offers the possibility of reduced timelines and inventory and, therefore, reduction of end product testing and manufacturing costs. RTRT dissolution models are key in completing the system, especially for extended-release (ER) formulations and drug products containing BCS class II/IV compounds. Without an RTRT dissolution model, companies are not truly releasing the drug product in the regulatory sense. The successful implementation of these models relies heavily on having exhaustive drug product understanding, which involves several steps, including identification of all relevant failure modes and their potential interactions; implementation of dissolution testing; inclusion of all relevant failure modes within the RTRT model; and adequate internal and external validation of the model showing its ability to accurately predict batches that are considered to be out of specification. Dr. Suarez-Sharp's presentation focused on describing a strategy that relies on modeling and simulation (i.e., physiologically based biopharmaceutics modeling [PBBM]) for developing a biopredictive dissolution method to ensure regulatory approval of RTRT dissolution models.

Among all steps that go into developing RTRT dissolution models, the application of a fit-for-purpose dissolution method (FPDM) as an endpoint in the DoE studies constitutes one of the key measures to ensure a successful RTRT strategy. In many cases, whether an attribute, parameter or in-process control is considered critical to the performance of the drug product will depend on whether the dissolution specification (i.e., the method and acceptance criterion) was met following variations of that specific attribute or parameter being evaluated. In addition, which attribute(s) and/or parameter(s) are considered for building the RTRT model is dependent on the sensitivity of the dissolution method used to identify the specific failure modes. Given the criticality of this step, efforts should be made early in drug product development to utilize a FPDM. In other words, a method for which its discerning ability/scrutiny has been established based on biopharmaceutics risk assessment (Fig. 9). The successful implementation of a FPDM will then facilitate the selection of the true CMAs and CPPs (*41*, *42*). To this end, FPDM testing then serves as both a sensor of potential interactions among parameters and

an indicator representing the impact of implemented CMC changes on in vivo performance. By varying one parameter at a time to determine its in vivo impact, or relying on quality attributes other than dissolution to define the performance of the drug product, the true net effect on product quality and in vivo impact may not be properly represented due to 1) the potential interaction among the CMAs/CPPs that could result in synergism or neutral effect and 2) dissolution being considered as the only quality attribute that proves both the rate and extent of in vivo drug release.

Figure 10 depicts a proposed path from QC method to an RTRT dissolution model that takes into consideration biopharmaceutics risk assessment. In other words, it is applicable to drug products other than IR products containing high-solubility drug substances. This strategy is centered around the development of a FPDM that is biopredictive/clinically relevant via the construction of an in vitro/in vivo relationship (IVIVR) and a safe space utilizing PBBM. Efforts for developing and selecting such a dissolution method should start early in drug product development by relying on the construction of a baseline PBPK model utilizing data inputs from preclinical PK studies and dissolution data generated from several methods (including biorelevant media) (*43*). A preliminary biopredictive method can then be used in DoE studies to make an informed decision on the selection of the CMAs and CPPs. The data collected from the DoE studies is valuable because one can continue making educated decisions on the relevant formulation variants to be considered in RBA/BE studies, which in turn will be utilized to build an IVIVR/safe space. The information gathered in this last step is critical to confirm the predictive ability of the dissolution method and criticality of the variables selected (which will be part of the RTRT model), based on clinical PK data.

In conclusion, robust and successful RTRT dissolution models necessitate the integration of FPDM (e.g., biopredictive methods) as part of DoE studies. RTRT dissolution models developed based on a dissolution method and acceptance criterion that do not meet expectations are the most common cause of revisions to the design space(s) and/or removal of RTRT dissolution models from regulatory submissions.

The broad applicability of Dr. Suarez-Sharp's presentation to all oral drug product submissions that are considering PDM development generated a robust discussion with the audience in the interactive question/answer session. Generally, audience questions fell into two broad categories: (1) how to ensure that a dissolution method

