

Changing regulatory requirements in ingredient manufacture and control

A recent meeting examined the manufacture and control of active pharmaceutical ingredients and included perspectives from opinion leaders in the pharmaceutical industry and regulatory agencies. **Joseph Chamberlain** reports

Changes introduced in EU member states over the past five to 10 years have had a significant impact on the regulatory requirements for the manufacture and control of active pharmaceutical substances, said Malcolm Dash, of the Medicines and Healthcare products Regulatory Agency, in a plenary lecture. Following a review of European pharmaceutical legislation in 2001 and transposition of Directive 2004/27/EC into UK law in October 2005, active pharmaceutical ingredients (APIs) must now be manufactured in accordance with the principles of good manufacturing practice (GMP). The new legislation also provides a legal basis for inspection of facilities used for the manu-

facture of active substances. The current European framework for the control of impurities evolved from the activities of the International Conference on Harmonisation (ICH). The work of ICH culminated in the current notes for guidance on control of impurities in new drug substances, the control of residual solvents, and standardisation of the requirements for validation of analytical methods. Revised guidance on requirements became effective in 2004.

Introduction of the general monograph Substances for Pharmaceutical Use (2004) and the general chapter Control of Impurities in Substances for Pharmaceutical Use (Chapter 5.10) into the European

Pharmacopoeia applies the concepts of reporting, identification and qualification thresholds to the monographs of the European Pharmacopoeia. In addition, the general chapter provides clarification on interpretation of statements relating to impurities that appear in the specific monographs.

The above concepts are brought together in the active substance specification. The specification typically includes limits for specified impurities, other detectable impurities, total impurities and residual organic solvents. Finalisation of guidance on genotoxic impurities and on limits for residues of heavy metal catalysts will extend control of impurities originating from chemical synthesis.

Metal residues: a complex issue

Bernard Leblanc, Pfizer, Amboise, France, gave an overview on the draft guideline on metal residues. From a quality and safety perspective, sponsors are obliged to show diligence in minimising human exposure to impurities in pharmaceuticals. However the designated acceptable risks posed by impurities in pharmaceuticals must be put in perspective. For example, the acceptable theoretical lifetime cancer risk for pharmaceuticals according to the Committee for Medicinal Products for Human Use (CHMP) draft guideline on genotoxic impurities is 1 in 100,000, equivalent to the risk of being struck by lightning. Based on conservative mathematical modelling, all default assumptions might overestimate cancer risks by up to a factor of 10,000.

The CHMP released the second draft notes for guidance on specification limits for residues of metal catalysts in June 2002, safe limits being set for metals based on permissible daily exposures that were defined using published data and evaluations by regulatory bodies. There are major issues with the notes for guidance according to Dr Leblanc, including the unprecedented two-step approach, defining a permitted daily exposure (PDE), as well as a factor for the fraction of PDE ascribed to pharmaceutical use, supposedly to compensate for dietary intake and other sources of exposure. The guideline should focus on drugs, he said; setting two values is an unnecessary complication.

The European Federation of Pharmaceutical Industries has proposed an approach to set limits for residual metals in pharmaceuticals, and the proposal has been discussed with CHMP experts. The intent is to provide a simple and pragmatic tool that addresses the issues and uncertainties associated with the determination of safe limits for metal residues in pharmaceuticals, with specific metals being placed into one of three classes based on safety considerations.

The issue of residues of metals in pharmaceuticals is a complex one with many unknowns, said Dr Leblanc. The challenge is to define a reasonable and pragmatic approach that is scientifically based and co-operation between industry and CHMP will allow the development of appropriate guidelines with worldwide acceptance he concluded.

Avoid genotoxic impurities

Genotoxic impurities (compounds that damage DNA) in drug products must be avoided, said David Snodin, Parexel Drug Development Consulting. Since no specific guidance on thresholds or limits is provided by the International Committee on Harmonisation, regulators and industry have attempted to meet this need. An EU proposal from the Committee for Medicinal Products for Human Use (CHMP), re-released for consultation in 2004, recommends that genotoxic impurities acting by threshold mechanisms (ie, not involving direct damage to DNA) can be regulated in a similar manner to non-genotoxic carcinogens. When insufficient information is available to establish that a threshold mechanism applies, a sequence of actions is recommended involving modification of the synthesis and the use of the TTC (threshold of toxicological concern) concept. In practice, the latter translates to a maximum intake of 1.5µg/day of genotoxic impurity over a patient's lifetime.

A proposal from an industry group under the auspices of the Pharmaceutical Research and Manufacturers of America extends the CHMP draft guidance by suggesting a three-step scheme. Alerts must be ascertained based on chemical structure. A qualification strategy is then established for each impurity based on its structural-alert classification. Acceptable impurity limits are then established based on the maximum daily intake of drug substance and the TTC concept.

This new paradigm, although feasible for drug substances in development, brings with it a range of chemical and biological uncertainties, such as those associated with prediction of likely side reactions during chemical synthesis and structure-activity relationships. Application of similar principles to existing drug substances could have profound effects on their cost and availability, and pharmacopoeias will undoubtedly struggle to keep track of the escalating number of impurity structures that will inevitably be identified. However, Dr Snodin suggested that compared with the many tens or hundreds of milligrams per day of genotoxins contributed by food, water and the environment, human intake from pharmaceuticals is minimal, and consequently the beneficial impact on patient safety of tightening genotoxic impurity limits for drug substances seems likely to be negligible.

The meeting of the **Joint Pharmaceutical Analysis Group** in association with King's College London Pharmaceutical Science Research Division took place at King's College London on 29 March

Opportunities from developing ICH guidelines

Representatives of the pharmaceutical industry described the developing International Committee on Harmonisation guidelines, specifically the new guidelines designated Q8: Pharmaceutical Development, Q9: Risk Management and Q10: Quality Systems, and their potential impact on manufacture and control of active pharmaceutical ingredients.

