The issue of validation/qualification of dissolution apparatuses

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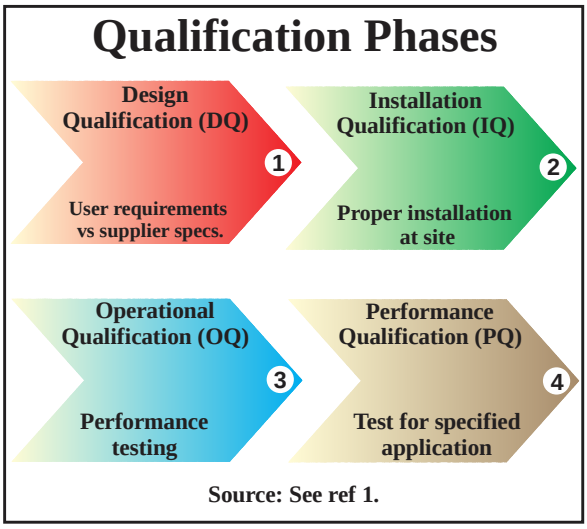
It is a well-established fact, and often a regulatory requirement, that one has to demonstrate that an apparatus can provide the intended and expected outcome. A simple and common example of this requirement is calibrating a laboratory weighing scale or balance. Initially when a balance is purchased, and then occasionally thereafter, it must be calibrated against reference weights to show that the balance can provide accurate weights of the references. If the balance does not perform as expected, it must be adjusted accordingly.

This calibration process establishes that the balance is good for providing weights of unknown samples and is described with different terminologies such as calibration, performance verification, validation, system suitability, and/or qualification. All of these terminologies, more or less, refer to the same thing. However, there is consensus regarding the terminology of qualification. Thus, the term qualification will be used in the remainder of the article, which would mean the process of establishing that an apparatus is fit for its intended use and capable of providing the expected outcome (results). To further clarify this concept, the following analogy may be useful: one should not use a volumetric flask for determining the weight of a liquid such as water, although one can make a fairly accurate estimate of it based on the volume. This is because the intended use of volumetric flasks is for measuring volumes, not weights.

The qualification process is usually divided into four phases: design qualification (DQ), installation qualification (IQ); operation qualification (OQ) and performance qualification (PQ). Collectively, these four phases are referred to as a 4Q-Model. A brief description of individual qualification phases is provided in Figure 1.

It may be important to note that regulatory bodies generally do not develop standards for qualifications but adopt, based on consensus and availability of the scientific data, as guidelines to facilitate efficient interactions between vendors and the users (analysts) for the benefit of the public.

From Figure 1, it can be observed that the first qualification (DQ) and the third one (OQ) are the most important ones from a user's (analyst's) perspective when an apparatus is purchased, i.e., the design of the apparatus and the operation of the apparatus. Repeating the analogy above, if the intent is to measure the weight and someone provides a volumetric flask, the flask will fail the DQ. On the other hand, if someone provides a balance but does not provide the results using the reference weights, then the balance will fail the OQ. No matter how small and insignificant, or large and sophisticated, of an apparatus one has to purchase these 4Qs are to be followed. For the user, the two mentioned earlier, DQ and OQ, are the most important.



Let us apply these criteria to the drug dissolution apparatuses, particularly the paddle and basket. What is the intended use of these apparatuses? These stirrers/mixers must provide homogeneous (gentle and thorough) stirring and mixing. A quick physical observation (e.g., cone formation), and now with the availability of large experimental data, clearly show that these apparatuses do not provide homogeneous (gentle and thorough) stirring and mixing. Therefore, these apparatuses fail the DQ.

The second aspect from the users' perspective is OQ. For OQ, the essential requirement is the availability of a reference standard, i.e., an approved **drug product for human use** with known dissolution results, to show that these apparatuses can provide the expected outcome. As there is no such reference product available at present, one cannot check the operation (performance) of the apparatuses, thus, the apparatuses fail the OQ as well.

Therefore, under the commonly accepted practices of qualification, these apparatuses cannot be considered as qualified or validated. Thus, their use has to be reconsidered.

On the other hand, these apparatuses have been in use for many years; therefore, the natural reaction to the new or recent observations must first be denial and then rationalization for their continued use. I believe we have passed the denial phase and are in the rationalization phase. How does one rationalize their continued use by inventing new terminology and practices? What are the new terminologies: MQ (Mechanical Qualification) and PVT (Performance Verification Testing)? How do these address the deficiencies in lack of appropriate stirring and mixing and availability of reference standards? They do not; otherwise, inventing new terminologies would not be necessary. One would have used the commonly accepted terminologies of DQ and OQ. Another common rationalization is that much research has been done to develop the standards and guidelines for MQ and PVT; therefore, these must be useful and acceptable.

Certainly, apparatuses will meet the MQ and/or PVT requirements. Unfortunately, apparatuses are not used or developed to meet some arbitrary set of qualification requirements; they are developed and used for evaluating drug products, and one requires DQ and OQ.

Therefore, in the future, when you hear a recommendation or see support (advertisement) for MQ and PVT, then become alert and request again and again, and then again for DQ and OQ, until you are heard. **There is a serious oversight here in recommending and using the apparatuses without meeting the qualification requirements (DQ and OQ), which must be addressed.** In my opinion, the vendors and the users (analysts and manufacturers of drug products) have to address the missing of DQ and OD components. As stated above, the regulatory bodies will react accordingly and accept the new developments by setting new standards or guidelines. It is just like companies develop drugs and consumers use, the regulatory bodies set the standards based on what is available and what is needed to facilitate smooth interaction.

References:

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