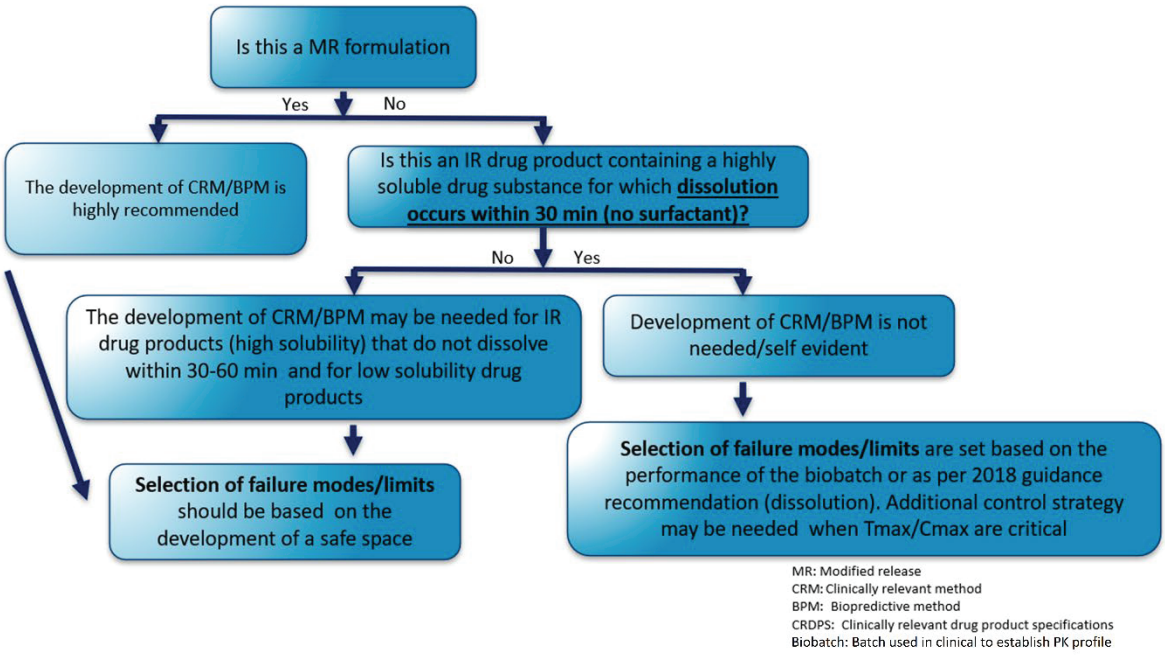

Figure 9. Biopharmaceutics risk assessment decision tree for determining the criticality of developing a biopredictive/clinically relevant dissolution method, with reference to the 2018 FDA guidance for dissolution of highly soluble drug substances.
Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evalution and Research (CDER), August 2018.

is discriminating at different stages of development, and (2) how many and what variations to the drug product need to be made to demonstrate dissolution method discriminability.

Early in development, prior to availability of clinical data, dissolution should be understood across the physiological pH range and in biorelevant media (e.g., fasted/fed-state simulated intestinal fluids). If no such media provide full release of the drug product at those stages, addition of surfactants should be explored. This work will elucidate the potential for a physiologically relevant dissolution method, as well as providing the basis for early-phase modeling of in vivo performance. A method that provides a dissolution profile with full but not instant release, ideally with physiological relevance, should be selected for early formulation discrimination and dissolution model building. Subsequently, as clinical data become available, they should inform whether or which dissolution method provides discrimination for variations that result in in vivo performance differences. Such a clinically relevant dissolution method is ideal for selecting CPPs and CMAs.

Selecting variations in drug product to determine the discriminability of the dissolution method is also dependent on the phase of drug development. Early understanding of dissolution behavior, combined with modeling and simulation, can help select meaningful variations for formulation development. To justify a proposed QC method, it is necessary to demonstrate sufficient variation in clinically tested drug product. The predictive ability of the method is best justified through verification against actual in vivo performance. Additionally, selecting variations that lead to non-BE performance is highly beneficial because it can inform the borders of a process or attribute safe space and help in setting specifications that offer the greatest flexibility for the applicant.

QUALITY CONSIDERATIONS

Next, Melanie Dumarey, PhD (AstraZeneca, Sweden) presented the quality considerations of implementation of PDM for RTRT (*44*). Predictive models are a critical part of RTRT for dissolution as they enable linking measured PAT signals and/or process parameters to the dissolution profile of a formulation. Following the ICH-endorsed guide for ICH Q8/Q9/Q10, these models are classified as high-impact because they are a significant (and sole) indicator of product quality (*7*). Similar models could be used solely to support product development, in which case they are classified as low-impact. A current gray area is the use of predictive dissolution models to define a safe space, i.e., a multivariate design space where observed variability in dissolution has no clinical relevance (*9*). Further detailed studies are needed to demonstrate to regulators that the latter approach does not compromise patient safety.

