Turning Point

Excipients Facing New Regulations in EU

Sharp Focus – 2010 could be a watershed year for the excipient sector in Europe as amendments to the falsified medicines directive bring excipient quality and safety considerations to the fore. As the second decade in the 21st century gets underway, it is a pivotal time for excipient suppliers and users, with greater attention being paid than ever before to the quality and safety of materials used to manufacture pharmaceuticals.

That heightened focus is a consequence of recent incidents where pharmaceutical ingredients – both active and inactive – have caused harm to patents, as well as rising concerns about the risk of counterfeit and substandard medicines infiltrating the supply chain. It also stems from a greater desire by the pharmaceutical industry and excipient manufacturers to gain greater understanding of the functionality of excipients and how they contribute to the safety and efficacy of pharmaceutical products.

The 2008 cases of adulterated heparin and contaminated glycerin finding their way into finished pharmaceutical products, as well as other scandals such as melamine contamination of food, have prompted regulators, politicians and industry to look at ways to tighten controls over the sourcing and quality of raw materials.

That effort is made all the more important by the rapid globalization of the pharmaceutical industry, with a greater emphasis on procuring raw materials from distant areas of the world and more emphasis on outsourcing of business processes, such as manufacturing and R&D, which have traditionally been carried out largely in-house by drugmakers.

These factors all contributed to the decision by the European Commission (EC) to develop a basket of various pharmaceutical regulations and guidelines, collectively known as the pharmaceutical package, in December 2008.

Falsified Medicines Directive

A key element in the package was a proposal to develop a directive on falsified medicinal products, which in the EC's first draft introduced a range of measures designed to guard against the entry of counterfeit or adulterated finished medicines and active pharmaceutical ingredients into the supply chain.

The proposal is now under consideration at the European Parliament, with the lead parliamentary committee (the Committee on Environment, Public Health and Food Safety or ENVI) having published amendments to the proposed directive on March 12.

Amongst many other things, those amendments have expanded the scope of the directive to include excipients throughout the document, proffered a definition of excipients for use in the final version of the directive, and have added provisions for the application of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) to certain excipients.

The addition of GMP is an interesting development, as last year the EC drew back from plans to develop a dedicated directive of GMP for certain higher-risk excipients after an impact assessment concluded the cost of implementing tougher controls would outweigh any public health benefits.

The initial amendments proposed by the ENVI rapporteur, MEP Marisa Matias in December 2009, indicated that "excipients shall be subject to the same conditions of good manufacturing and distribution practice" as active ingredients.

The latest round of amendments voted in by the ENVI MEPs appear to have stepped back from this stance, indicating the level of GMP applied should be proportionate for excipients and not aligned with those for APIs.

Meanwhile, another parliamentary committee tasked with responding to the EC's draft, the Committee on Industry, Research and Energy (ITRE), has added amendments asking for inspections at the premises of excipient producers, importers and distributors in case non-compliance is suspected, and says that the marketing authorization holder must ensure that excipients used in drug products are made in accordance with GMP and that the process is described in a quality system available for inspection.

The amendments now go forward for a full plenary debate in the European Parliament in the coming weeks.

GMP And GDP

At present, excipients are the only component of a pharmaceutical that do not have a set of legally-mandated GMP standards – a somewhat counterintuitive scenario given they often make up the bulk of a dosage form.

The European branch of the International Pharmaceutical Excipient Council (IPEC Europe) has long maintained that formalized GMP should be applied to excipients and developed its own guidelines for GMP (with the help of the Pharmaceutical Quality Group) as well as GDP back in 2006.

If APIs are at risk of falsification, then it follows that excipients are also at risk, but IPEC Europe believes the new directive must take into account the differences between APIs and excipients when used as starting materials. It is important that a balance is struck between the burden of implementation and the need to ensure a viable and thriving European excipient industry.

In many cases, excipients are not intended or designed specifically for such applications, being manufactured and sold outside pharma, for example in food and personal care products. Insisting on API-level GMP could well see some excipient manufacturers refuse to supply their products for pharmaceutical uses.

Certification

In the absence of a regulatory framework for GMP and GDP for excipients, IPEC Europe and its partner organizations have been working on a voluntary certification scheme that could go a long way towards improving quality and by extension patient safety.

The objective of the scheme – known as Excipact – is to develop a classification scheme for excipients according to their risk profile, as well as a set of standards for GMP and GDP that manufacturing authorization holders can use to gauge the suitability of excipient suppliers and can be used as in an independent audit.

This is a means of ensuring patient safety, improving assurance of supplier quality, while minimizing the overall supply chain costs. It also solve the problem of a supplier receiving multiple audits from users who are assessing supplier's quality management systems.

It does not envisage mandatory certification of excipients nor additional legislative or regulatory burden. However, should regulatory agencies require third party certification or a mandatory GMP for excipients, industry wants to be ready with a consistent, harmonized science- and risk-based approach.

There have been signals from both the U.S. Food and Drug Administration (FDA) and the European Commission and Parliament that third-party auditing is acceptable – in principle. The pharmaceutical package expressly indicates this approach would be acceptable for APIs, while an industry meeting with the FDA in July 2009 also indicated that they were supportive of third party auditing and could even exercise oversight on such organizations (as they do for medical devices).

Meanwhile, the latest amendments to the falsified medicines directive make provision for the use of third-party auditors to ensure that not only APIs but also excipients have been made to GMP and distributed in accordance with GDP.

IPEC Europe and sister organization IPEC Americas are developing the certification scheme along with other partners such as the European Fine Chemicals Group (EFCG), European Association of Chemical Distributors (FECC) and the PQG.

IPECs Unite

Above all, it is important that any quality system implemented for excipients is international in scope, is applicable to as many excipients as possible and makes use of existing best practices, guides and standards.

With that in mind, IPEC Europe and its affiliate organizations around the world recently set up a unified body – the IPEC Federation – to allow the excipient industry as a whole to speak with one voice and promote the best use of excipients in medicines as a means of improving patient treatment and safety.

The IPEC Federation represents the four existing regional IPECs – IPEC Americas, IPEC Europe, IPEC Japan and IPEC China – and will concentrate on the harmonization of standards, promoting supply chain security, and the further development of third-party certification, as well as providing a source of advice and expertise for other stakeholders on excipients.

See also our interview with members of the EFCG on pages 11–12.

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After years of API production being moved to Asia, Europe is becoming attractive again as a location for manufacturing. Dr. Keith Schagbauer of Frost & Sullivan examines the reasons why.

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