The science and regulation of packaging

The current regulatory landscape for pharmaceutical packaging and the analytical strategies to assess the quality, safety and efficacy of product packaging were examined at a recent symposium. **Joseph Chamberlain** reports

The pharmaceutical industry now recognises well that the regulation of product quality must be science-based, said Jason Creasey (GlaxoSmithKline). Quality cannot be tested into a product, and risk analysis is a key element of pharmaceutical development.

Enlarging on the advice in the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines on pharmaceutical quality, Mr Creasey said that the risk-based approach is explained in documents Q8 (on product development) and Q9 (on quality risk management) of the guidance. ICH Q9 provides principles and examples of tools of quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution and the inspection and submission or review processes throughout the life cycle of drug substances and products, including the use of raw materials, solvents, excipients, packaging and labelling materials.

Extractables are defined as compounds that can be extracted from packaging when in the presence of a selected solvent or process, whereas leachables are defined as compounds that leach from packaging as a result of contact with the formulation of the drug product and thus become potentially dosed to a patient.

Application of the principles of risk analysis to extractables and leachables gives an opportunity to move from a traditional test and specification culture to a quality by design culture. The studies start with the design (including the risk assessment) and conclude with a control strategy. The most important steps are identifying potential critical quality attributes and critical process parameters. Ultimately this means regulatory approval with the right controls to produce a high quality product.

The favoured risk assessment is via a failure mode effects analysis (FMEA), which can be conducted to identify areas which are high, medium or low risk, and balancing probabilities and severity of the consequences of failure. The risk assessment is an opportunity to focus on all unit operations that may be a source of leachable exposure to patients, such as the materials of construction, the manufacturer's supply chain, the actual manufacturing of the device, the manufacture of the primary pack, and the way in which the device and primary pack interact with the environment and the patient (both in use and during storage).

During the FMEA process, mitigation activities can and should be discussed. A risk-based approach is therefore at the heart of ICH and Food and Drug Administration guidance on drug product development. ICH Q8 and Q9 guidance can be easily translated into a risk-based approach which is relevant to the study of drug product leachables. A risk-based approach allows the organisation to focus resources and time on specific areas that are scientifically most relevant to the primary objective — demonstrating patient safety, concluded Mr Creasey.

Jason Creasey: quality must be science based

Tim Lukas: importance of packaging properties

The regulatory framework for packaging

The symposium began with an overview of the regulatory requirements for pharmaceutical packaging, given by Dima Al-Hadithi (Medicines and Healthcare products Regulatory Agency), who said that all medicinal products are regulated by the applicable sector-specific legislation. The relevant directive lays down provisions governing the marketing authorisation, manufacture and distribution of medicinal products and the requirements for the container and closure system of the active substance and finished product are briefly described in the directive. Thus the legal framework is to be found in the requirements for the quality dossier.

Dr Al-Hadithi drew attention to the publications and guidelines which can be drawn upon in compiling the dossier for the packaging component of a medicinal product. These included pharmacopoeial monographs, guidelines on suitability of materials in contact with food, sampling and routine testing, stability of packaging or product, and child-resistant packaging.

To the uninitiated, packaging is no problem and can easily be dealt with at the end of initial development. Not so, said Tim Lukas (Pfizer). It is not unknown for products to fail in development because of a failure to develop an appropriate packaging.

Among packaging scientists, the wide-eyed novice may be innocent of the real requirements and importance of packaging properties and is prone to question established procedures. The battle-hardened veteran will have most of the pragmatic answers and can bring his experience to bear on novel solutions if required but has learned to treat innovation for the sake of it with caution.

Packaging has a protective function, sitting at the interface between formulation and the external environment. Although seemingly inert, packaging may have key interactions with the formulation and these interactions need to be understood. The packaging material has to provide the robustness and flexibility for handling during manufacture and in use, and must come from a secure source giving appropriate quality for the commercial life of the product.

Although packaging selection may seem to be a quick job, it uses years of product development knowledge. The success of any packaging programme can be measured retrospectively; packaging success is inversely proportional to the number of supporting stability programmes run from initial formulation design right through the commercial life of the product.

Packaging selection is most effective when there is a clear, well defined product profile. There should be clear marketing needs to justify any deviations from proven tried and tested packaging systems or combinations. In-house veterans will have an understanding of manufacturing site capabilities and pack handling experience and will identify early sourcing of the correct materials for trial evaluation.

By keeping packaging straightforward a company can can save resources and stability programmes for the challenging candidates that have complex packaging demands. It is advisable to remain circumspect until the whole product is defined, but the formulation nomination is only the beginning; there is no such thing as a package holiday, concluded Dr Lukas.

This one-day symposium, held at the Royal Pharmaceutical Society's London headquarters on 3 December, was organised by the **Joint Pharmaceutical Analysis Group** and the **Pharmaceutical Analysis Sciences Group**

Stability aspects of packaging

Roy Gray, a packaging consultant, said that packaging for pharmaceutical products had a number of roles. It should:

- Keep the product safe and in good condition, from filling and manufacture until fully dispensed
- Protect the product from the environment at least until the specified expiry date
- Protect the environment from the product (a task not necessarily complete by the expiry date)
- Provide all the necessary information for identification and safe use of contents plus safe disposal of the packaging and any unused or remaining content

Failure to deny access of moisture and air into a product may have adverse effects related to humidity and oxidative degradation of the active ingredient. So packaging requires barrier properties, meaning the ability to resist ingress by atmospheric gases, volatiles, vapours, liquids, bacteria, light (and other radiation) and insects, combined with the ability to resist egress by materials that should stay in the pack such as the product and its constituents. There may be constituents (inks, adhesives, additives, colorants, solvents, etc) of the pack that might well migrate into places where they were not wanted, said Mr Gray.

