

# What the drug industry thinks about the concept of risk management

Joseph Chamberlain reports on what industry representatives think about risk assessment in analytical applications and specific risk areas

The concept of risk management in pharmaceutical manufacturing is not new. It is the rationale underpinning most current good practice protocols. However, the disinclination to adopt risk management principles formally is now widely seen as limiting the development of a structured, cost-effective, cross-industry, scientific knowledge base. Many of the tools for risk management were developed in large engineering projects well before their application to pharmaceutical processes, said James Kraunsoe of AstraZeneca. For example, the Ishikawa fish bone analysis was introduced in the 1940s and applied to steel production processes. Fault tree analysis for visually displaying and evaluating failure paths in a system was used in 1961 in the US Air Force MinuteMan missile system, and hazard analysis and critical control point has its roots in food supply chain risk evaluation.

Risk management has been part of process development in AstraZeneca for many years but was formalised in 2001 by the introduction of the quality risk assessment concept with its central feature of a risk management framework. It was initially developed by the PAT (process analytical technology) Centre of Excellence in Sweden and is now deployed globally and applied during the development of about 40 products. Emphasis is on a structured, harmonised and documented approach, based on failure mode and effects analysis (FMEA), a risk assessment technique for systematically identifying potential failures in a system or a process.

FMEA uses a scoring system for severity (from a slight deviation to a total product recall), probability (from never to always) and

detectability (from detection before a unit operation to detection only by the customer). An important additional feature is comprehensive documentation.

Dr Kraunsoe recognised the potential pitfalls in the risk management approach. It can be subjective so that on another day or with a different group of operatives there may be a different outcome. Nevertheless, experience suggests that, with the right expertise, the absolute numbers may vary but the big picture remains the same. A proportionate view needs to be maintained of the regulatory relevance of the risks so that there is a clear understanding of the difference between what is relevant to the regulatory submission and what is only a business risk. These may be assessed together, but must be prioritised in the submission.

As defined by the International Conference on Harmonisation, risk management is a key concept that provides the foundation for science-based decisions when integrated into quality management systems and other business processes, said Thorsten Herkert, of AstraZeneca, developing the theme of risk management in a regulatory submission, including PAT.

The degree of rigour and formality of quality risk management should be commensurate with the complexity or criticality of the issue being addressed. For simple, less critical situations, an informal approach is usually sufficient; for more complex or critical situations, a more formal approach, using recognised tools to conduct and document the quality risk management, will be beneficial.

The US Food and Drug Administration PAT initiative is designed to do just that by

using an integrated systems approach to regulating pharmaceutical product quality. The approach is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality.

The systems approach is bound up with process understanding. It endeavours to identify and explain all critical sources of variability, and to verify process outputs or to predict product parameters. Based on process understanding, a quality risk analysis (QRA) can be developed to evaluate and mitigate risks in the process and of final product quality.

A QRA is performed to identify risks and to structure problems (a trouble-shooting tool). This can also be used to increase process understanding by identifying knowledge gaps regarding variations in starting materials (physical properties, which are not picked up by pharmacopoeia tests) and processing conditions.

Real time release — the ability to evaluate and ensure the acceptable quality of in-process or final product based on process analytical data — is the logical next step when PAT is rigorously applied. The risk assessment strategy becomes a core part of the dossier. Tests that are regarded as essential for good manufacturing processes become important information on product quality.

The risks need to be classified and controlled in different ways. The influence of variations should also be controlled with a risk-based concept. Good science should always be the focus and there should not be an insistence on conventional working. Industry needs ongoing debate on these points, concluded Dr Herkert.

## Analytical methodology must be fit for purpose

To understand and control manufacturing processes and products, we need to ensure that our analytical methodology is fit for purpose, said Phil Nethercote of GlaxoSmithKline. Methods need to be designed to quantify target analytes with appropriate accuracy and precision while being robust, rugged and efficient to operate. An approach for applying quality by design (QbD) principles to the design and evaluation of analytical methods has, therefore, been developed within GSK, he said. This approach is based on concepts similar to those being developed for manufacturing processes; that is, there is a clear identification of the desired method

performance requirements, risk assessment tools are used to focus on identifying quality-critical analytical parameters and statistical approaches, such as design of experiments (DOE) and measurement system analysis (MSA) are adopted to provide a thorough understanding of the impact of variability on the method performance.

The analytical methods quality by design approach represents a paradigm shift in the way methods are developed, validated, transferred and controlled. It will result in more robust methods designed with the end user in mind, a leaner science and risk-based approach to method validation and transfer, a

method change control process based on structured risk assessments and reference to existing method understanding, and significantly increased regulatory flexibility in relation to introducing method improvements. The quality by design approach is the way forward for method life cycle management, concluded Dr Nethercote.

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The meeting on the involvement of the analytical sciences in risk management was arranged by the **Joint Pharmaceutical Analysis Group** and held at Church House, London, on 11 October

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The selection of the solid form for development is a milestone in the conversion of a new chemical entity into a drug product, said Robert Docherty, of Pfizer. An understanding of the processes of crystallisation and particle characterisation of a new active pharmaceutical is crucial at the interface of drug substance manufacturing and drug product processing. The development of maraviroc, a chemokine receptor antagonist for use in HIV infection, was used as a case study to illustrate how the elements of polymorphic form, formulation composition and particle size were considered to show the importance of a fundamental understanding of the material science of a new chemical entity in the context of the new emerging quality by design regulatory environment.

