



Tech Talk

Supply Chain Assurance

As the European Union tries to get a grip with counterfeit medicinal products through legislation, Pete Gough discusses the headache globalisation of pharmaceutical API manufacture is causing to the industry

The discovery of contaminated Heparin in 2008 focused global attention on the need for greater security of pharmaceutical supply chains. Preceding this there had been a worrying increase in the number of counterfeit medicinal products reaching legitimate supply chains but it was the Heparin incident that really brought the issues into sharp focus. Since 2008 various events have only confirmed that there are real risks to patients from deliberate adulteration and counterfeiting of medicines or their ingredients; e.g. melamine in milk, chromium in gelatine, plasticisers in antibiotics, fake Avastin, to name but a few. It has been estimated that globally around 10% of medicinal products are counterfeit, however, the proportions are still much lower in the developed world but can be as high as 80% in parts of the third world.

In July 2011 the EU published Directive 2011/62/EU, the Falsified Medicines Directive (FMD) and in June 2012 the US Congress passed the FDA Safety and Innovation Act (FDASIA). Both of these far reaching pieces of legislation seek to impose much stronger controls on pharmaceutical supply chains and the implications for the manufacturers of medicinal products and their suppliers are very significant.

Looking at the FMD first, many of its provisions are sensible, proportionate and should provide increased safety for patients:

- Active Pharmaceutical Ingredient (API) supply to comply with Good Distribution Practice (GDP) as well as being made to GMP
- Excipients to be made to an appropriate level of GMP determined by a formal risk assessment
- The legal obligation for the users of APIs and excipients to map and audit their supply chains for GMP and GDP compliance
- The need for “importers, manufacturers and distributors of active substances” in the EU to register with the Competent Authority of the Member State where they operate and be required to submit at least annual reports of changes to the Authority
- The addition of “Safety Features” to packs of medicinal products

Unfortunately, the FMD also contains a requirement that has the potential to seriously reduce the availability of medicinal products in Europe and to drive even more medicinal product manufacturing out of the EU/EEA. This is the poorly thought through requirement that, from 2 July 2013, APIs shall only be imported if the active substances are accompanied by a written confirmation from the Competent Authority of the exporting third country, and the plant manufacturing the exported active substance confirms that the standards of GMP and control of the plant are equivalent to those in the EU.

By early November 2012 just five countries had applied to the Commission to be added to the list of countries exempt from the need for this certification; Switzerland, Israel, Australia, Singapore and Brazil. None of these had been approved at that time. Many countries have responded negatively to the

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requirements from Europe seeking to impose this extra-territorial obligation on them. Even the EU's ICH partners, the USA and Japan, have yet to decide if they will be prepared to issue the required API certificates.

India and China are, reportedly, considering jointly referring this to the World Trade Organisation (WTO) as it constitutes a technical barrier to trade. S Eshwar Reddy, India's Deputy Drug Controller, was recently reported in the online newsletter in-Pharma Technologist.com as having stated that "If the importing country has specific GMP requirements, that is their responsibility to audit the facilities. It is the responsibility of the importing country, not the exporting country."

India is a major supplier of APIs to the EU and whilst it has indicated that it will set up an Authority to issue the required certificates it will do so on the basis of just a half-day visit to each API site, which while complying with the letter of the new requirement offers no real additional supply chain assurance.

This potentially means that after 2 July 2013 if a medicinal product manufacturer is unable to obtain the required certification for the API imported into the EU they will have to cease production of their product. This will potentially lead to the shortage of some medicines across the EU, which perversely may encourage counterfeiting to fill the gaps. It is possible that in their naivety the European Commission introduced this requirement in an attempt to drive more API manufacture within the EU. However, it is far too late for this as over the past 15 or so years much of the EU's infrastructure to manufacture APIs has closed and there is little prospect of significant re-investment in this area in the currently depressed economic climate. The more likely consequence is that companies will choose to also move their secondary manufacturing outside of the EU as the importation of fully finished medicinal products avoids the need for the certification of the API. This requirement can only do further damage to the pharmaceutical industry in Europe, which

was once such a powerhouse of the European economy, but is now shrinking rapidly under an ever increasing burden of poorly thought through legislation coming from Brussels.

Most of the provisions of the FMD are sensible precautions to protect EU citizens from counterfeit products. It is a shame that the European Commission chose to try to impose their certification scheme for APIs on the rest of the world; it would have been far better to foster co-operation with foreign governments to try to defeat this immoral trade. The current certification requirement will almost certainly be ineffective and counterproductive, antagonising and annoying the rest of the world and driving even more medicinal product manufacturing overseas while providing little or no extra supply chain assurance.

The US FDASIA appears to be a better thought through piece of legislation, although there is still a lot of detail to be clarified in new rules and guidance from FDA. For a review of the FDASIA see the 'News' section on page 8 of this issue of the Journal.

One feature of both the European FMD and the US FDASIA is the introduction of a system to verify the authenticity of a medicinal product at the point of dispensing, what the EU has called "Safety Features" and the Americans call "Track and Trace". Both regions are working on this and it would certainly be helpful to the manufacturers of finished product if the requirements were, if not identical, at least similar. The implementation costs of these systems are going to have to be largely borne by the pharmaceutical industry. The industry literally could not afford to equip its packaging facilities to accommodate totally different systems in the EU and US. There have been good links forged between the EMA and the FDA over the past 10 years or so, hopefully, they will not develop totally different systems. Most people in the EU are expecting the system for adding the serialisation number to packs to be based on a 2D bar code as the most practical and economic option.

Concerns over pharmaceutical supply chains and the implementation of the new legislation requirements are set to dominate the industry for at least the next 5 years or more. This will add to the ever increasing burden on companies' audit systems and on the Qualified Persons who certify medicinal products for release.

NOTE: This Tech Talk on Supply Chain Assurance focuses on the start of the supply chain, ie purchasing of starting materials.

Future Tech Talks will cover other aspects, eg Good Distribution Practice (GDP) and, when the Commission has decided how they will work, safety features.



NSF-DBA's four-day course on Active Pharmaceutical Ingredients will take place 17 to 20 June 2013