Establishing safety, efficacy and quality of drugs and drug-products (tablet/capsule) – serious confusion!

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These terms (safety, efficacy and quality) are frequently used in literature, apparently without clear description and relevance. The lack of clarity and relevant use of the terminologies appear not only to cause confusion, but also at present seriously hinders the development and assessment of pharmaceutical products, such as tablets and capsules. It is highly unlikely that improvements in manufacturing practices of pharmaceuticals and their assessment, including associated regulatory standards and assessments, are possible without clearly explaining and objectively defining these terms. The purpose of this article is to help in explaining these terms considering the underlying scientific concepts in order to facilitate improved product development and assessment.

Perhaps, one of the main confusions in this regard is not differentiating clearly and explicitly a drug from a drug product. Often people, not only the general public but even the scientific and engineering community, seldom differentiate these two. This not only causes problems in appropriately manufacturing and assessing pharmaceutical products but also on focusing the problem and/or addressing the issues of the quality.

In this regard, it should be noted that a drug is usually a pure chemical compound. It could be as simple as an inorganic salt (such as lithium carbonate) or organic compound (acetylsalicylic acid commonly known as aspirin). It could also be a large or complex molecule such as Cyanocobalamin commonly known as vitamin B_{12}. The complexity of the molecules is usually a reflection of their chemical formulae or structures, and also often processes of obtaining these in their pure forms through synthetic or natural/biological methods. However, an important thing to note is that these are chemical compounds and often can be obtained from chemical manufactures or suppliers around the world. In addition, these chemical compounds are sold with documented chemical analysis reports from manufacturers or suppliers e.g. Sigma/Aldrich.

In certain cases, when a chemical compound is noted for its beneficial effect (i.e. efficacy) to treat some underlying abnormality or disease then it (the chemical or chemical compound) will be described as a drug or pharmaceutical and often it sales and distribution becomes controlled. Point being, that drugs or pharmaceuticals are chemical compounds and are manufactured and characterised by following all the underlying scientific principles of chemistry and related chemical sciences. Therefore, it may be more advantageous that for manufacturing purposes a drug/pharmaceutical should be considered as a "regular" chemical compound.

As noted above, beneficial effects are described as efficacious; on the other hand, any undesired effects with the use of the drug become its toxicity and generally described as a safety aspect. Therefore, as expected, a drug comes with efficacious effects along with its associated toxic effects. The efficacy and toxicity of a drug can only be established and evaluated with human studies, commonly known as clinical tests and not by chemical tests. Obviously, one would seek chemical compounds (for medical use) with high efficacious rating while low toxic rating. It is very important here to note that efficacy and safety (lack of toxicity) are related to drugs, i.e. efficacy and toxicity are a drug/pharmaceutical (chemical compound) property. As these properties are directly linked to the chemical compound, and if the compound is not-pure, or not-pure enough, then the efficacy/safety would not be as desired or expected. Therefore, the drug has to be of certain purity. This certain expected purity level becomes a quality parameter of the drug. In general terms, the purer the compound, the better the quality would be. This purity aspect, which reflects quality of the drug, is determined and established by chemical tests, and not by clinical tests.

In short, it is critical to note that usually a drug/pharmaceutical is a chemical compound and efficacy and safety are its properties, which are established and measured by clinical tests. On the other hand, quality of a drug/pharmaceutical is directly linked to the purity of the compound which is established and measured by chemical and physical tests.

The above description was regarding the drug/pharmaceutical, not about a drug product at all. Now, the question is what is a drug product and what does it do? First the question is, why one even needs a drug product when one has a drug which is efficacious, safe and of high quality as described above. The answer is that as a drug, it is usually in solid powder or liquid

form. To be useful and effective this drug has to be introduced into the human body in a correct amount and in a consistent manner. Although, a drug may be applied locally (e.g. on skin) for a local effect, in general drugs are delivered into the body. This delivery into the body means, usually into blood stream so that the drug should reach its appropriate site of action. Therefore, most often, the objective is that the drug be delivered into blood flow or stream.

The same effect can be achieved if one takes the drug powder and swallows it with or without small amount of water, or simply makes a solution of the powder in water and drinks it. Taking a drug through mouth constitutes as an oral route of administration of drug. The same drug can also be delivered into body by different routes such as intravenous, rectal, nasal, vaginal, dermal etc. Most often, the end results is the same or similar i.e. delivery of the drug into body or blood stream. The oral route for drug administration (e.g. tablets/capsules) is often the choice because of its convenience; however, products for other routes of administration follow similar principles/steps.

