Why did the quality-by-design (QbD) approach fail? One reason: Lack of availability of relevant and reliable data reflecting the "quality" of products (tablets/capsules).

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Recently I participated in a discussion on a LinkedIn forum (Quality by Design or QbD) explaining relevance and critical importance of drug dissolution testing for QbD, manufacturing of the products (tablet/capsules) and their evaluations.

Continuing on the topic, I believe a better organized explanation may be useful in clarifying issues related to the assessment of quality of pharmaceutical products. This article provides the explanation. It is important to note that the following discussion is restricted to tablet and capsule products only.

The development and production of pharmaceuticals (drug products) may be divided into three inter-linked components: (1) Manufacturing of drug products; (2) Drug products and their development; (3) Drugs and their development

Suppose someone takes a tablet of a drug (e.g. ibuprofen) to obtain relief from tooth ache or any other ache. In all likelihood, the tablet will work in relieving the pain. However, for our discussion purpose let us assume that the tablet did not work and in fact the consumer/patient had a severe adverse reaction to the product. Obviously the product had a problem. However, what exactly is the problem? Until, the nature of the problem is not established, one cannot fix it. In this regard:

It is possible that one of the ingredients got mixed up i.e. the ingredient may be substituted, absent or lower than expected. This is certainly a manufacturing problem. However, if the complaint is that the drug produced its intended beneficial effect (relieving in pain), but with an adverse effect such as a severe abdominal pain, this may be an indication of poor design (prototype) problem. For example, the drug was intended not to be released or dissolved in stomach, but it may have. That is, the design of the product (tablet) may not be robust and did not behave the way it is supposed to. The third one, is that the product did not provide its beneficial effect but caused a severe unknown adverse reaction. This should be considered as an issue of the drug itself and not the issue with the product and/or its development.

Now, if the topic under consideration is manufacturing then in a sense one should only be concerned with the first item in the above mentioned list. That is, some how the product was manufactured poorly by a mix up or of poor quality control, some refer to it as poor process control. The two other issues are not because of the manufacturing. No matter how good the manufacturing is, if the drug itself or product development is not robust, manufacturing will not help.

Before moving further, let us outline what drug product manufacturing is. In a very simple terms, it is the process of making a "dough" from some very well established ingredients (pure or almost pure) including drug (active pharmaceutical ingredient or API) and then making millions or billions of small pieces (granules) which are compressed into tablets or filled into capsule shells. There is no intent here to diminish the manufacturing aspect (its sophistication and complexities), but to indicate that it is a relatively straight forward and simple process, often times streamlined and highly automated. Then, why are manufacturing or the quality issues so often discussed? The reason is that people often mix the issues of two other categories (drug and product development) with manufacturing.

To keep the discussion or explanation simple from the manufacturing aspect, let us ignore the drug development aspect because when chosen for manufacturing (e.g. generics) often drug properties, as chemicals, are usually well established. One needs to develop a product i.e. a prototype which is passed onto the manufacturing.

What is the process of product development? Again in simple terms it is the mixing of appropriate ingredients, converting it into "dough" and then cutting it into millions of pieces and compressed into tablets or filled into capsules. Basically it is exactly like any other manufacturing perhaps very close to food (candies) manufacturing.

Like any other manufacturing, pharmaceutical manufacturing has relevant manufacturing standards or specifications, so are for the products, tablets and capsules. However, ***there is one very important and critical difference here from food manufacturing, which is, how specifications are developed and set for pharmaceuticals.***

Let us start with a food product such as candy. If one wants to develop a new flavour or taste for a candy, obviously based on his/her experience, a fabricator will prepare multiple samples and will conduct taste and smell evaluations. The candy which comes with the most acceptable outcome will become the prototype and its ingredients, composition and processing will be fixed and manufacturing will translate this (prototype) into a commercial production. At the end of manufacturing, the product will meet its specifications as well as taste and smell criteria.

However, unfortunately, pharmaceutical product development does not offer such taste and smell tests. In fact, in some cases, taste and smell of pharmaceuticals are intentionally masked. So, how should one develop and establish specifications for pharmaceutical products. This is where the difference is and the major problem for manufacturing and evaluation of pharmaceuticals.

Rather than a taste and smell test, the pharmaceutical industry works on the basis of the assessment of drug delivery or release from products in humans, because if the drug is delivered or released as expected then its therapeutic effects (taste and smell equivalent) will be as expected. This is the fundamental law/assumption based on which product safety, efficacy and ***quality*** of pharmaceuticals is evaluated. Therefore, the product designer (formulator) has to prepare different prototypes, just like for a candy, which are tested to establish delivery or release characteristics of the drug from the product. To evaluate these release characteristics, designer or formulator uses a test known as a drug dissolution test. Once a suitable "recipe" is developed based on a dissolution test, as a confirmatory test, the prototype is tested in humans. Such testing is known as bioavailability and/or bioequivalence testing.

At present, the major and serious problem is that the dissolution testing currently used all over the world is neither validated and/or relevant i.e. not capable of reflecting drug release characteristics of a product in humans for which it is conducted. Moreover, ***mechanical*** designs of the testers (commonly known as dissolution apparatuses) are such that these cannot provide reliable/reproducible results i.e. drug delivery/release characteristics.

This is the test on which pharmaceutical manufacturing depends for the development of prototype and assessment of product, or its ***quality***, during commercial production. Now, it should be obvious that if the test is not relevant and reliable, then how can the quality of the manufactured product be assured? It cannot!

It will be safe to say that products manufactured now-a-days are simply based on a trial and error approach. At present, manufacturing and quality assessment may be summarized as follows that "dough" is prepared, cut into millions of small pieces and compressed into tablets or filled into capsules, and then some of them are tested in humans for their drug delivery or release characteristics. If the drug delivery characteristics comes out as desired, then the specification (ingredients and their amounts or ratios) are frozen which are established and tested with chemical tests. These chemical tests establish the content and uniformity of the API only in the products. For comfort, often a ***product specific*** dissolution test is included which is usually designed and ***adjusted to show the results one desires to see***. It is important to note that it is the same dissolution test, which is very well established for not providing relevant and reliable dissolution results.

In short, it may be stated that at present one develops a product on a trial and error basis. ***The manufacturing depends on the characterization of drug release/dissolution in humans which is however, measured using a flawed test, thus one cannot monitor the quality of the product appropriately let alone to improve on it.*** People thought that it was the lack of systematic approach and/or proper controls of manufacturing which may be handled better using QbD principles or approach. However, unfortunately QbD depends on the outcome of the analytical (dissolution) test results which are obviously faulty, where QbD could not help and thus failed.

In conclusion, if quality of pharmaceutical products (tablets/capsules) is to be monitored and/or improved then one requires a new approach for drug dissolution testing which should be relevant and reliable. The irony is that developing a new or modified dissolution test may be perhaps one of the simplest things to do. There has been a suggestion in literature which may be considered (Further information on the topic may be found here). However, at present, national and international regulatory requirements/suggestions are such that manufacturers are compelled to accept to use flawed apparatuses and methods for drug dissolution testing, therefore, these requirements need to be re-evaluated.