near-infrared (NIR) spectroscopy sensors matched with multivariate analysis software to monitor classical blending and drying processes. The easy part of all these examples was that all of them were agitated processes where a single sensor was able to monitor representatively the whole batch. As already mentioned before, lyophilization has been a process up to now still dominated by non-PAT approaches due to the lack of available sensors.

This guidance, nevertheless, has to be understood as the trigger enabling the regulated pharmaceutical industries to embrace new technologies that can monitor the real process parameters of interest, which in turn should allow manufacturing better products, increasing their quality, maximizing the production, and reducing the rejections.

Soon after the release of the PAT guideline, the first contradictions appeared. If a process has to be flexible to adapt itself to the inherent cycle variations to produce a constant output, then it conflicts with the existing paradigm of validation. The first attempt to smooth it was with the introduction of the term design space. FDA defines design space in its Guidance for Industry Q8: Pharmaceutical Development (9), as

> The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

So, in the development of a lyophilization cycle, different sets of variables, that is, shelf temperatures and chamber pressures, could be tested to produce an acceptable product, but unfortunately any change on these variables have a direct impact on the mass flow and thus the drying speed. If there is no way to monitor the flow, the longest cycle resulting from all these combinations should be defined in the step durations. Unfortunately, this has a severe impact on productivity, just to cover the unlikely event of having a batch with deviations but still within specifications (i.e., within the design space) to be considered fully compliant.

A new concept emerged: quality by design (QbD) as the opposite of the classical approach of quality by testing (QbT). QbD consists of three key elements: the use of design space to establish elastic quality standards, the use of risk assessment to define the boundaries of those standards, and the implementation of PAT to monitor and adjust to those standards. The resulting cost controls and regulatory streamlining should significantly increase the efficiency of the industry and the oversight process.

The acceptance of a risk-based approach to regulation, emerging within the FDA since 2001, made possible the monitoring of process variables without forcing the costs and complexity of trying to measure every conceivable variable in an ever expanding potential situation. Without this acceptance, the application of statistical tools and regulatory guidelines would create a self-defeating situation jammed in expensive and unnecessary data.

It is clear that two of the three elements needed for the QbD concept can be readily available: design space definition and risk-based approach, but it is