Pharmaceutical Excipients: Where Now for GMP?

Phil Taylor reports on efforts to develop a consistent set of GMP standards to ensure the quality and safety of pharmaceutical excipients in Europe.

Regulating the large and fragmented group of companies that manufacture pharmaceutical excipients for the European market is a challenge, but the present lack of a legally enforced good manufacturing practice standard is arguably the most pressing regulatory issue affecting the sector.

GMP is a legal requirement for every component of a medicine, including the active pharmaceutical ingredient and packaging materials, but excipients are currently an exception to that rule. That seems counter-intuitive when one considers these ingredients are very often the largest constituent in a medicine by weight.

The main problem is that the excipient "industry" is in fact hard to define. It is made up of hundreds of companies, selling thousands of products which often have uses outside the pharmaceutical industry, such as in food or personal care products, and so adhere to different production standards. Often the supplier may not even be aware of all the intended uses for its excipient products by its customers.

Suppliers of excipients and the pharmaceutical manufacturers that use them have worked around this hole in the regulatory fabric for years, and in most cases have relied on self-regulation and internal auditing systems to ensure quality. From a regulatory viewpoint the responsibility is clearly on the marketing authorisation holder to ensure the quality of its medicines, and this extends to their constituent ingredients.

Many now believe that excipients should be brought into line with other constituents of medicinal products and be manufactured in accordance with appropriate GMP standards. Concerns about the risks of contamination with viruses or transmissible spongiform encephalopathies (TSE) through some excipient materials, or a repeat of incidents in Haiti, Panama and Bangladesh where substitution of the excipient glycerol by counterfeiters had lethal consequences, have provided a contextual driver to mandate GMP for excipients.

In the 2006 Panamanian case, for example, a Chinese factory was found to have exported diethylene glycol mislabelled as the glycerol suitable for use in medicines. The result was some 100 fatal poisonings.

Earlier occurrences make for similar grim reading. In 1990, cough syrup contaminated with solvents led to 47 reported deaths in Nigeria. Between 1986 and 1998 in India and Bangladesh, paracetamol syrup contaminated with diethylene glycol resulted in 236 reported deaths, while a similar case of diethylene glycol poisoning led to 88 reported deaths in Haiti in 1996.

Low-cost competition from emerging markets as a consequence of the globalisation of pharmaceutical trade has intensified competitive pressure in a market where margins have already been squeezed by increasing commoditisation.

One driver for the move to introduce mandatory GMP in the European Union has been the growing presence of imported excipients from countries such as China and India.

There have been fears that overly stringent GMP requirements – for example at the same level as those applied to active pharmaceutical ingredients – could levy a disproportionate cost burden for excipient manufacturers whose business is largely concerned with non-pharmaceutical applications. This has even led to suggestions that some manufacturers could exit the marketplace entirely.

Regulations in flux

In Europe, the control of excipients is achieved via the directives applying to the medicines themselves and the onus is on the drug manufacturer to demonstrate the safety and suitability of the excipient. There is no direct supervision of excipients defined in law, and regulatory authorities do not tend to inspect excipient manufacturers.

In effect, a pharmaceutical company's qualified person – the individual identified as responsible for quality in the organisation – "regulates" excipients on the basis of compliance with pharmacopoeial monographs and quality control specifications. In practice, that means expectations and implementation differ in line with company philosophies and strategies.

The most plausible scenario in which an excipient supplier might be inspected would be if the regulator considered the excipient an API. However, unlike in the US, API facility inspections are not mandatory under European law.

The regulatory environment for excipients is subject to change in Europe, however, as part of the new legislation amending the existing pharmaceutical laws that was introduced in 2005[1-3]. This

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new legislation requires API manufacture to be performed according to GMP, ie the harmonised, International Conference on Harmonization GMP standard ICH/Q7A[4]. Directive 2004/27/EC specifically mandated the implementation of GMP for "certain excipients" including:

- excipients prepared from materials derived from a TSE-relevant animal species, with the notable exception of lactose;
- excipients derived from human/animal material with potential viral contamination risk;
- excipients claimed to be sterile (or sold as sterile) and used without further sterilisation;
- excipients with the specification or claim that they are endotoxin/pyrogen controlled; or
- specific excipients, namely propylene glycol and glycerol.

The European Commission consultation process on "certain excipients" raised concerns that the implementation costs of GMP for excipients could be greater than the patient safety benefits. Industry was keen to move towards a risk-based selection for regulation, in line with the principles laid out ICH guideline Q9, on quality risk management[5].

The consultation process reached a head earlier this year, when an independent impact assessment report carried out by consultants Europe Economics on behalf of the commission recommended a "no-change policy", as it concluded that the risks to patients were low[6].

