Statistical Methods in Quality by Design Approach to Liquid Chromatography Methods Development

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Analytical quality by design (AQbD) approach is more and more advocated for the development of analytical methods. In brief, AQbD is a systematic and risk-based approach to method development and optimization that begins with predefined objectives, seeks method understanding and defines a method control strategy based on scientific knowledge and quality risk management tools. Contrary to the classical quality-by-testing (QbT) approach, which is rather unstructured and proceeds mostly by trial-and-error, AQbD approach is a structured and science-based. It enables an efficient search for optimal conditions and a deeper understanding of the underlying separation processes. As results, effective optimization of the method, robustness building and quality risks management as required by regulations may be more easily achieved. A key output of the AQbD strategy is the design space, which defines an envelope of operable region of method parameters that guarantees with a high probability acceptable method performances in routine.

Statistical methods play a prominent role in the learning process and computation of the design space in the QbD process. Therefore, any statistical method that is meant to support a liquid chromatography (LC) method development by QbD should not only be statistically correct but also QbD-compliant. To be concrete, this means the statistical method should: (1) enable a deep understanding of the LC method, that is how important method parameters and uncertainty factors combine to affect the method performances; (2) help to build robustness and provide assurance that the method is fit for use in routine.

Several statistical methods are currently used in the development method by a QbD approach, each claiming to be innovative, accurate and QbD-compliant. Unfortunately, very few of these methods are both statistically correct and QbD-compliant. A major part of them is misleading and often falls into pitfalls of poorly statistically defined robustness. These statistical methods do not truly reflect the goals of AQbD strategy and the related concepts of quality assurance, design space and robustness.

In this chapter, we present a critical review of current and emerging statistical methods supporting the development of LC methods by a QbD approach. We discuss the concept and components of a QbD approach to method development, with an emphasis on the meaning of the key concepts of robustness and analytical design space. Then, we present the current and most common statistical methods supporting QbD methods development. We distinguish between two categories of statistical methods. First, the design of experiments (DoE) and semi-empirical retention models-based methods are discussed. These methods combine in a fully automated approach, the DoE and retention models such as linear solvent strength (LSS) or the quantitative structure retention relationships (QSRR) models derived from the solvophobic theory. Second, the DoE and fully empirical (i.e. data-driven) models-based methods which are based on empirical models such as the multivariate multiple linear regression and similar techniques are presented. We argue that the empirical models-based methods are totally risk-oriented and interestingly more flexible and open to innovations. Two case studies illustrating the DoE and Bayesian method for design space — what the authors believe is the most appropriate risk-oriented empirical method — in LC methods development are presented.