Does the application of the principles of quality by design represent a revolution in method cycle management? A large audience of analysts from the pharmaceutical industry attended a recent symposium to consider this question. Joseph Chamberlain reports

The pharmaceutical industry has traditionally controlled analytical methods via a well defined sequence of development, validation and transfer exercises in line with agreed standards such as the quality guidelines Q2 of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Q2). But such an approach limits the scope for technological innovation or improvements in quality or efficiency of methods for established products.

In a keynote lecture, Imogen Gill, from Pfizer, described the application of principles of quality by design (QbD) in method life cycle management. It all starts, she said, with creativity — the ability to produce a new concept through the imagination. It is the process of successful implementation of ideas and inventions. Innovation is the first occurrence of an idea for a new product or process, whereas innovation is the process of successful implementation of the concept to create value.

Reasons why the industry needs to be innovative range from financial benefits to improving the quality of life for society as a whole. Developing new medicines is a long, risky and expensive business (current estimates being the investment of $0.8–1.3bn over 15 years) and the industry must take the opportunity to improve the situation by identifying winners early and carrying out some procedures in parallel. The drivers for change in developing an analytical strategy include the urgent need to reduce costs in product development and in production while limiting any increase in risk, and the opportunities presented by advances in science and technology.

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To apply the QbD approach for analytical methods the concept of an analytical target profile (ATP) has been developed. ATP is the documentation of the predefined objectives for the method. The justification of the characteristics and criteria included within it, therefore, becomes critical.

An example of an ATP would be: “This method needs to be able to measure analyte A in the presence of B, C and D over the range E to F with a precision of G and an accuracy of H.” Significantly the ATP does not describe the method, but stipulates the characteristics of the method, so that it represents a potential opportunity to facilitate innovation and reduce the burden when variation of the licence is proposed.

Adoption of QbD for analysis will result in the method performance requirements being more closely linked with process needs, concluded Ms Gill.

Industry collaboration
Phil Nethercote, from GlaxoSmithKline, talking on the current status of industry collaboration, said he had received his invitation to speak at the meeting and had signalled his acceptance while on a ski-slope in Italy. But that astonishing advance in communications technology had not been matched by progress in analytical procedures, and the reasons could be surprising.

For example, at GSK’s active pharmaceutical ingredient (API) site in Singapore it could be shown that all 19 existing high performance liquid chromatography (HPLC) assay methods could be replaced by a common technique or even a favoured chromatographic column, said Craig Donnelly, from Pfizer. Perceived speed may not be actual speed, and there could be lack of understanding of method robustness, with little opportunity for continuous improvement.

Approaches to analytical development
Historically, many different approaches would lead to a developed analytical method, but they often relied on the analyst’s favoured technique or even a favoured chromatographic column, said Craig Donnelly, from Pfizer. Perceived speed may not be actual speed, and there could be lack of understanding of method robustness, with little opportunity for continuous improvement.

Quality can be built into the analytical method by following a structured approach, defining up front the success criteria for a method, and using the correct tools. Therefore a contemporary approach must first define what the method needs to do (what is being measured, what the performance criteria are), provide a basis for potential regulatory flexibility, and allow for future innovation and continuous improvement by implementation of new technologies.

The future will see the ATP forming the basis of agreement with regulatory agencies...
Case studies in the applications of QbD principles to analytical methods

In the first of several case studies, Andy Rignall, from AstraZeneca, described the application of QbD principles to analytical methods associated with orally inhaled and nasal drug products. Defining an analytical target profile should start with the patient (product safety, efficacy, quality) and use prior knowledge, regulatory guidance and voluntary consensus standards.

A necessary understanding of what needs to be measured required identifying which product, material and component properties are critical to process or product performance. And there is a need to define the level of precision and accuracy required to demonstrate that product safety and efficacy requirements are routinely met. There must be an understanding of the operating environment for the method, throughout its life cycle.

Dr Rignall explained that applying QbD principles to analytical methods committed an organisation to incorporate the best scientific practice by linking prior knowledge of techniques and methods to an ATP, a mechanistic understanding based on chemical and physical knowledge of the factors that influence method performance, an investigation of multivariate relationships across method factors and an understanding of how variation in these method factors affects the analytical result. This knowledge provides an insight into the contribution that variability in the method makes to the overall product and process variability, ensures a more focused method control strategy and provides a thorough understanding of the impact of planned method changes, all resulting in better methods in both their operation and outcome. For the future, the ATP concept may be a means of proposing more advanced regulatory approaches to method submission and review.