Although, the administration of powder with water, or in solution, is a perfectly acceptable way, to administer the drug, however, accuracy, consistency, and convenience dictates that choice of tablets and capsules is a better alternative. For example, a commonly suggested dose of a drug known as prednisone can be 1, 2 or 5 mg, which obviously would be difficult to routinely measure and administer accurately and consistently by patients, therefore, tablets of such drugs provide a convenience for patients. Thus, for all practical purposes, a tablet or capsule is a delivery form or vehicle to deliver the drug into the body.

In this respect, a product (tablets/capsules) is usually a compressed composite of a drug with some other inactive ingredients to create some bulk (fillers, binders etc.) for convenient and reproducible drug manufacturing and administration. Just like a drug, the product development/formulation and manufacturing is also usually based on commonly accepted and well established principles of chemical science. It is important to note that all the parameters of the drug i.e. efficacy, safety and quality (purity) remain exactly the same, in fact these must remain exactly the same, because it is the drug in its native form which is required to be available for its therapeutic effects. The purpose of the drug product, in this case tablets/capsules, is to deliver the expected amount of drug into the body in a consistent manner without changing the drug's inherent chemical and physical characteristics.

This leads to perhaps the most critical and important conclusion, that although quality of a drug is reflected by its purity as a chemical compound, the quality of a product, however, is reflected by its ability to deliver/release the drug (chemical compound or the active pharmaceutical ingredient or API) from the product in the human body accurately and consistently. A drug (chemical compound) manufacturer must watch for the purity of the drug, while the drug product manufacturer must watch for delivery or release characteristics of the drug from the product. A perfectly acceptable drug may result in a substandard product if the product does not provide expected accuracy and/or consistency of the drug delivery/release, which then will be problem of the product and not that of the drug.

Further, it is also important to note that most drug products manufacturing, and the associated regulatory standards and assessments, are mostly concerned about producing/manufacturing of products i.e. these should be capable of delivering/releasing an expected and consistent amount of the drug, not per se the efficacy and safety of the underlying drug. Suggesting that efficacy and safety, or lack of these, as a part of manufacturing is like suggesting that an equipment/product (e.g. spectrophotometers, computers) is of poorly manufactured, when in fact it is the packaging which was of poor quality or strength resulting in delivery of the poor quality equipment.

In short, drug product quality is defined as its ability to deliver a drug in humans accurately and consistently. Therefore, to establish or assess quality of a drug product one would require a technique or method to measure this ability of drug release or delivery. In this regard, the drug product manufacturing industry, in particular for oral products such as tablets and capsules, heavily relies on a test known as drug dissolution test. This test is based on measuring drug release from a product and its dissolution in an aqueous based solvent. The scientific rationale behind this testing is based on the principle that for a product to appear in blood it has to be absorbed from the GI tract which generally requires that the drug should be in solution form. Industry performs this test which in practice is one of the simplest analytical tests (link).

The dissolution test as currently suggested and performed is a blessing (because of its simplicity) but a big curse on the pharmaceutical industry as well. The

reason for the curse is that the test as suggested and/or performed has no relevance to evaluate drug release characteristics of the products. The recommended testers have never been qualified and/or validated for such dissolution testing purposes as well, i.e. in general these would not meet GMP requirements. It is clear that test results commonly reported in literature, using dissolution testers in particular paddle and basket apparatuses neither reflect dissolution characteristics of the products nor their quality.

It is, therefore, very clear that at present, as these products are not being evaluated for their release characteristics, it is difficult, if not impossible, to assess or establish their quality. If the quality of drug products manufactured is to be assessed and established adequately then flaws and deficiencies of the current practices of dissolution testing have to be addressed on an urgent basis.

The deficiencies of the current dissolution testers have also been extensively studied indicating that the testers do not, and cannot, provide required reproducible and homogenous stirring and mixing environment. Thus, it is not possible to appropriately evaluate dissolution characteristics of drug products using these testers. However, fortunately, the described deficiencies of dissolution testers can be addressed with relative ease by altering the stirring and mixing element/mechanism. One suggestion in this respect is the use of crescent-shape spindle set at 25 rpm. With such a modification, the dissolution testing can become relevant and scientifically valid (link).

In conclusion, the safety and efficacy are inherent properties of a drug (Active Pharmaceutical Ingredient or API) which are established using clinical tests. The quality of the drug is reflected by its purity, which is established by chemical and physical tests. On the other, quality of a drug product is reflected by its ability to deliver/release the drug from the product in an expected and consistent manner. For manufacturing purposes, this delivery/release characteristic is monitored using a drug dissolution test. As the currently suggested dissolution tests/apparatuses are not validated or qualified for the purpose, thus it is difficult, if not impossible, to establish quality of drug products in particular during manufacturing. The deficiencies of the currently suggested dissolution testing/testers should be addressed on an urgent basis.