Promoting quality standards for drug products: Scientifically speaking, please be systematic and logical!

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It appears that talking about the quality of drugs/pharmaceuticals and their products has become a fashionable topic, in particular with respected scientists and regulators. There appears to be clear fearmongering and a blame-game approach that is taking place to discuss the subject and perhaps to gain personal or professional recognition along the way. Such human elements are natural or expected; however, when it comes to science then such emotional distractions should be managed, preferably set aside. This article is an attempt to provide a rationale and scientific point of view to highlight current difficulties in setting standards for developing and manufacturing quality drug-products, in particular tablet and capsule.

It is normal and expected that before one talks about a subject/topic, the subject/topic must be clearly defined with associated boundaries/space. Unfortunately, it has become quite common that when discussing the subject, the discussion and focus go well beyond the intended objective and boundaries. For example, often when people talk about pharmaceuticals and their products, they tend to extend it to the healthcare system as a whole. It is to be noted that pharmaceuticals and their products developers are a part of the healthcare system, but not the healthcare system itself. Pharmaceutical professionals/scientists are as much part of the healthcare system for promoting and maintaining the safety and wellbeing of humans/public as producers of food products and restaurants (e.g. McDonalds) owners. Considering the vast business and consumption proportions of food, these industries perhaps may have more significant impact on the consumers' health and safety. Even in the hospitals during their stay, perhaps, the food component could be more relevant to the safety and wellbeing of the patients than medication aspect. Should the food and chefs be part of the healthcare system as well? Of course, food and chefs are significant contributors towards safety and healthy life style. Point being that in larger scheme of things, drugs and their products are a part and should be treated as such i.e. developing and manufacturing of drugs and their products.

Drugs and their products development and manufacturing must be considered as a standalone entity and must be evaluated by its own standards, scientific though, which should feed into the overall healthcare system.

Certainly, high levels of academic backgrounds and expertise are required for the development and manufacturing products, a drug and its product can be exemplified very effectively with food equivalent of sugar (drug) and its candy. From a consumer/patient perspective there is no difference in these two. When a person feels feverish he or she requires an acetaminophen candy (Tylenol). On the other hand, if a person has low sugar levels or has a craving for sugar he or she would require a sugar candy. Scientifically and conceptually, from the manufacturing perspective, there is no difference in the two. From the patient and consumer perspective, the requirement is that the "candy" (product) must contain the desired ingredient/drug in an expected amount which must also be delivered or released in an expected and consistent manner. No efficacy or safety issue of the active or desired ingredient (drug) should be of concern here, because safety and efficacy of both acetaminophen and sugar are well established and documented. If the ingredient/drug is delivered in the desired amount in a consistent manner, and the product is manufacturer under common and standard GMP practices, then the product (candy) will be considered of quality.

The important conclusion from the above discussion is that quality of a pharmaceutical product is its ability to deliver/release the desired (active) ingredient in a consistent manner. The safety and efficacy is secondary to this quality aspect i.e. if the active ingredient is delivered as expected the product will become safe and efficacious.

So why are the sugar candy and acetaminophen candy treated differently from the manufacturing perspective that acetaminophen (or any other drug) candy has to go through strict regulatory assessment process, but not the sugar candy? The reason is that one can easily test and establish quality of the sugar candy by tasting it as to whether the sugar (active) ingredient is released or not, but acetaminophen candy cannot be, as drugs are not tasted, or may not provide taste, and also these candies are usually swallowed, as a whole, thus provide limited chance of tasting it. Therefore, the release or delivery of

acetaminophen cannot be tested as easily as for a sugar candy. This is the fundamental difference in these two types of candies for their assessment. By the way, in the pharmaceutical world, these candies are called tablets, capsules, pills etc. Therefore, in the following discussion pharmaceutical products will be referred as tablets and capsules only. The discussion in this article is limited to tablet and capsule products only, however, principle of evaluation for other types of products remains the same or similar.

So, how does one establish drug release characteristics of tablets and capsules? Simply, by swallowing the tablets and capsules and by taking some blood samples and measuring the drug amount in these; because most often when the drug is released in gastrointestinal (GI) tract it will appear in the blood. If the drug levels in blood are as expected and consistent, then drug release characteristics of the product are established and the product become a quality product and is good to go. There are certainly a number of scientific principles involved in this regard along with numerous regulatory standards and requirements. However, conceptually, this is how the quality of the pharmaceutical products is tested and established. By the way, determination of drug blood levels and their evaluation, in technical terms, are known as bioavailability/bioequivalence (BA/BE) testing, assessment or studies. There is no magic or extra ordinary scientific complexity involve here; these are basically average level analytical chemistry tests. It is not clear why such testing is part of pharmaceutical or medical discipline/industry.

In short the quality of a drug product is its ability to deliver or release the active ingredient in an expected and consistent manner. This expected and consistent release is established by testing drug blood levels based on well-established principles and practices of analytical chemistry, also known as bioavailability or bioequivalence (BA/BE) testing/assessment.

