PHARMACEUTICAL EXCIPIENT REGULATIONS: HOW THE EXCIPACT CERTIFICATION SCHEME CAN REDUCE THE AUDIT BURDEN FOR BOTH SUPPLIERS AND USERS

by Tony Scott

Pharmaceutical manufacturers are legally required to assess the suitability of their excipient supplier's GMP to satisfy the outcome of the formalised risk assessment. As supplier questionnaires do not usually provide evidence of GMP compliance, physical audits are the only answer. One solution to overcome an otherwise unsustainable audit burden is the use of certification schemes. Regulators have already indicated that such approaches would be acceptable, provided the such schemes were demonstrably credible. The EXCiPACT Certification Scheme meets these requirements and provides a win-win-win solution for pharmaceutical excipient suppliers, their customers and regulators.

Tony Scott graduated in organic chemistry in 1965 and joined PPL – an ICI/Zeneca/Syngenta legacy company in R&D and serving in many of their international commercial teams before leaving in 1994 to become a Dti Export Promoter for N. America, and in 1995, an Executive Director of the UK Chemical Industries Association until 2004. He then began his own consultancy and created the European Fine Chemicals Group (EFCG) within Cefic. From 2008 he helped co-develop a pharma excipients certification scheme that became EXCiPACT asbl in 2014. Tony is presently a Senior Adviser in the EXCiPACT Operations Team.

Excipients are a diverse collection of materials sourced from many diverse origins including animals, minerals, agriculture, and synthetic chemicals. Over 1400 excipients are being used in pharmaceutical products and of these, only about 500 presently have monographs in various pharmacopoeia. They range from basic food ingredients to specialist functional chemicals such as adhesives, binders, coatings, and release modifiers.

Unlike active pharmaceutical ingredients (APIs), excipients are not usually manufactured specifically for use in medicinal products. Excipient manufacturer's standards are primarily focused on compliance with requirements for the manufacturer's intended market. This can provide many challenges in the assurance of suitability for use in pharmaceutical applications.

Historically, specification was often the only attribute considered in the assessment of suitability. ISO 9001 has been widely adopted globally by the manufacturing industry as the basis for Quality Management Systems. Additionally, the quality management systems being used by excipient manufacturers and distributors have been enhanced by other standards mainly to ensure food safety (such as HACCP, FEMA, and FSC 22000). However, none of these quality management systems was focussed on the pharmaceutical industry and recent regulations have required that excipients must be of 'suitable GMP' and from known pharmaceutical supply chains.

This requires users of excipients to be aware of the many different sources of supply and the need to adopt an adequate system for quality assessment of suppliers for their intended use. Excipient supply chains are generally very complex and can often involve repacking and recertification. The excipient supplier's position in the supply chain will pre-determine the quality of information available to their customers. This will reflect how far down the chain they are from the original manufacturer whose detailed knowledge of an excipient's properties and characteristics knowledge ought to be paramount. The following table summarises the key characteristics of different types of suppliers (*courtesy of IPEC-Americas*).

The increasing globalisation of the pharmaceutical supply chain and the instances of deaths over recent decades from sub-standard and falsified medicines ranging from children's cough medicines to heparin anticoagulant, have demonstrated the need for risk assessments and transparency of supply chain integrity.

Whilst the pharmaceutical industry is increasingly using risk management principles to improve product quality and better protect patients, regulators have called for more secure supply chains and defined quality measures for excipients. However, regulating pharmaceutical excipient quality is not easy as only a small percentage

Supplier Type	Key Characteristics
Manufacturer	'Realises' excipient (performs first of processing steps where product is designated for excipient use
Distributor	Reseller of excipient Takes possession of and title to excipient
Broker/Agent	Connects buyer and seller Takes neither possession of nor title to excipient
Trader	Connects buyer and seller Usually sells before buying Takes title to but not possession of excipient
Supplier	Supplies excipients – broadest, most general term; includes manufacturer
Reseller	Resells excipients – broadest, most unspecific term for seller who does not make excipient

of excipients are made solely for pharmaceutical use which presents its own regulatory challenges. It would be impractical to directly regulate all excipient suppliers, and may even encourage some suppliers to leave the pharmaceutical sector. There is now an emerging regulatory trend globally to improve the quality of pharmaceutical excipients that goes well beyond accepting 'pharmaceutical grade' or 'certified to pharmaceutical monograph' attributes.