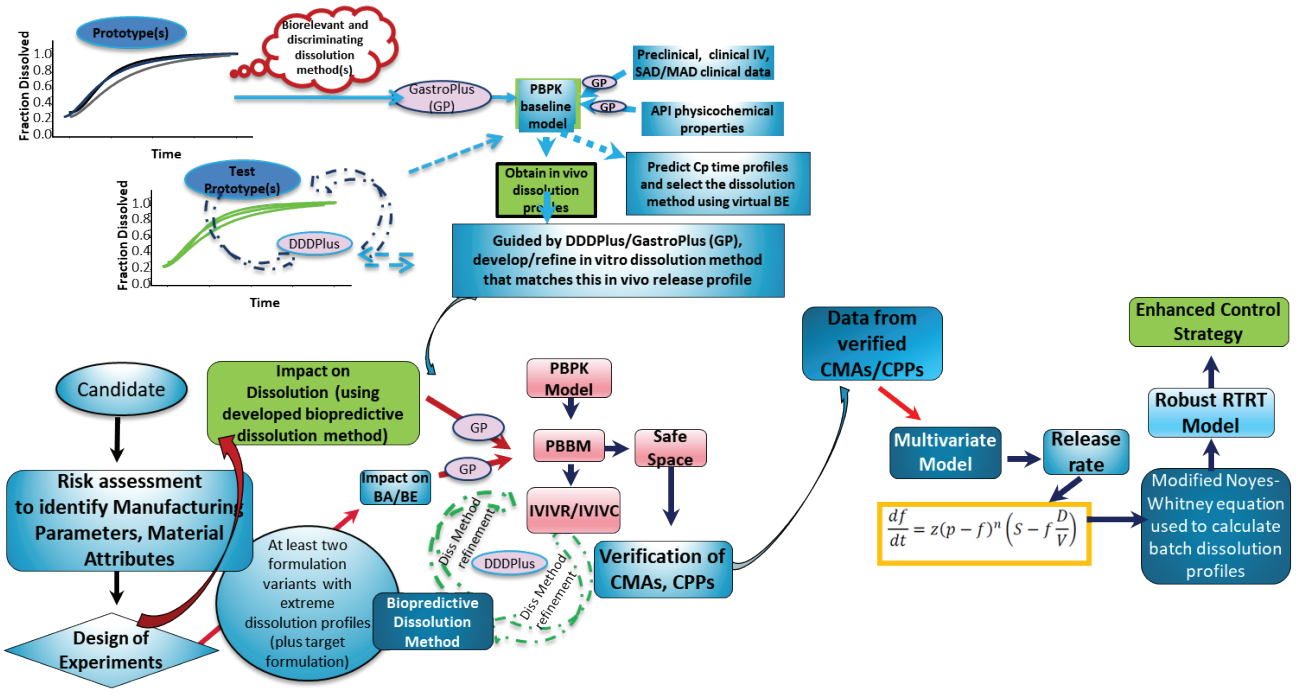

Figure 10. Proposed strategy for developing a biopredictive dissolution method and building clinical relevance into RTRT.
PBPK: physiology-based pharmacokinetics; SAD/MAD: single/multiple ascending dose; API: active pharmaceutical ingredient; Cp: concentration in plasma; BA: bioavailability; BE: bioequivalence; PBBM: physiologically-based biological model; IVIVR/IVIVC: in vivo-in vitro relationship/correlation; CMA: critical material attribute; CPP: critical process parameter; RTRT: real-time release testing.

High-impact models, such as models supporting RTRT for dissolution, require a detailed description in the common technical document (CTD), including a justification for the selected model parameters. In the prior section, current and former regulators stressed that the relationship between process variability and the complete dissolution profile should be fully understood to ensure all relevant CPPs and CQAs are included in the predictive model. This can be achieved by performing a dedicated DoE and/or by applying first principles (*45*). Regulators strongly recommended to model the entire dissolution profile rather than dissolution at a selected time point. Model robustness should be maximized by accounting for all process variability as expected during routine manufacture, e.g., excipient variability (*45*). The model description in the CTD should also contain model assumptions, sampling plan (number and justification), data pre-treatment, and a statistical evaluation of the model (*7, 45*).