The high-level purpose of Q8, which mirrors the pharmaceutical development section of the Common Technical Document, is to provide harmonised guidance on the components, not the format, of that section, said John Berridge, of Pfizer UK. The desired state was the mutual goal of industry, society and the regulators, well-described by Janet Woodcock, of the US Food and Drug Administration, as "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight". Q8 was also designed to encourage quality by design, recognising that quality cannot be tested into a product. Quality has to be designed and built into it from the initial concept through to all elements of production. The Q8 philosophy is that pharmaceutical development is a learning process. Information from pharmaceutical development studies is a basis for risk management. This assessment helps define "design space" — the limits within which changes can be made without going outside broad parameters.

With an enhanced understanding we can benefit from risk-based regulatory decisions, manufacturing process improvements, within the approved design space described in the dossier and without further regulatory review, leading to a reduction of post-approval submissions. Real-time quality control will be achieved, leading to a reduction of end-product release testing.

Q8 will be implemented in May 2006 and an API development concept paper is being prepared for presentation to the steering committee. We need to unlock all the quality-by-design advantages now conferred on drug product, both environmental and financial, said Dr Berridge.

Earlier ICH guidelines used risk management principles to protect the patient by en-

sureing that the quality of the commercial product remained consistent with that of the product used in clinical trials, said Chris Beels, of GlaxoSmithKline, in his review of Q9: Risk Management. Q9 introduces no new expectations, except that regulatory reviewers and inspectors will expect to see more documented evidence of good risk management. It is critical to integrate risk management into quality management using a systematic, comprehensive and proactive approach based on scientific knowledge. Q9 gives principles and examples of tools that can be applied to manage risks to quality in both development and manufacturing.

The first step in any risk management process is to identify all the harms or hazards by asking what might go wrong. This is followed by analysis and evaluation of the risks, addressing the likelihood of occurrence and the severity of potential harm. The combination of these factors gives a measure of the overall risk, allowing risks to be ranked. A subsequent assessment of the effectiveness of existing control measures allows definition of further actions or controls to minimise the risks individually or collectively.

Risk identification, analysis and evaluation should use interdisciplinary teams familiar with all aspects of the process under examination. Key risks may be associated not just with methods and procedures, materials, facilities and equipment, but also with personnel, the environment and interfaces and handovers.

Significant risks to API manufacture are those with a high potential to affect its quality-critical attributes. Identity testing needs to take into account the potential presence of isomers and close analogues in the same supply chain. Newer drugs seem to carry significant risk of polymorphism. The need to understand the origin and fate of impurities is enhanced for drugs used at high doses and those which may contain impurities of high concern such as potential or actual genotoxins and some heavy metals and biohazards. These may require control at very low levels using highly sensitive analytical techniques. Physical properties affect the manufacture and quality of drug product,

particularly as there is an increasing focus on manipulation of particle size to facilitate drug product manufacture and to promote bioavailability. APIs are increasingly used in complex drug products, for example, controlled release oral products and fixed dose combination products, which are more sensitive to the physical properties of both the API and excipients. Thus ever greater scientific understanding is required for the manufacture of APIs with desirable crystal habit and particle size, said Dr Beels.

Q10 addresses quality systems. As Neil Wilkinson, of AstraZeneca, pointed out, the pharmaceutical industry is woefully inefficient compared with other major industries, such as food and cars. Divergent approaches to quality systems across regions result in potential delays in the implementation of innovation or improvement in pharmaceutical manufacturing. Potential complexity and delays in product launches have an impact on availability of medicines. There are inconsistent approaches to compliance inspections, and there is sub-optimal deployment of resources by both industry and regulators with the focus not always being on the science that really matters. The potential benefits of Q10 include harmonisation of the concept of quality systems for the pharmaceutical industry, realisation of the potential benefits from other ICH guidelines, and encouragement for industry to improve manufacturing processes thus reducing undesired variability and leading to a more consistent product quality, improved process robustness and more efficient processes. Additionally industry and regulatory commitment to robust quality systems and technical innovation will enhance assurance of consistent availability of medicines around the world, and innovation and improvement will continue throughout the product life cycle.

To deliver the ICH vision and modernise pharmaceutical manufacturing and associated regulatory processes, both industry and regulators need to work to change the current paradigm and mindsets. The set of guidelines Q8, Q9 and Q10 provides that opportunity. We should all strive to take it, concluded Mr Wilkinson.

Inspections by regulatory authorities show few critical deficiencies

The onus is on manufacturing authorisation holders (MAHs) to ensure starting materials are manufactured to good manufacturing practice standards, said Graeme McKilligan, of the Medicines and Healthcare products Regulatory Authority. Manufacturers of active pharmaceutical ingredients should ensure they fully comply with the EU GMP guide, part II, the standard against which any inspection will be carried out. Certification by a competent authority can no longer be used

in place of assessment by the MAH but can be used as contributing information.

GMP certification will be provided to API sites that meet the minimum GMP criteria. Action can be taken against sites failing to meet the criteria depending on the importance of the issues identified, defined as critical (leading to a significant risk of producing a product which is harmful to the patient), major (a non-critical deficiency which has produced or may produce a product which

does not comply with its regulatory filing or which indicates a major deviation from the EU GMP guide) or other (neither critical nor major but which indicates a departure from GMP).

Over the past two years the inspectorate has uncovered few critical deficiencies. The most common major deficiency was in documentation, followed by the potential for non-microbial contamination, and poor design and maintenance of premises or equipment.