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Can Regulatory And Pharmacopeial Compliance Practices Establish Quality?

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The stated mandate of the regulatory authorities (such as the FDA) and pharmacopeias (such as USP) is that they establish and monitor safety, efficacy, and quality of the manufactured drug products that patients need.[1, 2, 3] It is important to note that at the manufacturing stage, safety and efficacy are seldom – in fact, almost never – established and/or measured. Establishing the quality of the manufactured products acts as a surrogate for the safety and efficacy; hence, claims are always limited to the quality aspect.

Another confusion or inaccuracy that exists at present is the use of the terms drugs, medicines, and/or pharmaceuticals. In true (technical or scientific) sense, these terms in general represent pure chemical compounds in their native forms, which patients seldom buy or use. What patients buy or use in most cases are drug, medicinal, and/or pharmaceutical products (such as tablets and capsules). These products are formulated composites of a drug, medicine, or pharmaceutical (commonly referred to as an active pharmaceutical ingredient or API) and some inactive ingredients such as fillers, binders, etc. (commonly referred to as inactive excipients or simply excipients). These excipients are also, for all practical purposes, pure and well-defined chemical compounds or mixtures.

It is important to distinguish drug products from drugs when describing the quality aspect, because they require completely different sets of criteria for their quality assessments. Unfortunately, serious confusion and lack of understanding exist in this regard, including at the authorities and in the pharmacopeias. For example, for regulatory approval purposes, a generic product manufacturer has to submit an application to market the product, which in the FDA's terminology is called an Abbreviated New Drug Application or ANDA. However, such an application is not about a new drug but is rather about a new product of an old drug. Similarly, pharmacopeias (such as USP) provide reference standards for the manufacturing of quality products. However, they seldom provide reference standards for any quality products — tablets/capsules — that patients use, but instead only for pure chemical compounds. Therefore, claims made by both authorities and pharmacopeias about the quality, and its assessment, of medicines are often incorrect. Correcting this, which needs to be considered, requires the use of an objective and scientifically valid description and terminology of the entity for which quality is to be determined and established.

The above used an example of a generic product; however, it applies equally to innovators' products as well. There is no practical difference between brand product and generic product manufacturing – both follow exactly the same scientific and manufacturing principles and practices. Thus, it could be argued that generic product manufacturers, considering their experience and expertise in manufacturing a multitude of different drug products using different types of drugs, would offer better experience and expertise in product development and manufacturing than their brand-name counterparts. The innovators, or brand-name product manufacturers, work with their own developed drugs, which are limited in number, so they would have relatively limited experience and expertise in the area of drug product development and manufacturing. However, public perception is the opposite: that generic products and their manufacturing are somehow less developed and/or substandard. The reason behind this (incorrect) perception can be found in considering the drug and drug products as the same. It is generally assumed that as the innovators develop the drugs, with their safety and efficacy profiles, their products would be of better quality compared to the generics, which do not have the corresponding profiles. This is not a correct perception. Safety and efficacy profiles are developed for drugs only. Once the drug has been developed, products and their manufacturing become exactly the same for both types of manufacturers, i.e., brand name and generic.

Quality of drugs is established by their purity characteristics or profile, just like any other chemical compound. These must fall within acceptable purity levels, along with acceptable levels of impurities. From the product manufacturer's perspective, a drug is just like any other standard raw material for the manufacturing of the finished drug product. The finished product manufacturer relies on the drug manufacturer's certificate of analysis for proceeding with its use. It is just like manufacturing any other product, such as in the food area, where a bakery buys the ingredients (flour, sugar, cream, chocolate, etc.) from the open market to make products (breads, cakes, muffins, donuts, etc.). Their focus is not on the raw ingredients' manufacturing (which meet their respective specifications) but making the "products" as per customers'/consumers' requirements.

Compliance Requirements And Their Shortcomings

Regarding the quality assessment of pharmaceutical products, consumers/patients are usually unable to establish the quality of the products. For most food products, quality can be assessed by tasting and/or by the visual appearance. Drug products such as tablets/capsules are swallowed whole, without having a chance to taste or test them. Furthermore, such products are sometimes made tasteless by coatings, and they also could potentially be toxic. Therefore, different means of testing and establishing quality of the products are used and often described by the authorities and pharmacopeias.

The puzzling aspect is that the authorities do not define "quality," or its measurable parameter; however, they provide suggestions (guidances, procedures/methods, standards/specifications) for testing and establishing it as well as making claims of it. The suggestions for testing and establishing quality are commonly known as the "compliance requirements," often described as "guidances or guidelines," which the industry has to follow. It is very important to note that as the term quality is undefined, compliance requirements cannot reflect the quality of the products, but they in fact are hindering efficient assessments, along with preventing the availability of quality products to patients at affordable prices.

