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The EU's Falsified Medicines Directive and APIs

Siegfried Schmitt, a principal consultant with PAREXEL, discusses how the EU's Falsified Medicines Directive will affect US API production.

Q. The European Commission (EC) has published The Falsified Medicines Directive (Directive 2011/62/EU). What elements are covered by this directive and how does it affect the pharmaceutical industry?

A. This directive covers three items, namely safety features (common logo provisions), Internet supply of medicines, and quality of imported APIs. There are differing timelines for these elements to become effective. The first one is the provision on imported APIs, which comes into effect July 1, 2013. The directive applies to any imported active ingredient.

Q. Is it sufficient to assure that the API was manufactured to GMPs (e.g., in accordance with 21 *CFR* Parts 210 and 211)?

A. Unfortunately, no. The new prerequisite is that the API must have been manufactured in accordance with GMP that is equivalent to that of the European Union. Such proof requires either a GMP certificate from an EU National Competent Authority (NCA), a "conformity of equivalence" statement from the authority of the non-EU country, or a positive assessment (white-listing) by the EC that the non-EU country's regulatory framework provides equivalent assurance of compliance.

Q. The EU already has mutual recognition agreements in place and is a member of the Pharmaceutical Inspection Co-Operation Scheme (PIC/S). Will these countries be automatically on the white list?

A. No. Non-EU countries must actively apply for an assessment by the EC before they can be added to the white list. Alternatively, these countries could issue a certificate of equivalence. The issue with such a certificate is, however, that its acceptability by the European authorities is uncertain.

The vast majority of APIs imported into the EU originate in China, India, USA, Japan, and Switzerland. So far, only Switzerland is on the white list; Japan is considering applying for white-listing; India considers issuing certificates; China's activities are as yet unclear; and the US FDA has not started considering their options.

Some companies have already taken steps to move their drug product manufacture out of Europe.

Q. Assuming FDA will not take any action, what does this mean for APIs originating in the US for import into the EU after July 1, 2013?

A. These APIs will be illegal and cannot be placed on the market. Given the extremely short timeline, this has already caused some NCAs, such as the United Kingdom's MHRA, to publicly voice concerns over drug-supply shortages as a result of this legislation. Of course, the EU agencies could go and inspect API manufacturers in non-EU countries, something that is happening already. The problem is the sheer number of these manufacturing sites and the limited resources for inspection. It simply isn't an option for most sites.

Q. Are there options for transitional solutions?

ASK THE EXPERT

A. The EC has remained adamant that the law (i.e., the directive) cannot be changed and must be enforced. Nonetheless, there are many diplomatic missions underway to assure a continued drug supply in Europe. But, some companies have already taken steps to move their drug product manufacture out of Europe.

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And do not forget that this directive affects not just the manufacturers, but all involved in the import and handling of the APIs, such as importers, wholesalers, and brokers. They must comply with good distribution practices (GDP) and may be inspected. It is not helpful that the new EU GDP guidelines are only expected for publication in early 2013. This leaves very little time for industry to become compliant.

Q. What do you think industry should do?

A. Industry associations are already working very hard and in collaboration with the EU authorities to gain as much clarity on what needs to be done and how. Engaging with industry associations or non-profit organizations such as the International Society for Pharmaceutical Engineers (ISPE) and the Parenteral Drug Association (PDA), next to carefully watching information coming from the agencies are the best sources of information. Unfortunately, there is very little that industry can do, but a lot that must be done by a number of agencies. At the moment, the verdict as to whether this directive proves to benefit the patients or brings about drug shortages is wide open. **PT**

More information on the organizations mentioned in this article can be found at their respective websites:

- ISPE—www.ispe.org
- PDA—www.pda.org
- PIC/S—www.picscheme.org