

## Some Thoughts on a Recent US FDA Document “Quality by Design for ANDAs: An Example for Modified Release Dosage Forms”

The US FDA (CDER) released a document on the above mentioned title ([Link](#)). This single spaced 161-page long document provides an example of conducting and reporting studies for developing generic drug products as per the QbD (Quality by Design) approach.

It appears that this document may also be considered a “How-to manual on drug dissolution testing”, as a significant portion of the document describes the development and application of the dissolution testing.

It may be argued that if current practices of drug dissolution testing would not have faced so many problems/deficiencies and uncertainties, the procedures and documentations provided would certainly be simpler and shorter. Therefore, indirectly, the document may be considered as a long awaited recognition of the fact that current practices of drug dissolution testing are complicated and complex, and may not be working as well as one should expect.

In the spirit of simplification/clarification, the following comments are provided to reflect potential issues which may arise from the suggested recommendations. Please note that comments are restricted to the drug dissolution testing area only (method development and their applications). *Text in red is from the FDA document, while comments are in black.*

*“Note to Reader: In order for accurate measurement of the product attributes at in-process and finished product stages, the analytical methodology should be evaluated for its capability of producing test data that are closely representative of the true attributes”.*

This is a critical and essential requirement. However, at present none of the apparatuses commonly referred, including the USP Apparatus 3 as described in the document, would meet the requirement. Although generally assumed, commonly used apparatuses have never been validated for their intended purpose. That is, these apparatuses have never been shown to be able to provide (bio)-relevant dissolution characteristics of a product. For further explanation please see the [link](#). Industry, in particular the research and development area, would be ones to seek some guidance in this regard.

In continuation of the previous text in the document, it is further stated that,

*“ Before a formulation or manufacturing process is studied for a given product, the analytical method should be assessed to determine the degree of variability in the test data imparted by the analytical method itself versus the degree of variability inherent to the product.”*

The industry, and the research and development group in particular, would seek guidance in this regard as to which product/reference should be used to establish the variability of an analytical (dissolution) method. ANOVA-based statistical analyses are fine, as suggested in the document, however, the question is how the quality i.e., relevancy, accuracy (“trueness”) and reproducibility of the data be established prior to the relevant statistical analyses. For relevant discussion please see [link](#). At present,

there is a lack of availability of a reference standard which can be used to generate relevant dissolution results thus method.

*“1. In Vivo – In Vitro Correlation (IVIVC): Establishment of an IVIVC is one of the more robust options to assure continued BE of the commercial lots. It establishes a control for post-approval changes to the critical material attributes (CMAs) and critical process parameters (CPPs) and ensures continued product quality and BE. However, IVIVC is difficult to establish.*

*2. Predictive in vitro method (In Vivo – In Vitro Relationship (IVIVR)): A product designed and developed using QbD principles should lead to the establishment of a predictive in vitro dissolution method. Establishing an IVIVR, although less robust than an IVIVC, may be sufficient to assure product quality when combined with product and process understanding. Such an in vitro method will also be useful in assessing post-approval changes”.*

This text appears to create significant confusion in the mind of an analyst/formulator for the following reasons: (1) It appears that regulatory emphasis/requirement is moving from the practice of IVIVC to IVIVR. It is not clear what the differences in these two terminologies are. From the text, they appear to be the same, but with a different name. (2) For all practical purposes, the suggested approach of IVIVR (or IVIVC) and for developing predicted in vitro dissolution methods, is an exercise of seeking experimental conditions for a dissolution test to obtain results (dissolution profiles) which would fit preconceived and desired dissolution expectations. In principle, a true predictive dissolution test, or any test, should be independent of the test product (a product which is under evaluation). From a dissolution testing perspective, a truly predictive dissolution test should reflect the environment of the GI tract which most often remains the same or constant from product to product. Therefore, developing a dissolution method by selecting or choosing experimental conditions to match an expected behavior of a product, should be considered as a “matching exercise” rather than “developing a predictive method”. Therefore, in the absence of a truly predictive dissolution method, it is highly unlikely that the recommendations will provide anticipated success in using the QbD principles for product evaluation.

In addition, the length of the document may be overwhelming, shortening it may help in its speedier adoption.