Pharmaceutical Excipients—The View from the EU

Phil Taylor

A changing regulatory environment is on the horizon for excipient suppliers and users.

The European Commission's decision last year to take a long, hard look at the pharmaceuticals sector in a widening European Union has left some uncertainty about how the industry will be regulated in the future. At the same time, the commission's recognition that globalization, an expanding internal EU market, and advances in science and technology are changing the pharmaceutical environment has opened up debate over regulatory issues that affect all stakeholders in the pharmaceutical business.

A seminar held by the European International Pharmaceutical Excipients Council (IPEC–Europe) at the end of January in Cannes, France, provided an opportunity to review Europe's regulatory environment for excipients and to highlight the emerging issue of counterfeiting, among other growing challenges.

Counterfeiting concerns grow

The director of the European Directorate on the Quality of Medicines (EDQM), Dr. Susanne Keitel, told the IPEC–Europe audience that the Council of Europe has made counterfeiting a priority for EDQM as counterfeits entering the supply chain have become a major public health concern. EDQM is well-placed to coordinate anticounterfeiting efforts in Europe, said Keitel, particularly through its European network of Official Medicines Control Laboratories. "EDQM could contribute to knowledge sharing on analytical methods, setting of reference standards, and the coordination of testing and inspections, for example, as well as education and training exercises," explained Keitel.

Although the image conjured up by pharmaceutical counterfeiting is of bootleg copies of finished medicines, there is increasing concern about the possibility that raw materials, including excipients, may be present in the supply chain.

Counterfeiting of excipients is certainly a concern at the US Food and Drug Administration, according to Dr. Steven Wolfgang of the agency's Center for Drug Evaluation and Research. He said that recent cases involving the substitution of melamine for protein and diethylene glycol (DEG) for glycerin in drugs suggest that "commodity ingredients—not necessarily expensive drugs—are being targeted by unscrupulous individuals out to make a quick profit."

After last year's crisis, FDA issued guidelines recommending that a specific limit test for DEG be added to glycerin identity testing. The agency also now asks that glycerin be tested every time a shipment of the ingredient changes hands.

Wolfgang confirmed that supply chain integrity continues to be a hot topic in the United States. He noted the government's Interagency Working Party on Import Safety and the November release of an action plan that calls for a risk-based approach focused on prevention. Interestingly, among the proposals covered in the action plan are a certification system for foreign producers, expanded laboratory capacity for testing, and greater use of electronic track-and-trace technologies, all of which could have a bearing on excipient producers.

The World Health Organization (WHO) is also tackling drug counterfeiting via its IMPACT (International Medical Products AntiCounterfeiting Taskforce) program, set up in late 2006. Sabine Kopp of WHO issued an invitation to IPEC–Europe and its sister organizations IPEC–Americas and the Japan Pharmaceutical Excipients Council (JPEC) to contribute to that initiative.

At the seminar, the IPEC *Good Distribution Practices Audit Guideline* document on Good Distribution Practices (GDP) was introduced, developed by IPEC–Europe's GDP committee. The document is meant to help audit companies in the excipient supply chain when used alongside the IPEC GDP Guide, published in 2006. IPEC–Europe is also working with IPEC–Americas to draw up principles for a document on excipient pedigrees as part of a broader guideline on excipient qualification.

GMP space to be watched

A new IPEC *Good Manufacturing Practice (GMP) Audit Guideline*, prepared in collaboration with IPEC–Americas and the Pharmaceutical Quality Group, was also introduced at the IPEC–Europe seminar to complement the group's 2006 GMP guide. This is particularly timely as GMP is at the top of the agenda in Europe, with industry waiting to see how the European Commission plans to implement GMP standards for excipients, after years of discussion.

The fact that GMP must be implemented for "certain" excipients according to current regulation is beyond question—it already has been voted for by

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IPEC, the International Pharmaceutical Excipients Council, is made up of three independent associations: the Americas, Japan, and Europe (www.ipec-europe.com).

One factor prevents companies from ignoring the regulation...

the European Parliament. The key questions are: What categories of excipients will be included, and what interpretation of GMP will be applied? Professor Henk de Jong, who last year acceded to the chair of the European Pharmacopoeia Commission, told the seminar audience there are four policy options on the table: legislation, adoption of guidelines, a risk-management approach, or self-regulation by industry.