While regulations regarding GMP for APIs clearly define compliance needs, the responsibility for defining necessary GMPs for excipients in a specific medicine rests with the Manufacturing Authorisation Holders (MAH). These regulations were not formalised in the EU until recently. They require pharmaceutical product manufacturers to have a risk assessment in place to determine the appropriate GMP required for every excipient they use. This focus on user risk assessment is particularly important as only they know the intended use of the excipient. Historically, supplier questionnaires potentially provided the detail necessary to meet the users' assessed requirements but these were reliant on the supplier's own answers rather than providing firm evidence of GMP compliance.

As well as the EU's regulated requirements for Excipient Risk Assessment, other countries are also developing formal requirements for excipient GMPs. The U.S. Food Drug & Cosmetics Act specifies that drugs must be manufactured, processed, packed, and held in accordance with current good manufacturing practice (cGMP), or they are deemed to be adulterated. In 2012, the FDA Safety and Innovation Act (FDASIA) Title VII became law, expanding the FDA's authority to safeguard public health by, *inter alia*, enhancing the safety of the increasingly global drug supply chains. This requires drug manufacturers to include as part of a drug listing, the name, address, and unique facility identifiers of associated excipient manufacturers.

In Brazil, GMP requirements for excipients in locally sold drug products became law in 2016. In China, there are the new 'bundling regulations', consideration of local GMP regulations and, in 2015, an upgrade to the local pharmacopoeia. Other global initiatives affecting excipient quality include ICH Q3D for elemental impurities, ICH Q1B for stability requirements, QBD requirements, a Pharmacopoeial Discussion Group (PDG) monograph on harmonisation, WHO initiatives on GMP and Good Trade and Distribution Practices.

In 2011, the EU's Falsified Medicines Directive established that the MAH must use a formalised risk assessment to determine the appropriate GMPs for ensuring excipient suitability. In 2015, the European Commission issued guidelines on the risk assessment for this purpose. In 2016, EU medicine manufacturers, and those importing them into the EU, were required to implement risk assessments for the appropriate GMP for each excipient used.

To help establish a consistent approach for the benefit of excipient suppliers and users, in 2016, IPEC Europe published a "How To" document which offers a way to apply the EU Guidelines of

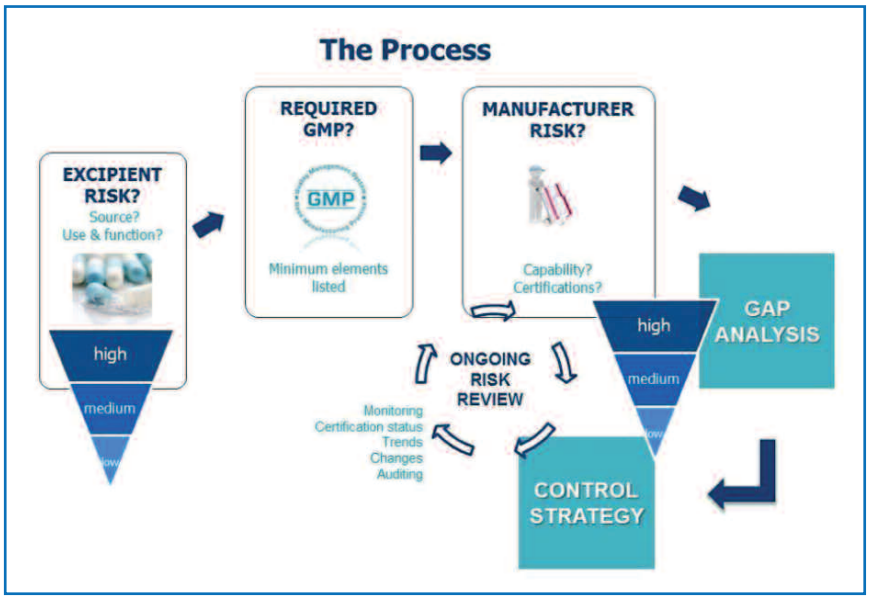

Figure 1. The Process

19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (OJ 2015/C 95/02). It represents IPEC Europe's views and interpretation only and provides detailed guidance on a standardised approach to risk assessment. **Figure 1** illustrates the process.