High-impact models also require a high level of validation implementing an external validation set, which consists of samples not included in model calibration (*7*). Hereby, the predicted model values should be compared to the values measured with a validated reference method. Moreover, it should be demonstrated that non-compliant tablets are detected by the RTRT. During the workshop, it was clarified that validation can be based on dissolution prediction at one single time point but should be based on commercial scale data. Additionally, simulations can be used to complement the experimental validation, e.g., simulation of a batch failure. The validity range of the model should be defined, as well as diagnostics implemented to prevent invalid model predictions. NIR guidance issued by the European Medicines Agency (EMA) and FDA both provide detailed information on regulatory submission requirements for multivariate models (*46*, *47*).

The long-term validity of a model is ensured by the implementation of a lifecycle management plan monitoring common and special cause variation over time and triggering model updates as needed (e.g., change of a PAT instrument) (*7*). When implementing model changes with a major impact on product quality and/or model performance as part of the life cycle management, regulatory actions are required. Regulators recommended to capture anticipated model changes and associated actions in a post-approval change management protocol (PACMP), enabling to decrease the reporting category and helping to ensure business continuity.

INDUSTRIAL CASE STUDIES

Finally, the podium speaker presentations concluded with a series of industrial case studies (*48*). Sara Manteiga, PhD (Vertex, USA) presented a case study of implementation of PDM for RTRT as an alternative release method in an original NDA of a CM process. Stan Altan, PhD and Sarah Nielsen, PhD (Janssen Pharmaceuticals, USA) presented a PDM for RTRT developed as a post-approval process change, implemented on a batch manufacturing process, using multivariate statistical process control (MSPC) to enhance batch release.

Case Study 1

Dr. Manteiga presented a case study of a Vertex drug product manufacturing process for which RTRT was accepted as an alternative dissolution method to the regulatory release method. The drug product in the case study is an IR tablet manufactured continuously. The CM process train is equipped with multiple PAT stations to assess in-process material attributes. Together with an automated control strategy, these PAT measurements enable real-time process monitoring, control, and RTRT. The automated control strategy consists of four levels of control, from the lowest level to highest level, including: control of unit operations to set point through feedback loops, process design space monitoring, in-process controls (IPC), and RTRT. The IPCs have been set to ensure the process stays within the design space and that product variability within a batch is acceptable. Non-conforming IPC results lead to the removal of material from the process.

The RTRT dissolution methodology employs a hybrid modeling approach that links inline measured attributes to the dissolution results through a dissolution rate model, based on a modified Noyes-Whitney equation:

$$\frac{df}{dt} = z\,(p - f)^n\,(S - f\,\frac{Dose}{V})$$

The rate equation describes the fraction of API (f) dissolved over time (t) expressed as percent label claim (%LC), z is the rate factor, p is the extent of dissolution, n is a fitted particle shape factor, S is the API solubility representing the surface concentration from the dissolving material, and the dose/volume correspond to the tablet strength and volume of dissolution media in the USP apparatus 2 vessel.

Implementation of the modified Noyes-Whitney equation allows prediction of the full dissolution profile from measured in-process material attributes. A segmented

sampling approach is employed in which each batch is divided into 12 segments of nearly equal size, and results are calculated on each segment. This segmentation strategy ensures results are reported consistent with USP <711> stage 2 testing criteria and affords increased assurance of product quality through comprehensive representation of the batch. To determine the batch dissolution result, first *z* is calculated using the measured material attributes results and a PLS model. For prediction of the dissolution curve's plateau, API content in the final blend, measured directly by in-line NIR, is utilized. The predicted *z* and extent of release are then used to calculate the full dissolution profile and obtain the %LC at the specification timepoint using the modified Noyes-Whitney equation.

The PLS model for rate factor *z* is calibrated by fitting the reference method USP apparatus 2 dissolution profiles curves to the modified Noyes-Whitney equation and determining *z* for each profile in the calibration set. The samples used in the model calibration span the process design space and desired manufacturing range. To generate the calibration data set, key raw material attributes and process parameters (such as granulation and compression parameters) were intentionally varied using a multivariate DOE to achieve a range of dissolution performance to ensure robustness was built into the PLS model. The PLS model inputs were selected from known measured in-process material attributes based on a risk assessment using knowledge of the process and factors influencing dissolution performance at the time of batch release. This approach enabled a direct link to be made from raw material and process attributes to measured physical and chemical in-process material attributes, and finally, to tablet dissolution.

