**Implementing principles of Quality by Design (QbD) in validation context**

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Analytical method performances have to be specified by the analyst trough the definition of the “Analytical Target Profile (ATP)”, as proposed by the regulatory bodies. In the specific context of the pharmaceutical industry, regulatory authorities have recently imposed the assessment and management of risk throughout the entire product lifecycle. This includes the analytical procedure and consequently its own lifecycle.

The development step of an analytical method is still largely addressed using a “Changing One Separate Factor a Time (COST)” approach (also known as the “Quality-by-Testing (QbT)” approach). This strategy can lead to a suitable method for assessing the risk of routine use, even where the experimental domain is not examined. However, in order to consider an experimental domain rather than a set of specific experimental conditions during the development phase, a multivariate approach must be considered: the “Quality-by-Design (QbD)” strategy. This strategy allows the definition of a “Design Space (DS)” by means of design of experiments (DoE). This DS, computed considering critical method parameters, allows the analyst to focus on the main objective of an analytical method: obtaining reliable results using a robust method. In the course of a specific case study, the benefits of the QbD strategy in terms of managing the qualitative part of the analytical process were highlighted.

Working in the context of analytical procedure, the validation step is a major part of the analytical method lifecycle. Indeed, the objective of analytical method validation is to demonstrate that this method is suited for quantifying the target analytes with an established and suitable level of accuracy, as defined by the “ATP”. This is sometimes called the “fit-for-future-purpose” concept. The decision regarding the validity of a method based on prediction can be achieved by using the “β-expectation tolerance interval” (accuracy profile). The capability of this approach to manage the quantitative part of the analytical procedure is nowadays largely illustrated in scientific literatures.

Considering the assessment and management of risk throughout the analytical lifecycle, a global strategy allowing the unification of the development and validation phases in a single step was considered. With this innovative approach, a strategy allowing the management of global analytical risk (i.e., for both qualitative and quantitative part of the analytical method) was proposed. Indeed, the developed strategy allows validating an entire experimental domain by means of the accuracy profile rather than a single set of specific experimental conditions. With this strategy, the DS is no longer simply the place where qualitative performances are obtained, but also the space where quantitative performances of the analytical procedure are assessed and managed.