Testing for light protection is not always easy to deal with. The fact that you cannot see through a package does not necessarily mean light is not affecting its contents. A plastic opacified with a titanium dioxide pigment may allow as much as 50 per cent of incident light to pass through. The titanium dioxide scatters the light but half may be scattered into the pack. Light reflected from the contents will again be scattered back into the pack. Hence the pack looks opaque but transmits much incident light to its contents. Brown glass is a barrier to the short wavelength light likely to do most damage but is transparent at longer wavelengths.

Using chewing gum packs, Mr Gray gave a practical demonstration of the effectiveness of packaging in retaining volatile aromatics in the product until the package is opened.

Leak detection technology continues to improve, said Mr Gray. The undetectable will soon be detectable, as older analysts would recognise. The question becomes: does the leak matter and, more difficult, can you prove that? He suggested not looking for highly sensitive leak detection methods but rather selecting a practical test that is useful within the desired parameters.

Practicalities of packaging technology

Modern warehouses are no longer large draughty sheds, pointed out Tony Hatton (GSK). Regulations stipulate that pharmaceuticals must be stored in controlled conditions, and this has implications for the design and operation of warehouses.

Deviations from the claimed conditions — "excursions" in the terminology of the practitioners — must be minimised, controlled and documented. Temperature and humidity excursions are almost inevitable. Although most excursions have no significant impact, a temperature or humidity excursion requires consideration of the impact on every item in store and a warehouse may contain hundreds of different items. The impact assessment therefore has the potential to become an enormous task. Broad rationales need to be created which define and justify excursion conditions that can be considered to have no product impact. This will underpin straightforward, defined and defendable procedures for dealing with most excursions.

For temperature excursions, there is guidance that can be used as the basis of a justifiable rationale, but there is no such guidance for humidity excursions. Mr Hatton described a simple model for simulating the change in moisture content on changes in relative humidity and applied the model to various products, including gelatin capsules in blisters, and an aqueous solution in a small plastic ampoule.

Even when the calculated impact makes combined worst case assumptions, it could be concluded that relative humidity excursions in environmentally controlled facilities need to be significant and prolonged in order to have the potential for impact on products stored in the facility. Such models can be used as the basis for technical rationales to underpin actions in response to excursions dependent on the types of products stored in the facility. For most relative humidity excursions, the main issue is liable to be the implications for maintaining appropriate levels of control of a GMP (good manufacturing practice) facility rather than potential impact on products.

Sampling packaging for analysis

Jason Creasey returned to deliver a paper prepared by the indisposed Shane Smith (GSK) on the practical aspects of preparing packaging samples for analysis. Ideally, at the start of pivotal stability studies, fully validated analytical procedures should be in place, capable of detecting all extractables identified as being significant as leachables in the final formulation. What was required, he said, were robust and reproducible procedures acceptable recoveries. They must produce samples that yield accurate and valid data. Speed and simplicity are essential with minimum manual handling and the minimum involvement of solvents. Ease of automation is also a consideration.

Commonly used extraction techniques include sonication (cheap, quick, simple but not efficient or reproducible, and difficult to transfer), Soxhlet extraction (efficient, cheap, slow, large solvent volumes), accelerated solvent extraction (automated method development feasible, efficient, fast, but expensive and uses relatively large volumes), microwave extraction (easy to generate an extractables profile, reproducible, simple sample preparation, but expensive, and inflexible regarding automation). Fortunately there is a range of novel techniques for sample preparation to overcome the mentioned deficiencies, many relying on commercial cartridges for the extraction and concentration of analyte such as solid phase extraction, solid phase micro extraction using a fibre to absorb analyte, membrane assisted liquid-liquid extraction through a polymer membrane, micro extraction by packed sorbent, and an ingenious use of magnetic fleas to absorb analyte out of a solution for subsequent analysis by thermal desorption.

Roy Gray: packaging has multiple roles that must all be tested

Drug-device combination products

Giving a paper on problems and solutions relating to drug-device combination products, Róisín Wallace (Pfizer) began by noting that combination was an FDA term, not officially existing in the European lexicon, but used colloquially in reference to drug-device products when used, packaged or manufactured in a unique or specific combination. It is, nevertheless, an emerging and growing field and the line between medical device and pharmaceutical drug manufacturers is becoming blurred.

According to the FDA, a combination device is a product comprised of two or more regulated components (drug, device, biological) that are physically, chemically or otherwise combined or mixed and produced as a single entity. Typical combination products are injection systems, prefilled syringes, pen injectors, auto-injectors, dry powder inhalers, metered dose inhalers and ophthalmic delivery systems.

Ms Wallace said that the researcher should start with a stability assessment through consideration of the type of product. Depending on classification and the specific combination, stability studies may be appropriate and due to the length of time these take, must be considered early on in development. Assessment is via a simulation process in which a well designed decision tree can be extremely useful, leading to a product that is stable at the point of manufacture, stable at the point of use, and safe and effective for the patient.