In a dual presentation, Jonathan Hammond and Paul Frake, from GSK, described practical challenges in the application of a QbD approach to analytical methods for process analytical technology, defined by the FDA as a mechanism to design, analyse, and control pharmaceutical manufacturing processes through the measurement of critical process parameters which affect critical quality attributes. GSK’s four stages of the manufacturing process were described as the design intent (characteristics of the active ingredient and formulation), design selection (the ingredient and product processes to achieve the design intent), control definition (the critical quality attributes), and control verification (the performance in routine commercial manufacture).

Key considerations that ensure the analysis is integrated with the work flow were determined as identification of the target user for routine operation, establishment of the instructions to be followed, whether the transfer is of operational knowledge or technical knowledge, system support mechanisms, and ongoing updates and maintenance. The proposed approaches replacing the traditional approaches were illustrated with several detailed examples, using NIR for real-time measurement of product attributes.

and a combination of modelling, prior knowledge, robustness and ruggedness testing will lead to the definition of method operable design region, so that the method will be validated as long as it is operated within a proven acceptable range. There should be greater regulatory flexibility and opportunity for future innovation and continuous improvement, concluded Dr Donnelly.

Is ICH Q2 still appropriate?

Phil Nethercote returned to the podium to ask whether ICH Q2 was still appropriate. Many validated methods did not work in a routine QC environment, and much of the time and energy spent on analytical method transfer using a tick-box approach did little to ensure the methods worked throughout their life cycle. Methods that were robust with respect to initial chromatographic separation may not be robust with respect to the future data generated. There is confusion over terminology, including conflicting understanding of the terms “validation”, “verification”, “transfer”, “qualification”, “equivalence” and “evaluation”.

Process analytical technology (PAT) had been increasingly used with much effort to align validation of PAT methods with ICH Q2 requirements and there is often an inability to account for requirements to methods because of regulatory hurdles.

Dr Nethercote went on to describe an alternative lifecycle approach to method validation and transfer. The principles defined in ICH Q8, Q9 and Q10, and being developed to deliver more robust manufacturing processes through a QbD approach, can also be applied to deliver more robust analytical methods. Although intended only as guidance, ICH guidelines should be regarded as the basis and philosophical background to analytical validation, not as a checklist.

Validation is fundamentally about demonstrating that something does what it is supposed to do, and the object of validating an analytical method is to demonstrate that it is suitable for its intended purpose. Suitability for use is strongly connected with the requirements and design of the analytical procedure and as this varies it must be reflected in the analytical validation, which will include identification of performance parameters relevant to the given procedure and the definition of appropriate acceptance criteria.

Consequently the analyst has to identify relevant parameters that reflect the routine performance of the given method to design experiments accordingly and to define acceptance criteria for the results. Validation should be about ensuring that a method continues to perform as required throughout its routine use and should not be regarded as a singular event.

The regulator

The final paper, by Chris Watts, from the give a regulatory perspective on advances in method life cycle management, stressing three areas of importance relevant to today’s topic — the needs of the patient, the objective of the analysis and the role of innovation. Data by itself was not useful, he said, and the current production of enormous amounts of data was overwhelming unless value could be extracted from it.

The 21st century has brought some new realities. Many more treatments are available, patterns of drug use and information have greater importance, as experienced in the PAT project. Dr Watts would perhaps not agree with Ralph Waldo Emerson’s observation that a foolish consistency is the hobgoblin of little minds. When properly conducted, standards development can increase productivity and efficiency in government and industry, expand opportunities for international trade, conserve resources, improve health and safety, and protect the environment. Standards are a core part of the infrastructure that supports efficient innovation. They promote and enable the diffusion of technology in a form that is readily assimilated by firms with the complementary capabilities to take up and use the new methods. Standardisation is desirable and need not stifle innovation.

Finally, Dr Watts summed up the tenor of the meeting and the approach of researchers in the area by quoting Leonardo da Vinci: “I have been impressed with the urgency of doing. Knowing is not enough; we must apply. Being willing is not enough; we must do.”