It does not matter, if one has well established drug (active ingredient) like acetaminophen for which safety and efficacy is well established or a new drug of which safety and efficacy has to established, if administered to humans as a product (tablets/capsules), the product quality must be established using the method described above. That is, it must be ascertained that the drug will come out of the product as expected and consistently.

It does not matter, whether a product is from a brand-name/innovator or generic manufacturer, quality of the products is established exactly the same way i.e. by conducting BA/BE studies or testing.

Considering the ethical reason of involving humans and extended cost and time requirements, the BA/BE studies are conducted to a limited extent. Often only one or two studies are conducted to establish the quality of the products and to gain regulatory approval for the sale of the products. It is important to note that such studies are conducted prior to any commercial production and usually only with one or two dosage strengths. Such BA/BE are seldom, or almost never, conducted during commercial productions of the batches for quality assessment purposes.

So, how does quality of production batches is established; by conducting a simple analytical chemistry test known as drug dissolution test. This test is based on the principle that if a drug is to be absorbed from the GI tract, it must be released and should dissolve in an aqueous based solvent representing the fluid within the GI tract. Thus if a product meets the dissolution test criteria, then it will be considered a quality product as well.

It should be extremely important to note, however, that this test as conducted currently has no relevance to BA/BE characteristics of a product. USP categorically acknowledges this fact that dissolution tests as described in the USP monographs are not BA/BE relevant, but are still required to be conducted to establish quality of the products. Can someone please explain the logic here that the test has no relevance to BE/BA but still is required to be conducted to indicate appropriate BA/BE and thus quality of the products.

An even more interesting aspect is that dissolution tests as conducted or required currently completely violate practically all scientific principles and GLP (Good Laboratory Practice) practices of analytical chemistry. The suggested apparatuses have never been validated and qualified for dissolution testing purposes. Not only does the testing lack BA/BE relevance, as an analytical test it has virtually no credibility in providing any reliable data. This test is very well known to provide highly variable and unpredictable results. So, the important thing to note is that at a manufacturing level, at present, practically there is no evidence or criteria available to establish the quality of a product, no matter how simple or complex a product or manufacturing is.

Therefore, in nut shell, at present no one is monitoring, or can monitor, the quality of the products during and/or

after manufacturing of commercially available products. The products are allowed into the markets based on assumptions that manufacturers are in ***compliance*** of regulatory standards (mostly record-keeping) of approved SOPs generally based on traditional observations and practices.

More recently there has been promotion of some concepts, such as PAT (Process Analytical Technology), QbD (Quality by Design), CoQ (Culture of Quality), data integrity, etc. for improved manufacturing and assessing quality of pharmaceutical products. In reality, however, these are different approaches of data handling, not about improving the testing and/or data quality or improving quality of pharmaceutical products. It is exactly like promoting improved productivity of an office by monitoring its cleanliness and shininess, availability of well-organized record keeping equipped with efficient record tracking and retrieval system, following codes for well-dressed and well-behaved working staff and noting that each office and record be marked with a word "quality". Such practices, though may be desirable, but would not reflect underline quality of results and/or approaches used to generate the results/data. Under such a scenario, offices will only be considered being in ***compliance*** for following the standards and requirement for their operation, without an ability to demonstrate an acceptable evidence of "quality" and/or relevance of their "work".

Point being, these currently promoted approaches, which are not only horrendously complex, time consuming and expensive to follow and maintain, do not provide any improvement in assessment of release characteristics of the products thus their quality. In addition, there is no evidence presented that if indeed such approaches have, or will have, any positive or value added effects on the production or improving the quality of drug products. Mostly it has been a guess work so far. In addition, such suggestions take away resources and time from the industry and scientists for addressing the actual problem i.e. not-allowing to determine drug release characteristics during manufacturing in a more prudent and scientific manner. A more systematic and logical consideration would certainly help in highlight and then addressing it. Scientific literature certainly provide some relatively simple solutions to address the underlying issues of monitoring quality of the products and thus can lead to development and manufacturing of quality products. Further discussion, in particular technical, on the topic is beyond the scope of this article; however, for further details in this regard, please visit (link) or contact (email).

In conclusion, drug/pharmaceutical manufacturing is one, perhaps small, part of healthcare system and not the healthcare system itself. The manufacturing of pharmaceutical products, in particular tablet and capsule, is relatively simple and standardized manufacturing process such as confectionary industry and alike. The quality of a drug/pharmaceutical product is measured based on its release characteristics; i.e. its ability to deliver/release expected amount of drug from the product (tablet/capsule) in a consistent manner. At present, the technique and methods used, at the manufacturing stage, are not scientifically valid and cannot provide assessment of "quality" of such products. Suggestions of improvement in such methodology and/or new approaches are urgently required.