Two different types of testing are required: (a) in vivo (bioequivalence assessment, aka clinical assessment); and (b) in vitro testing, such as drug dissolution testing for tablet and capsule products.

In Vivo (Bioequivalence) Testing

The idea behind in vivo testing is to establish that the product releases its drug as expected in human bodies. The underlying scientific principle is that if a product releases the expected amount of drug in a desired time period, then its therapeutic effect would also be as expected. Often, such studies are conducted for generic products, where a drug release profile of a generic product (or any other test product) is compared with that of the brand product (or reference product) in humans to show their equivalence (hence the name bioequivalence). It is important to note that the test is called clinical assessment, as dosing involves human subjects; otherwise, for all practical purposes, it is a relatively simple and standard analytical chemistry test.

Briefly, this test involves giving a dose to human subjects (divided into two halves – one for the generic and the other for the brand) of the same strength product, followed by switching the dosing between the subjects (known as a crossover design) to obtain drug levels from all subjects for both products. Blood samples are withdrawn and measured to create drug-level profiles over time and compared statistically to declare products' (bio) equivalency. In technical terms, if the means of the measured parameters, mostly area under the blood drug concentration-time curve, or AUC, and the highest observed drug concentrations, i.e., Cmax, fall within 80 to 125 percent, then these products are considered bioequivalent and substitution could be allowed between the generic and brand products.[4]

As stated above, this is an analytical test with the associated statistical data analysis to determine and compare drug levels in the body. For any analytical test, the fundamental requirements are that it must be accurate and precise. However, current testing as required and conducted cannot provide an accurate and precise assessment of product characteristics because the test itself has its own high variability (because of stomach motility and liver metabolism). This physiological variability is significantly higher than the expected variability of the products and/or their manufacturing. The variability of the products would be mixed (confounded) with the physiological variability. Therefore, for all practical proposes, the variability one observes in bioequivalence assessment is that of the natural/expected human physiological differences, not that of the products tested. This means that the bioequivalence assessments as presently conducted, as well as required by the regulatory authorities, do not or cannot measure product quality as presumed or described.[5]

In Vitro (Dissolution) Testing

The second test that is required is the in vitro drug release (or drug dissolution) test, at least for tablet and capsule products. This analytical chemistry test also assesses the drug release from a product, just like a bioequivalence test, but using laboratory equipment or testers without the use of human subjects.[6] This test is based on a principle that for a drug to appear in the bloodstream, it must be absorbed from the GI (gastrointestinal) tract, where the drug should be available in solution form. There is a direct link between solution formation (i.e., dissolution) and appearance of drug in the bloodstream. The drug dissolution test measures the ability of the drug to release or dissolution in the GI tract environment — in particular, in the intestine. The comparative assessment of the drug release from the products forms the basis of bioequivalence as well, however, without the requirement of human or clinical assessment.

The test is based on sound scientific principle and is a regulatory (compliance) requirement across the world to establish and monitor quality of the products. However, unfortunately, the test as required or conducted (testers/methods) has never been validated for its use. The recommended or required testers, because of their inherent design deficiencies, cannot reflect relevant and predictable dissolution characteristics of any product.

In fact, if one is asked to determine dissolution characteristics of any (blinded) product, it is not possible to establish dissolution characteristics of product at present.[7] The regulatory recommended testers are shown to have an inherent design problem and cannot reflect dissolution characteristics of the products and their quality. For example, current testers do not provide the required and needed soft but thorough stirring and mixing environment for an appropriate interaction between product and solvent. Therefore, this result in irrelevant, unpredictable, and a highly variable outcome unrelated to the product (quality) characteristics.[8]

Conclusion

The above-described two analytical methods that assess drug release from products form the basis of product quality assessment. Therefore, drug release characteristics define quality of the product and the test becomes a quality assessment, control, and/or assurance test for such products.[9]

The bioequivalence test as explained above cannot provide quality characteristics of the products because of the physiological variability of the subjects and, hence, needs to be discontinued. Not only could the test provide a false interpretation about the quality of a product and, by extension, their safety and efficacy, it also exposes the healthy human subjects to potentially hazardous chemicals.

The in vitro drug dissolution test alone could provide the needed drug release or quality assessments of the products. This test can be unbiased, accurate, and precise and would meet the requirements of any good analytical chemistry test. However, unfortunately, the testers currently recommended by regulators have inherent design flaws that lead to high variability in dissolution testing.[10] To address this deficiency, modifications to the stirring and mixing environment within the dissolution vessels are needed to reflect an appropriate simulation of the GI tract environment. Addressing these shortcomings would result in greater simplicity of testing, improved product quality assessment, and increased efficiency of product development and manufacturing, bringing products to patients in a cost-effective manner.

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