Method validation: A complex concept

I welcome all to the current issue of Pharmaceutical Methods, and thank all our contributors.

The reader will find that many of the articles that are published in the current issue refer to method validation and in particular to the International Conference on Harmonization (ICH) guidelines as the basis for their approach. The ICH was launched in 1990, with the objective of harmonizing technical and regulatory approaches in the Pharma-Chem industry between international markets, with the ultimate objective being the protection of human health.

Every analytical chemist and process owner knows the sequence of analytical validation requirements [linearity, level of detail (LOD), level of quantification (LOQ), precision, accuracy, robustness, etc.]. The requirements are universal; a measure to assure the quality of the results. However, the ICH along with organizations like the International Organization for Standardization (ISO) and the Food and Drug Administration (FDA) view their role as progressing and evolving the concept of analytical quality assurance into a multidimensional approach. Consider for example the 'simple' concept of 'precision'. In the Pharma-Chem industry there are no simple concepts, only 'far reaching' concepts. Determining the precision of the quantitation of a particular drug component using a given method demands the evaluation of system precision, sample precision, intermediate precision, and long-term and intra-laboratory precision; refer to the onion-like diagram below.

Precision (and of course accuracy) is also linked with the determination of process capability, process stability, and process improvement measures. Along with these considerations, regulators demand extensive investigative procedures to be deployed in the case of out-of-specification results.

Additionally, the analytical chemist and process operator must of course display a high level of competence, and along with the competence comes a personal responsibility. A veritable sword of Damocles is suspended above the head of each analyst, which extends right up, along the hierarchical chain of the organization! Naturally these measures are in place for

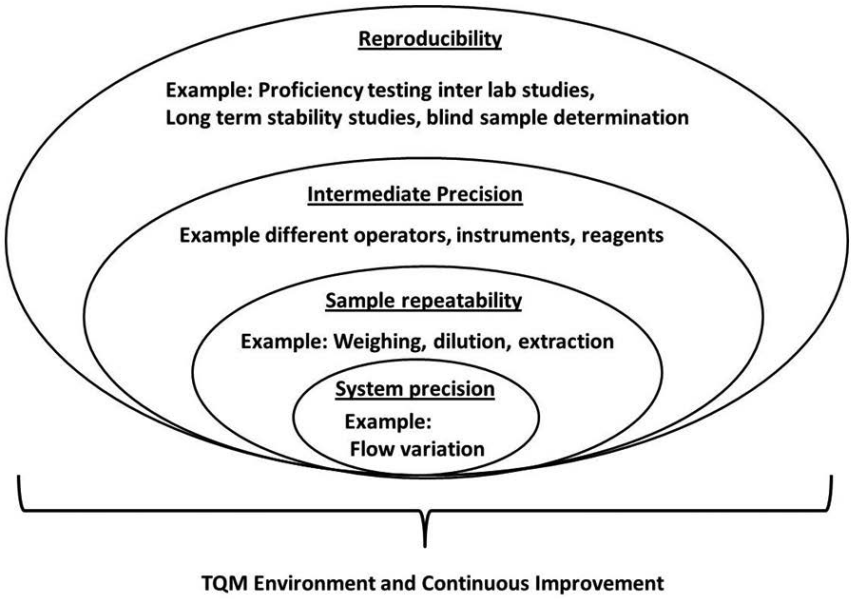

Figure 1: Multiple levels of precision

a very good reason: to prevent harm to the consumer, sometimes a very vulnerable customer.

In my opinion, one very innovative and enabling approach to the quality assurance of analytical methods is the process approach, advocated in recent years by ISO and a stalwart of process engineers. In its simple form, this involves producing a comprehensive and interlinked flow diagram of the process (the process may be a single analytical method using this definition) and sub-processes, and using this map as a basis for comprehending the process, controlling it, identifying the regions where data must be collected and analyzed, where SOPs must be written, and so on.

The other advantage of the process approach is that it facilitates a logical approach to quality risk analysis and thus management by expert teams. Quality risk management is indispensable in the analytical environment of the pharmaceutical sector. Risk management is a systematic and team-driven approach that tries to anticipate possible quality aberrations, their probability, their severity, and their consequences for the consumer.

Ultimately the point of all of this is that method validation is the tip of the iceberg when it comes to the control of quality of analytical methods in the pharmaceutical environment, where events of the past have taught us that there can be no room for complacency.

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Access this article online

Website: www.phmethods.org

DOI: 10.4103/2229-4708.81081

Quick response code