On that basis, Europe Economics said the preferred option should impose the lowest costs on excipient suppliers and users. Tighter regulation could make European excipient manufacturers less competitive and encourage manufacturers of pharmaceuticals to obtain supplies from outside the EU. While imported excipients should pass quality standards, if that is not the case it could lead to an overall reduction in average quality, says the report.

However, issue has been taken with some of the cost assumptions in the report. Among the predictions were that the cost of legal quality enforcement for certain excipients in Europe would come in at €26.5m per manufacturer, but that exceeds the average net sales of pharmaceutical excipients for European manufacturers by several-fold.

The impact assessment also predicts that the cost-impact of self-regulation would be €12m per manufacturer. However, there is already wide acceptance and implementation of voluntary quality guidelines, including those the GMP Guide for Pharmaceutical Excipients drawn up by IPEC Europe in association with the Pharmaceutical Quality Group in 2006[7].

Doing nothing is not an option

Legally, however, maintaining the status quo is not a viable option within the current regulatory framework. There is an unequivocal obligation on the commission under the amended pharmaceutical directive, Directive 2001/83/EC, to come up with new legislation for a specified list of excipients.

The Europe Economics document acknowledges that reality, noting that in order to preserve the status quo, this requirement would need to be removed through amending legislation. At present, Article 46f of Directive 2004/27/EC clearly obliges pharmaceutical companies to "use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials".

As a result the excipient sector is in something of a regulatory limbo at the moment, although there is still pressure from various quarters, including from IPEC Europe and other industry associations such as EFCG and FECC, to push through some form of excipient GMP legislation.

A certifiable standard

IPEC Europe's position is that, in the absence of a regulatory framework, it would be helpful for excipient users to have a consistent set of GMP standards that ensure the quality and safety of excipients. And while manufacturing controls are important to ensure patient safety, good distribution practices are also essential.

Much of the groundwork for an appropriate set of GMP standards has already been done with the publication of the IPEC Europe/PQG GMP guide[8]. Both organisations came up with their own set of standards in the 1990s, and joined together to update these. The 2006 joint guide provided a balance between controls that are suitable for the manufacture of excipients yet maintained the key GMP principles that ensure patient safety.

Meanwhile, IPEC Europe built on principles laid down in the World Health Organization's Good Distribution and Transport Practices Guide of 2003 and developed its own GDP guidelines, also published in 2006[9].

These guides have made it possible to match the GMP elements in excipient manufacturing operations and the GDP elements of the excipient supply chain using common standards and terminology. They are already being used by excipients users to audit suppliers with some success.

One way forward for the excipients sector would be to develop these principles into a "certifiable standard", which, for example, could define a GMP level associated with the level of risk to patients. Once agreed, this set of principles would allow excipient users to select suppliers that are in compliance

with that level of GMP and GDP, and have been accredited as such by a third-party organisation.
IPEC Europe is working with the European Fine Chemicals Group to try to bring a certification scheme for Europe forward. Work is ongoing to assemble a team of stakeholders not only from IPEC Europe and EFCG, but also from IPEC Americas, PQG and other interested parties.

To provide value and encourage adoption by stakeholders it is critical that the certification is acknowledged and endorsed by the European regulatory authorities. If regulators are confident in excipient audits by approved third parties, then it should impart some regulatory relief to users, as well as qualification relief to suppliers.

The aim is for the certification scheme to be international in scope, and it will be based on the third-party accreditation model already used in ISO 9001, the standard for quality systems maintained by the International Organization for Standardization. In this model, the most credible bodies granting certificates are themselves accredited as competent by government agencies. As a result these certificates are highly valued.

A large amount of work will need to go into defining the criteria for auditor qualification, training and competency, but organisations that issue ISO 9001 certificates and are accredited, for example by the UK Accreditation Service, which ensures that suitable auditor standards are maintained by the certification bodies. Overall, the ISO certification bodies are the only organisations with enough auditors to meet the potential demand from the excipient industry.

Given the diverse and fragmented nature of the excipient industry, a core feature of the scheme would be an excipient classification system, which would make it possible to apply ICH Q9 quality risk management tools to focus on those aspects that are critical to assuring patient safety.

Certification may not be as robust as legislation in applying appropriate GMP levels to excipients, but it does have the potential to strike a good balance between the needs of excipient users, suppliers and regulators, and be economically achievable – thereby meeting one of the key recommendations from the Europe Economics report.

While still very much in the early stages of the certification project, IPEC Europe and the EFCG intend to develop an ISO 9001:2008 certifiable annex, as well as develop training programmes for existing ISO 9001 auditors as a first stage towards developing a full sector-specific ISO standard for excipients.

