The killing of drug dissolution testing: what it means and how to achieve this objective.

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The following comments are noted from one of my earlier posts, as reported in the FDA transcripts (link):

(1) "It is noted that literally 50 percent of the batches are thrown out every year because of dissolution failures, …"
(2) "There is no evidence that the products out there on the market are bad products. There is no evidence that the agency has done a bad job in serving as a surrogate for ensuring good quality products for the consumer. And, there is no evidence that industry is not focused on quality as an important attribute to manufacturing products."

Putting these two together clearly shows that we are dealing with the problem of dissolution and not of products or industry?

If we agree and accept that the dissolution is the problem, then we can develop an approach to address the problem. This provides us with a focus or objective i.e. dissolution is the problem and we need to address it. I believe that dissolution is the problem, however, where I differ is as follows:

Unfortunately, people get confused (and emotional) in defining what the actual problem of dissolution is: without thinking they just declare "it [dissolution] has to be killed" because it is the problem. Please, hear me clearly here, dissolution is not the problem, but ***how we measure*** is the problem. If dissolution would have been the problem, it would have been killed a long time ago. We can neither live without dissolution evaluation nor can it be killed. The whole industry in particular generics depends on it, even the suggested QbD example documents heavily depend on it. The reality is, when people say that they want to kill dissolution, without realizing, they actually mean killing of dissolution testing (procedure of testing).

This is where the problem is: dissolution testing and not the dissolution (link). If you would like me to elaborate further on this differentiation. Let me know, and I will be happy to do so, because it is crucial to understand the difference between these two. I am probably the first or among the first ones to ask for the killing of dissolution testing.

Now, how are we going to address this problem (which is the killing of dissolution testing)? A simple and direct suggestion for this (in particular for QbD promoters) is to ask anyone to provide the dissolution results using appropriately qualified and/or validated apparatuses. Bingo, you will have your answer to how we can kill dissolution testing. Nobody can provide you dissolution results using qualified and validated apparatuses (link, link). Period!

This is a basic/fundamental requirement for any test, especially in the regulated requirement, GMP, etc. that before using or generating results apparatuses/techniques must be shown to be validated and qualified for the intended purpose. No one will accept results or outcomes from apparatuses/tests which are not validated or qualified, then why do we accept such results? The reason is that it is a regulatory (and compendial) requirement (link). Please, note this last sentence: it is a regulatory requirement to use these apparatuses, industry is just following it. I hope that you see the issue here. ***It is the regulatory requirement which is the problem,*** not the products, manufacturing or the industry. Kill the regulatory requirements for asking for testing of dissolution using apparatuses which are not validated or qualified, the dissolution testing will be killed by itself.

Promoters of the current dissolution practices have done a remarkable job of marketing the requirements of dissolution and the testing part as one and the same thing, which is just sad and very unfortunate. On the other hand, one often hears such comments that this (methods, apparatuses etc.) is the best we got. This is absolute nonsense! It is not the best, this is nothing, this is the problem, this is toxic. This promotion of dissolution testing (nonsense) using current apparatuses, in particular paddle/basket must be stopped. Let the industry and others decide how they would like to do dissolution testing, if they desire to. Delete the requirements.

So, in short, it is not dissolution that is the problem but dissolution testing. Current practices of dissolution testing uses apparatuses which are not validated and qualified, and by default all results obtained using them are null and void. Conclusions regarding the quality of the products or industry cannot be based on such (dissolution) results. The reason people are using these apparatuses is that regulatory requirements force them

to. Therefore, the regulatory requirements of using these are to be killed which are invalid to start with (requiring the use of not validated and qualified apparatuses). People may use other approaches for monitoring dissolution which obviously will have to be validated and qualified. This is exactly like for the requirement of an analytical method such as for establishing the potency of products, but how and which method is to be used (HPLC, GC, NMR, NIR, MS and so on), should be an open choice. However, prior to the use, the method of choice has to be qualified and validated.