Q*b*D (Quality by Design): The issue of defining and establishing "quality" of drug products

Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

A suggested definition of "quality" for QbD purposes is described. It is hoped that the article will help in highlighting the underlying scientific issues and deficiencies which will prevent in achieving the intended objectives of the suggested "QbD based ANDA example documents". It is argued that the documents are based on invalid analytical (dissolution) methodologies, which makes the suggestions/recommendations invalid as well. Suggestions for improvement are provided.

The concept of Q*b*D has often been promoted for the development, manufacturing and evaluation of drug products, so that "quality" of the products can be improved. To be successful in the implementation of the Q*b*D, i.e. improving the quality of drug product, it is imperative that one should set a goal post i.e. define the quality of a drug product. For this article, the concept of quality is explained based on an oral drug product e.g. tablet.

A working definition may be as follows: The quality of a drug product, such as tablet, may be defined by its ability of delivering/releasing the labeled amount of drug in an expected manner with consistency.

The "ability of releasing the labeled amount", refers to potency, "expected manner" refers the time factor (fast or slow) and "consistency" to content uniformity i.e. tablet to tablet variability. It is important to note that even if the product contains an expected amount of the drug but does not release it then the product is considered as substandard. Therefore, the drug releasing ability of a product defines its "quality": expected drug release, good "quality" product, unexpected drug release, bad "quality" product.

Once again, the drug releasing ability of a product defines its "quality", a one liner people sometimes ask.

To explain it further, when a patient/consumer buys an acetaminophen tablet product, he/she is expecting that the labeled amount of acetaminophen will be delivered into the GI tract as expected or stated. If one follows this definition, it would not make a difference if the product is a prescription or OTC, the definition of quality is the same for both types of products.

In my opinion, it should be relatively easy to prepare/manufacture such products. Basically, it is mixing ingredients and passing through tablet production process. Now-a-days, the process of tablet manufacturing is highly automatic, so the manufacturing is relatively a routine process. I think that the manufacturing of tablets and capsules should in fact be a cottage industry. I really feel that it is quite unlikely that things can "uniquely" go wrong for the pharmaceutical manufacturing, other than related to "acts of God" similar to those observed in other industries.

So then what is the (current) problem? In my view, the following describes the problem Pharma is facing:

It is not the "quality" per se but ***monitoring*** of the "quality" is the problem. The quality of a product or anything else will be as good as a gauge which is to be used to monitor or measure it. As stated above, quality of the drug product depends on its ability to release the drug. The measuring tool, or the gauge, in this case is drug dissolution testing. Published literature clearly demonstrates that dissolution methods which are used are neither relevant nor precise. The other way of saying this is, that the methods currently used are not validated for their intended use. The methods used have never been shown to reflect drug release in humans and the expected variability of the methods is 25%+ (CV or coefficient of variation). So, even though the quality of a product may be good, the bottleneck in establishing the quality is the analytical methodology ***not the manufacturing***, at least at this time. My view in this respect is that manufacturers tend to set tighter tolerances for their products (obviously it would look awful to present one's product with 25%+CV), but when samples are analyzed at random, the real variability of the method became visible. Obviously the product is going to fail and will make a good case for Q*b*D promoters. ***If the QbD concept is to be applied successfully in this area, the first requirement is to ask for and to include a better analytical methodology.***

The other problem is, which is also not related to manufacturing, but to product development, because once the product is developed, the manufacturing takes over which then will fall in the category described above. The suggested Q*b*D based ANDA documents (*link1*, *link2*) fall in this category i.e. product development.

To explain the situation, let us consider a simple case of a generic product development. Here one makes a straight copy of an existing branded product. The development stage is in fact an exercise for establishing release characteristics of the product to match the branded product. At this development stage, one prepares a generic version and tries a number of formulations to obtain an appropriate match to the branded product. This development of the product for its match is based on drug dissolution testing, the same drug dissolution testing described above as irrelevant and highly variable for the evaluation of products for human use. Usually based on trial and error, some formulation(s) are selected which most likely will provide similar release characteristics as that of the branded product in humans.

It is important to note that a human study, known as bioavailability/bioequivalence (BA/BE), is the one which decides about the equivalency of the products. In the industry, it is a quite common that products tested based on dissolution testing and then evaluated by human BA/BE studies often shows very different result. Therefore, repeated BA/BE (human) studies are conducted to achieve appropriate formulation which matches the release characteristics of the branded product. Dissolution testing usually does not help at all, and it should not, as it is not a relevant technique in its present form, however, ***it is required that such studies must be conducted***, why? This is a serious wastage of resources.

Further, even when dissolution studies are completely failed, it is stilled required to establish a certain (simple) dissolution test, often even more irrelevant to human physiology, so that this "simple dissolution test" can be used as a QC test (commonly known as pharmacopeial test), to alert about a potentially sub-standard product. How? Does this make any sense? Note that the dissolution test will be used as a QC gauge to show expected release behavior of a product in humans. It is the same dissolution test, which was found irrelevant during product development.

The practice described here in essence summarizes the Q*b*D documents regarding establishing/evaluating release characteristics of a product thus its quality. This suggested practice of dissolution testing has been in use for the past at least 30 years and now is being suggested to continue in the future, with Q*b*D concept. It is not clear how it will help in improving the product development, manufacturing and its quality.

In conclusion, quality of a drug product is linked to its ability to release the drug from the product. If the quality of the manufacturing or products is to be improved, and Q*b*D principles are to be applied successfully, it must be recognized that the currently suggested analytical (dissolution testing) methodology, as described in "ANDA example documents" is the root cause of the problem. Therefore, currently suggested Q*b*D documents which are based on flawed dissolution methodologies should not be considered useful in particular for improving development and evaluation of products. The documents need to be revised either by removing the flawed methodologies or by including a new, relevant and reproducible methodology.