"The indications are that there is little support for legislation. Based on the recommendations of the EC's Pharmaceutical Committee on Dec. 12, 2007, it seems that a risk-assessment approach is favored," he said, but stressed the matter is now in the hands of EC Industry Commissioner Günter Verheugen.

While this news is encouraging for excipient suppliers and users, De Jong cautioned that IPEC needs to keep an eye on the process and be prepared to react if events do not proceed as expected.

Master files need expansion

Another piece of legislation high on IPEC– Europe's agenda is the European Master File system, and specifically the fact that the system is limited to non-biological active pharmaceutical ingredients (APIs). This limitation serves as a disincentive to bringing novel excipients to market, and presents intellectual property issues for companies who have invested in developing them, according to Kate Denton of Novozymes Biopharma (Lund, Sweden), and who serves on IPEC–Europe's regulatory affairs committee. In contrast to the situation in the US and Japan, a novel excipient cannot be filed in Europe with the regulatory authority for reference by pharmaceutical manufacturers who want to use it. Instead, the developer has to make that proprietary information available to its customers, and must file it alongside marketing authorization applications. The nature of excipients often means that protection *via* patent is not possible.

For APIs, this route is well-established. The procedure allows generics companies to source actives for their products, referring to the master file in marketing applications. The API manufacturers' process and production approach remains confidential. This approach also prevents duplicated efforts because it avoids multiple assessments and duplication of reviews, reducing administrative workload on excipient suppliers, pharmaceutical manufacturers, and regulators.

IPEC–Europe has put forward a position to lobby the European Commission to place adding an extension to the Master File system on its agenda. There are encouraging signs that this may occur, as the EC's consultation paper on the Future of Pharmaceuticals for Human Use in Europe has flagged the need to review the Master File system.

Caution urged on REACH

REACH, the EU's landmark new legislation covering the Registration, Evaluation, Authorization, and Restriction of Chemical substances, has been a source of considerable controversy and debate over the past few years and instituted a major change in policy. In effect, the legislation puts the burden of proof on manufacturers—not authorities—to show that a substance used in a product is safe.

Although REACH covers all chemicals produced or imported in quantities greater than 1 tonne per year, medicinal products are exempt, provided they are used in accordance with EC Directive 2001/83. But one key factor in the law prevents pharmaceutical companies from choosing to ignore the new regulation. Any substance that is used in other applications as well as pharmaceuticals has to be preregistered this year, and fully registered between 2010 and 2018 depending on the tonnage produced or imported into the EU each year.

"Preregistration must be done before Dec. 1, 2008 in order allow a substance to stay on the market thereafter," Sylvie Thevenet of Dow Corning (Lyon, France) told the IPEC–Europe seminar. "Those that are not preregistered by that date will have to undergo a full registration process in December, or be withdrawn from sale."

A failure to preregister or register could affect the continuity of supply of ingredients. Companies should consider whether to preregister substances if their supplier does not intend to, make sure nonEuropean suppliers are aware of REACH, and comply when supplier asks for usage information.

Harmonization efforts in question

Janeen Skutnik of Pfizer Global Manufacturing (Belgium), chair-elect of IPEC–Americas, addressed the IPEC–Europe group as well, focusing on the slow progress with harmonization of the US, European, and Japanese pharmacopoeias. She boldly asked, "Is it time to circumvent the entire process by allowing mutual recognition of monographs between the European, US and Japanese pharmacopoeias?"

"If it could be accepted that all three have valid processes, and that monographs from any of the three could be cited and accepted without additional filings, variations or validation, this would minimise use of resources at companies and regulators, and reduce non-value-added testing," said Skutnik.

Duplicated testing because of a lack of harmonization provides no benefit to patients, wastes time and resources, and creates environmental problems: tons of solvents are dumped because duplicate and triplicate tests are required.

Acknowledging that this revolutionary approach to compendial harmonisation is a long way from reality, Skutnik noted that an evolutionary approach—such as prospective programs to develop monographs and new chapters with involvement from the three pharmacopoeias—could accelerate the process.

The seminar clearly revealed that EU regulation of pharmaceutical excipients is in a state of flux. Also present was a sense of optimism that, with collaboration between industry, regulators, and other stakeholders, improvements to the operating environment for excipient suppliers and users are possible. **PT**