The PLS model for determining dissolution rate was rigorously assessed during development to ensure accurate prediction without overfitting. Samples used for model development were collected throughout development and analyzed by the PAT methods and the reference dissolution method. Selection of the calibration samples and appropriate number of latent variables for the PLS model was achieved through evaluation of calibration and cross validation statistics. An independent test set, including clinical batches and a parallel testing batch continuously manufactured at full-scale, was evaluated to ensure suitability of the model for its intended use.

For validation of the RTRT dissolution method, each PAT input method was validated in accordance with ICH Q2 (R1) (*49*). Additionally, direct comparison between the RTRT dissolution method and the reference dissolution method was made for a batch and shown to meet the established acceptance criteria. To further demonstrate the capability of the RTRT dissolution method to properly characterize the dissolution performance of a batch, comparison of results obtained using the reference dissolution method and the RTRT dissolution method was carried out for 25 continuously manufactured batches intentionally designed to span the desired manufacturing range, producing a range of dissolution performance. The RTRT results were consistent with those obtained from the reference dissolution method indicating good prediction accuracy, including the ability to detect non-conforming material.

A model lifecycle management strategy was also described for the RTRT dissolution method, to ensure performance of the RTRT method throughout its lifecycle. The PLS model maintenance practice requires assessing the performance of the model on a periodic or event driven basis, including routine parallel testing, changes to materials/instruments/process, observation of trends (including model diagnostics), and investigations. Based on the outcome of the assessment, a model update may be warranted. This may entail but is not limited to adding or subtracting calibration samples, changing the model prediction range, changing variable preprocessing, or changing the number of latent variables in the model. An updated model is ready for routine use upon successful completion of supplemental validation. Model updates are governed by a change management process.

Last, some of the key elements for successful implementation of the RTRT method in this case study were summarized:

- Knowledge-based justification for selection of input parameters to the RTRT PLS model, based on significance of impact of input parameter on drug release.
- Calibration and verification of RTRT method showed similar prediction outcomes with those obtained from the regulatory dissolution methods.
- For batch release using the RTRT method, the sampling approach ensures compliance with USP <711>.
- Demonstration that the RTRT model can detect non-conforming batches.

Case Study 2

Drs. Altan and Nielsen presented a case study of a real-time release strategy of a fluid bed granulated BCS class IV batch manufactured drug product, showcasing Janssen's unified approach to RTRT in the context of traditional batch manufacture. The approach involves monitoring CPPs at the dispensing and granulation steps, identified from earlier experimental manufacturing designs, that allowed the creation of a "health check" model to evaluate current batches against a historical standard (Fig. 11). The importance of comprehensive and adaptive experimental designs to provide the basis for de-risking was emphasized, as well as to set the stage for the development of a surrogate dissolution model. A comparison of the current release methods with the RTRT methods indicated greater assurance of quality due to larger sample sizes.

The surrogate dissolution model developed by Janssen relied on a comprehensive DoE (*50*). The designs provided a clear identification of the CPPs used to develop a "process" model in the first step. The process model related dissolution variables as the response variables to the CPPs. Dissolution variables, for example, could be specific selected time points on the dissolution profile, e.g., release at 20 and 30 minutes, or they could be the parameters of the Weibull function describing the full profile. In the former, it is a specific time point(s) model, whereas in the latter, it is a full dissolution profile prediction model. Once the response variables are defined as a multivariate vector, augmented by the content of the tablet measured by NIR, a conditional regression method was applied to the process model. The second step was to develop a predictive surrogate model of the dissolution response vector, relying on a population average approach, with process parameters and NIR content as inputs. The use of this statistical approach, in a Bayesian context, permits simulations that can characterize future manufacturing performance with respect to USP <711> testing, as well as estimates of the surrogate model's accuracy and precision in relation to the standard in vitro release test, on a batch average basis. It was also emphasized that the experimental manufacturing protocols be coupled with in vitro dissolution testing that orthogonalizes dissolution/high-performance liquid chromatography (HPLC) run effects with vessel and experimental batch effects.