Once the GMP and GDP requirements have been defined for the excipient and supplier, a gap analysis has to be conducted against the GMP implemented by the supplier. This is usually based on an audit or on information received from the supplier. Pharmaceutical companies' expectation is that they should perform a physical audit at the excipient suppliers manufacturing and/or distribution site(s) to confirm that GMP/GDP is implemented. But more and more physical audits cannot be accommodated either by suppliers or users, and there is a risk that suppliers of excipients for mainly non-pharma markets may simply decide to exit the pharma market. For the pharma manufacturer, the audit burden would be too high even for large multinationals with dedicated auditors, and smaller manufacturers may be without any such resources at all. It became clear that an alternative approach was needed to provide the required regulatory assurances without generating unsustainable workloads on either the manufacturer or the users of excipients.

One solution is the use of certification schemes that are independent and credible.

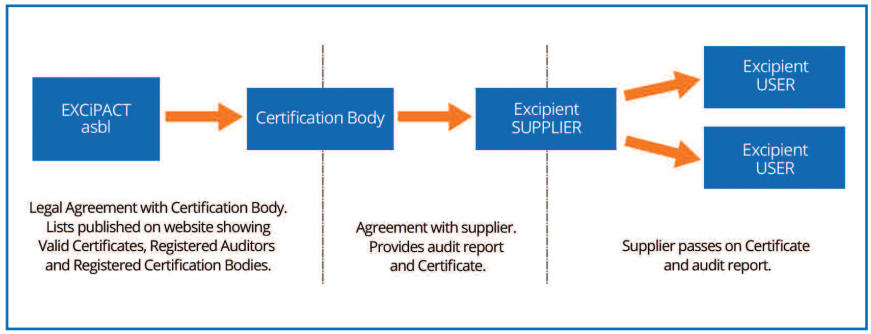

Figure 2. The Process Relationship

Regulators have indicated that third party auditing would be acceptable subject to certain conditions, viz., the use of creditable Certification Bodies who employ qualified auditors, issue certificates and audit reports, and use auditors who are demonstrably competent in these standards and the needs of the pharmaceutical industry. To manage this, an independent, high quality, third party audit and certification scheme is the solution. The EXCiPACT Certification Scheme, launched in 2013, was designed to fulfil these conditions.

EXCiPACT GMP and GDP Standards were developed from the IPEC-PQG GMP and IPEC GDP Guides and first published in 2012 based on ISO 9001:2008. A revised version was published in 2017 based on ISO 9001:2015. They were designed to be applied by manufacturers and distributors who already have ISO 9001 certification. The EXCiPACT Standards allow for objective and consistent auditing. These Standards are the key components of the EXCiPACT GMP/GDP Certification Scheme for pharmaceutical excipients provided since 2013 by independent, registered, third party certification bodies employing registered auditors and in conformance to the ISO 17021-1:2015 standard.

Figure 2 shows the independent relationship between EXCiPACT asbl, its Certification Bodies, Excipient Suppliers (who own the audit reports) and Excipient users:

EXCiPACT asbl is a non-profit organisation whose members are industry associations with members from excipient manufacturers and users. As an 'association of associations', its independence is assured. As the owner of the standards, EXCiPACT has oversight of the Certification Bodies and their auditors.

By the end of 2017, an ever-growing global list of pharmaceutical excipient suppliers have been certified for GMP and/or GDP by EXCiPACT registered Certification Bodies and published on www.excipact.org. This list is being regularly used by MAHs as a reliable source during their supplier qualification process as it offers direct access to audit reports and certificates and has taken the place of many individual audits.