Maraviroc is highly soluble across the physiologically relevant pH range, with a classification of III (high solubility/low permeability) in the biological classification system. It is chemically and physically stable with a well characterised and defined polymorph, with excellent stability with common excipi-

ents, giving rapid disintegration in its preferred excipient combination. Company knowledge has shown that a microcrystalline cellulose/dicalcium phosphate diluent combination is a robust formulation platform for a dry granulation process, a preferred process within Pfizer, which has a wealth of experience with associated unit operations and understanding of the performance of the selected excipients in this process. Dr Docherty concluded that, because particle size is a non-critical attribute of the drug substance, crystallisation parameters could also be designated as non-critical.

It is vital to understand the matrix contributions that can compromise solid dosage form performance, said Roger Hutton, of GSK, who described the value of terahertz imaging for the non-destructive testing of solid dosage forms. The terahertz spectrum lies between the microwave range and the infrared range. Pulsed imaging is used to detect differences in refractive indices and density changes in solids and hence has applications in three-dimensional analysis of tablets —

coatings, water content, mechanical properties. Thus this non-destructive technique is useful in assessing risks associated with tablet manufacture and prediction of tablet properties. For example, terahertz spectroscopy can be used to characterise enteric and cosmetic coatings and predict where failure might occur. Care, however, is needed in interpretation and results must be compared with other techniques, such as X-ray microtomography.

Generally, terahertz information is confirmed by X-ray analysis. However, on occasions there are inconsistencies between the data received from each instrument. Discrepancies may be due to cracks on the tablet being suffered in the time between the analyses, but it should also be remembered that the X-ray method allows a high spatial resolution with a low sensitivity to density changes, whereas terahertz analysis with low spatial resolution has a high sensitivity to density changes.

Data from terahertz analysis helps us understand critical parameters in risk assessment, concluded Dr Hutton.

## Continuous verification approaches are vital

Sampling is pivotal to the integrity and validity of the analytical measurement, said Dave Rudd, of GlaxoSmithKline, presenting an alternative view of process analytical technology (PAT). Unawareness of this key consideration may seriously compromise any decision-making process. Using some everyday examples, Dr Rudd demonstrated that we must learn not to make assumptions about the distribution of analytical measurements, to use a valid sample size, to appreciate the dynamic nature of the population from which our samples are taken, and to remember the population may not be homogeneous. For some, the assessment of risk is all about the balance between the investment and the return on that investment, he said. For others, it is about the probability of failure and the consequence of that failure.

Within the context of quality by design, a risk-based approach demands that emphasis is placed on those activities and aspects of product and process development that are likely to have greatest impact on final product quality — that is, the product performance as experienced by the patient. As an example, he showed how a rational scientific approach to reduction of moisture (or solvent) content to a pre-determined minimum could be applied. In such a procedure there is a need to avoid chemical degradation because this could occur if the drying process is carried out too aggressively and to avoid adverse changes to physical aspects of the particles (such as particle attrition), which could occur if the drying process is carried out for too long. It was shown that rather than measure the properties of the material during a drying stage, it was more useful (and, incidentally, cheaper and simpler) to monitor and change

the conditions for the process (air flow rate, drier temperature, duration of second phase of drying process). In effect, the focus is away from the product and towards the process.

It is vital that we develop continuous verification approaches to ensure (and to demonstrate) that the information we are obtaining, and the decisions we are making, are founded on a sound scientific basis, Dr Rudd said.

Chemometrics is the science of relating measurements made on a chemical system or process to the state of the system via application of mathematical or statistical methods. Many users of chemometrics are currently not completely satisfied with, or are even suspicious of, the state of the art, and not without reason, said Ralph Marbach, of VTT Optical Instruments Centre, Oulu, Finland, in a controversial presentation pointing out that we must ensure the asset that is chemometrics does not become a liability. The conclusions apply to all areas of spectroscopy, but near-infrared spectroscopy is in particular need of an overhaul of practices. The uncontrolled application of so-called statistical calibration methods such as principal component regression (PCR) and partial least squares regression (PLS) must stop, he said. Suppliers of commercial chemometrics software should enable the user to plot the response spectrum that is implicitly used as the signal in their calibrations, and scientific journals should no longer accept manuscripts that do not show a figure of the response spectrum used.

The mathematical definitions of sensitivity and specificity in the multivariate case were discussed. Both limits are testable from first principles — that is, from measurable pieces of spectroscopic data. Applying the limits post

factum to today's statistical calibration practice reveals why many PLS and PCR results are affected by unspecific correlations (which, unlike spurious correlations, do not disappear when applying PLS or PCR to larger and larger calibration data sets).

Current practices and standards of testing for specificity were claimed to be insufficient and misleading in the case of PLS and PCR, and need to be amended. Taking control over both is the only way to prove specificity from spectroscopic first principles and to trade off specificity and sensitivity in an effective and user-controlled way. There is an urgent need, however, for the spectrometric community to engage in discussion.

The role of chemometricians will grow in future. The focus will shift back to spectroscopy and chemistry with a new job description of "responsible application scientist" being established. With sensible application of chemometrics the best days of spectrometry are still ahead, said Dr Marbach.

The Joint Pharmaceutical Analysis Group is a focus for the presentation and discussion of matters of importance to those interested in pharmaceutical analysis. The group's sponsoring bodies are the Royal Pharmaceutical Society and the Royal Society of Chemistry. Membership of the group is open to member of either society.

Pharmacists wishing to join the group should apply in writing, giving their registration number, to the Secretariat, Joint Pharmaceutical Analysis Group, Science Division, Third Floor, Royal Pharmaceutical Society, 1 Lambeth High Street, London SE1 7JN. A programme of forthcoming scientific meetings is available from the secretariat.