DISCUSSIONS

Each of the 2 days of the workshop was capped by a panel discussion, allowing for interaction among the speakers and with the audience. The speakers participating in the first day's panel were Nikolay Zaborenko, Tessa Carducci, Alexander Ryckaert, James Drennen, Haritha Mandula, and Sandra Suarez-Sharp, moderated by Carrie Coutant (Eli Lilly & Co., USA) and James Mann (AstraZeneca, Sweden) (*51*). Discussion included the following topics:

- The skills necessary for developing PDMs for RTRT
- Global regulatory climate for accepting PDMs for RTRT
- Acceptance criteria for PDMs in relation to USP <711>
- Resources required to develop a PDM for RTRT as

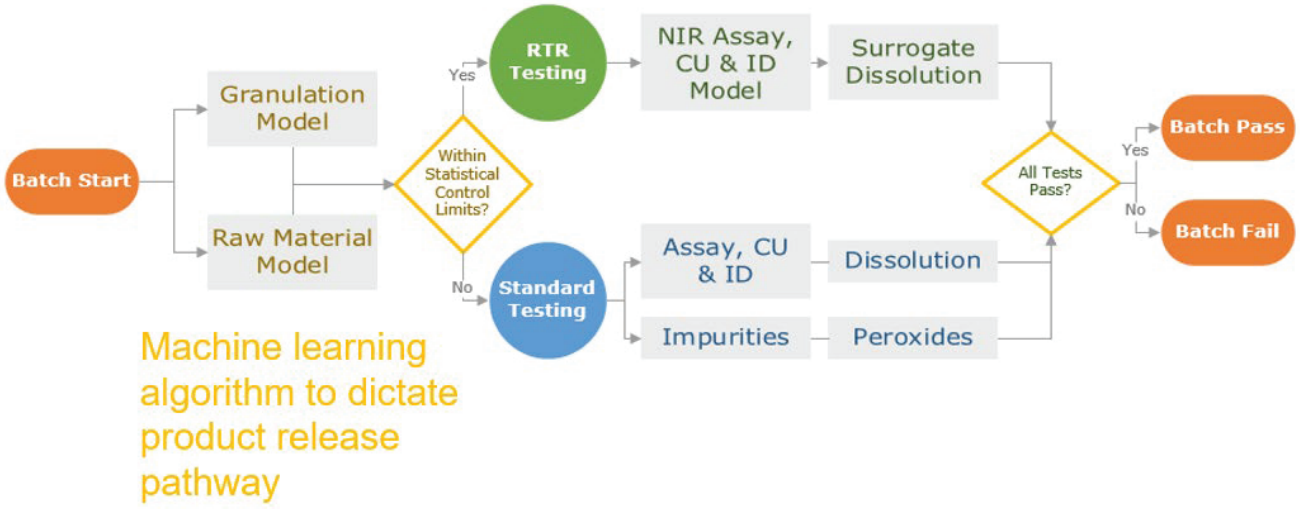

Figure 11. Real-time release using a "health check" model to evaluate current batches against a historical standard. RTR: real-time release; NIR: near infrared; CU: content uniformity; ID: identity.

compared to traditional dissolution

- Future direction of PDM

The first question was around what skills are important for developing PDMs for release. The importance of knowing and understanding regulations, the business case, having a good understanding of the manufacturing process and product dissolution including the method, specification time point, and failure modes, and multivariate modeling skills were all mentioned. The panel was asked a follow-up question on how to approach modeling if the dissolution is very fast or if the product is highly soluble (BCS class I or III). The risk for dissolution failure is seen as low for these products, and Dr. Mandula mentioned that there have been models of disintegration for release testing of products previously approved by the FDA.

The panel was then asked about the regulatory climate for PDMs for release and the importance of global acceptance. The business case is magnified when approved globally, and conversely, the benefits to a company could be questionable if routine traditional dissolution testing is still required for some markets. Approvals have been realized in the US and EU, and South Korea has just approved a new RTRT guideline that mentioned PDM.

There was robust discussion around assessment of acceptance criteria and whether PDM for release should follow USP <711> criteria. The panelists generally agreed that a larger number of replicates should be used to compute confidence intervals but that there may be additional approaches that would be successful, and applicants should make a proposal with justification of sampling plan as addressing the risk of failing to capture out-of-specification results. A related question asked was about how to handle error introduced through model inputs. This was seen by the panel as being analogous to any other type of analytical measurement where there are multiple contributing sources of error, and it is important to define the appropriate statistical sample size and confidence interval considering variability of model inputs. It is important to understand and minimize error in the traditional dissolution method because a PDM model will be based upon the reference method like other PAT-based models.