There is a precedent for this, as the PQG developed a similar standard (PS 9001) for pharmaceutical packaging materials, although this took nearly ten years to complete.

Excipient master files

IPEC Europe believes the adoption of GMP is one of core elements for the effective regulation of excipients, but another element – the development of an effective master file system – is also critical.

Manufacturing according to GMP provides assurances that batch after batch of an excipient is being made to a high quality standard, but how does an excipient manufacturer show that an excipient is fit for purpose in the first instance?

As there is no positive list of excipients in Europe, manufacturers currently use the pharmacopoeias or other authoritative texts to try to demonstrate precedence of use. For example, a certificate of suitability can be submitted to the European Directorate on the Quality of Medicines to demonstrate that an excipient meets the monograph requirements laid out in the European Pharmacopoeia. However, if no such precedence can be found, use of the excipient is deemed to be "new".

In Europe there is still no simple way to demonstrate the safety and efficacy of a new excipient, other than to win approval of its use as part of a medicinal product via the usual marketing authorisation application procedure. As a consequence few new excipients are introduced in Europe, as developers tend to introduce them and try to show precedence elsewhere first.

In the US, the situation is very different. When a pharmaceutical manufacturer wants to use a novel excipient in a medicinal product, it can provide information on the excipient to the Food and Drug Administration in two ways: either the manufacturer files the supporting data as part of its new drug application; or the manufacturer can reference a drug master file which the excipient supplier has already lodged with the FDA.

The DMF system is invaluable to excipient manufacturers, and avoids potential conflicts related to the submission of intellectual property from the excipient supplier to the excipient user. In other words, a DMF can be used to keep manufacturing or formulation information – that may be sensitive from a competitive standpoint – confidential.

There are also benefits to the other stakeholders. Pharmaceutical manufacturers can simply reference the DMF and do not have to include exhaustive information on the excipient in their own marketing applications, or indeed keep it updated if changes (variations) are made to the excipient manufacturing process.

Similarly, the DMF system allows the regulator to have all the complex information on the excipient in one centralised location where it can be reviewed in conjunction with drug licence applications. That does away with the need for duplicative assessments of the same information if

the excipient is cited in more than one marketing application, reducing the administrative burden on agency staff.

Europe does have a master file system in place, but this only applies to APIs. Moreover, in October 2004 the European Medicines Agency's Committee for Medicinal Products for Human Use advised that biological active substances should be excluded on the grounds that they are not sufficiently well-defined, so the procedure is now effectively only open to chemical APIs.

The CHMP also expressed its concern that the use of master files limits the amount of information available to the marketing authorisation holder, which is not in line with the need for the licence holder to take responsibility for the finished medicinal product.

IPEC Europe has published a position paper (currently available only on the members' section of the IPEC Europe website) which maintains that Europe's current Active Substance Master File guideline – within the context of Directive 2001/83/EC – should be revised such that it applies to both biological and non-biological active substances and novel excipients and that the directive be amended accordingly.

The lack of a workable regulatory mechanism in this area creates a burden to industry and an innovation barrier in the EU compared with other regions, eg the US, Japan, Canada, New Zealand and Australia, where the authorities permit master files for a range of drug product components including biologics, excipients and even, in some cases, packaging components.

There are indications that the European Commission is open to expanding the uses of the master file system. It has already accepted that it can be applied to certain biological materials such as plasma products and vaccine antigens, although at present the information in these master files still has to be made available to marketing authorisation holders.

An opportunity to update the master file system and bring Europe into line with other countries has been provided by the establishment of the regulation on advanced therapy medicinal products (Regulation (EC) No 1394/2007). This legislation covers products based on genes (gene therapy), cells (cell therapy) and tissues (tissue engineering) and necessitates a revision to the Annex I requirements for registration for pharmaceuticals, and provides a good opportunity to update legislation on master files.

An IPEC Europe member company raised this point during the ATMP consultation period on amendments to Annex I, which ended on 10 June 2008. It remains to be seen whether this positive step forward – which would benefit a large proportion of the pharmaceutical industry by reducing the barrier to innovation in this area and bringing Europe in line with other global markets – will be included in the final version.

Conclusions

This brief overview on regulatory trends relating to excipients highlights the difficulties associated with providing an appropriate legal framework for regulating such a fragmented, poorly defined industry.

Applying regulations that exist for APIs and finished pharmaceutical preparations often do not translate well to excipients, and it is critical that the specific requirements of excipient users and suppliers are taken into account. IPEC Europe is a dedicated forum where some of these issues are being addressed, in the interest of pushing forward the quality of medicines and improving patient safety.

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