The next question was if the panelists have any advice for managing the increased resources required for development of a PDM as compared to traditional dissolution including those required for the model validation and maintenance efforts. In reply, it was suggested to convince the manufacturing teams of the benefits of eliminating dissolution testing, especially for high-volume products. Additionally, integrating model development with product development and starting early during development seems to help so that it is not seen as a separate or additional effort. Finally, implementing PDM for multiple products is more valuable than for only one product, and subsequent efforts should be easier since the experience and infrastructure can be leveraged.

The panel was concluded with a question on future directions in the field of predictive dissolution modeling. Research into models beyond simple PLS to improve quality of predictions, terahertz spectroscopy as an alternative method for dissolution, and sensor performance advancements to enable use of PDM as a process performance algorithm were mentioned as valuable future novel advancements.

The speakers participating in the second day's panel discussion were Nikolay Zaborenko, Melanie Dumarey, Sandra Suarez-Sharp, James Drennen, Matthew Walworth, Sarah Nielsen, and Stan Altan. The panel was moderated by Andre Hermans (Merck & Co., Inc., USA) and Siddhi Santosh Hate (Eli Lilly & Co., USA) (*52*).

The day 2 panel discussion included the following topics/questions:

- Panel experience of implementing apex vessels and global regulatory outreach
- How to build a PDM as an alternative QC method related to in vivo performance
- How many different formulation variants are needed for PDM model validation
- How the framework of RTRT models can be extended to non-oral drug delivery systems that require dissolution testing
- How a model fitting function and its parameters are selected for a dissolution profile prediction model
- Circumstances where a disintegration test may replace dissolution methods that only reproduce assay results

The first question was about the initiative by the IQ Consortium's Dissolution working group and AAPS In Vitro Release and Dissolution Testing community to implement apex vessels into USP testing. Apex vessels

were introduced to improve the hydrodynamic situation in the USP apparatus 2, the most commonly used apparatus for oral solid dosage forms (*53*). Several efforts have been made for global outreach to both the scientific dissolution community and the regulatory community worldwide. The topic was brought up to stimulate discussion and conversation with a diverse audience, especially for those people from countries that are newer to RTRT modelling and can share new global perspectives.

Then there was a follow-up question to the panel about PDM, which can be used as a surrogate to QC methods related to in vivo performance. Dissolution models used as a surrogate for QC release tests are high-impact models. These predictive models are typically built based on CMAs and CPPs, with a good understanding on how the QC method reflects in vivo performance. The panel shared their futuristic view of how a direct linkage can be made to model in vivo performance directly based on variations in CMAs/CPPs. It is also possible to simulate the process to link the multivariate models to drug safety and efficacy. It can be achieved by leveraging the available PK data that were already collected during development to train the models.

The panel was also asked if there is an ideal number of different formulation variants that need to be generated for validation of in silico modeling, such as the software DDDPlus, which could potentially link to PBBM. The panel commented that a minimum of two formulation variants are typically needed. The panel also discussed if validation should include batches with expected out-of-specification performance. The failing batches are often generated in early development when they are not fully representative of the final process or at scale and often use parameter values that are outside of the working model that eventually ends up being built. Using them to build the model will be challenging, and generating them at scale expends materials and time. Therefore, simulation tools such as DDDPlus might be used to do multicolumn analysis of variations and show that the deviation can be picked up by the model. It is appealing to generate the simulated data to support the dissolution model.

The examples presented in the workshop were focused on RTRT models for IR dosage forms. The panel was asked for opinions on expanding the framework to other drug delivery systems, such as extended-release dosage forms. RTRT modeling for other dosage form might be found acceptable, but it is handled on a case-by-case basis when advancing to complex dosage forms. The panel also mentioned that when using the framework for prediction of performance, replicates of 6 or 12 are recommended during model building and model validation. Sufficiently reproducible data is needed to build a PDM confidently. It is important to consider this so that DoE studies performed in early development can be designed in such a way as to provide useful data for PDM building.

The panelists were asked for their advice on the selection of fitting function and parameters for dissolution profile prediction models. The Noyes-Whitney function and Weibull function (with two parameters and a plateau multiplier) are the most commonly used functions in literature for fitting dissolution performance. Some experts commented that generally there is no dictating factor for selecting a function, as long as it provides adequate and consistent description of the dissolution profile. In addition, the calibration approach used should be robust over time to reduce errors in the long term.

Finally, it was asked when the dissolution method is very robust and a disintegration test can be used instead, is a PDM still needed? Some participants commented that it should not be necessary, as a process/material safe space for dissolution performance can be established and maintained to provide confidence of acceptable dissolution for every batch. However, the regulatory position on this has not been established. The panelists shared an experience where disintegration had been used as surrogate for dissolution and approved by FDA, but this was for a very low-risk product, where disintegration was more discriminating than dissolution. The group all agreed that this is a regulatory question, so in such cases, discussion should be had with the health agencies well in advance of submission.

CONCLUSIONS AND FUTURE DIRECTIONS

RTRT of dissolution based on PDM has been shown to enable QC release of drug products with equivalent or better quality assurance compared to traditional dissolution testing. In fact, the development of a PDM for RTRT necessitates a high degree of understanding of the drug product, including the interactions of its CPPs/CMAs and the sensitivity of its in vivo performance to the potential variations in the drug substance and drug product. Thus, the development of PDM for RTRT can be an integral part of a QbD approach, providing confidence in the consistent and satisfactory performance of released drug product.

The development of a PDM for RTRT requires a great deal of understanding and effort. However, it is not an insurmountable challenge. In fact, much of the work

required to develop an appropriate dissolution method for release is foundational and applicable to PDM development. Beyond dissolution method development, many approaches are available to build a PDM, with a high level of flexibility based on the needs of the drug product. A PDM can be applied to CM or to batch processes, with different PAT needs and opportunities presented by each. It can incorporate spectroscopic measurements, whether in-line, at line, or offline, or a PDM based only on process parameters and material attributes can be developed. However, in all cases, the PDM development submission must demonstrate the applicant's understanding of all factors that can influence dissolution behavior and show that those that are critical to dissolution performance are discriminated for by the PDM. CPPs/CMAs should be demonstrated through a DoE specifically designed to ascertain dissolution behavior across changes in these variables. Although a single DoE can be designed to serve multiple CQAs, including dissolution or dissolution surrogate release, it is important that it be designed explicitly with dissolution as one of its purposes. Attempts to repurpose post-hoc prior DoEs for PDM development have generally been met with skepticism from health authorities; however, it should be theoretically possible to demonstrate the applicability of a previously executed DoE to a new CQA (e.g., dissolution) as being equivalent to one designed solely for that purpose.

In developing a PDM for RTRT, it is critical to select an appropriately discriminating dissolution method for which the PDM is predicting release. Ideally, the dissolution method should be clinically relevant (differences in dissolution release behavior correlate with differences in in vivo performance) and able to detect non-bioequivalent product (preferably demonstrated clinically). If no clinical relevance can be established, then the method must be shown to ensure adherence to a safe space within which drug product quality has been ascertained. A PDM for QC must be able to detect non-conforming material by demonstration on physical non-conforming batches. Although simulating batch failure is a potential alternative approach, regulatory authorities express preference for and higher confidence in physical demonstration of the ability to detect non-conformance.

Development of a PDM for RTRT should be done in partnership with health authorities throughout the development process. The FDA and EMA encourage and welcome communications regarding dissolution method development as early as the IND stage, with opportunities for applicants to ask questions and solicit feedback at various stages of the process. Discussions of dissolution method appropriateness for quality control, the development of a PDM based on said method, the discriminating ability of both, and the level of support and justification for the method and model are all topics that should be discussed with regulatory agencies during drug product development prior to the final regulatory submission for the process utilizing the PDM (whether for a new drug product or a post-approval change).

Currently, the primary barriers for drug product applicants to consider developing RTRT for dissolution are the lack of concrete (published) guidances and expectations around PDMs for RTRT and the uncertainty around acceptability of this approach to global regulatory agencies. The uncertainty of successful acceptance of an RTRT approach in all intended markets results in applicants questioning whether or not the investment of developing a PDM will lead to realization of the benefits associated with reducing/eliminating destructive in vitro testing of the drug product. As such, it is imperative for industry members to continue collaborating with global health authorities to establish a common framework of expectations for regulatory submissions containing PDMs for RTRT. As more guidances are published or adopted in global markets, these can serve as the foundation for eventual harmonization. Original NDAs and post-approval changes introducing PDMs for RTRT as alternatives to traditional dissolution testing submitted to regulatory agencies around the world will provide evidence of assurance of drug product quality and generate confidence in acceptability and, eventually, desirability of this approach to drug product release.

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CONFLICT OF INTEREST

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DISCLAIMER

This article reflects the views of the authors and should not be construed to represent their organizations' views or policies.

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