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Industry consortium aims to take the pain out of ICH Q3D compliance

By Phil Taylor, 09-Mar-2016

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With the first deadline for the ICH Q3D guideline on elemental impurities just a few weeks away, pharma companies are still facing some uncertainty about how to comply with the requirements.

After June of this year, any pharma company in ICH regions wishing to file a marketing application for a drug will have to comply with the guidance, while established products will have to be ICH Q3D-ready by December 2017.

In essence, ICH Q3D introduces a risk-based approach to the control of elemental impurities in the finished dosage form, taking into account potential sources such as the active pharma ingredient (API), excipients, manufacturing equipment, processing aids such as catalysts or water and container closure systems.

Finalised last year, the ICH Q3D guideline details new testing methods and upper limits for 24 elements - including the 'big four' (mercury, lead, cadmium and arsenic) - which need to be analysed by pharmaceutical manufacturers to create impurity profiles for their finished products.

It is well recognised that bringing all products into compliance will be a lengthy and expensive task , which is one reason why the timelines have been kept fairly long. However, it is important to note that under the guideline there is scope for the extent of quality control testing may be reduced, or even eliminated, provided there is adequate control, according to Andrew Teasdale, who chairs AstraZeneca's impurities advisory group.

Teasdale also heads the Elemental Impurities Pharma Consortium, which was formed in 2013 with the aim of building a database of elemental impurity data for excipients (and some reagents) that could help companies meet the risk-assessment requirements.

The emphasis on excipients comes because they are generally considered to be the primary concern when it comes to impurities. Some are dug out of mines, and tend to be variable in nature, while others are made using metal catalysts. Lower risk examples include those synthesised without a metal catalyst such as colloidal silicon dioxide.

"*If a good risk assessment is established, based on a good understanding of the product and processes used to make it, then potentially no extra controls or commitments to ongoing testing can be filed*," Teasdale told the IPEC Europe Excipients Forum in Nice, France, recently.

The EIPC hopes that by collating data on excipients pharma companies will be able to provide evidence for risk assessments and reduce the testing burden.

To that end, there are encouraging signs. A study carried out by the FDA on around 200 excipient samples found little evidence of substantial levels of even the 'big four' in mined excipients. Where impurities were found they tended to be at low levels, and in no case was there a suggestion that limits could be exceeded or even approach in dosage forms.

The FDA data is being incorporated into the EIPC database, which is also pooling data from 12 pharma companies based on testing of excipients used in their own organisations. By the end of the year, the intention is to have data on around 800 samples and - to date - there has been no evidence of contamination in any excipients being used.

Teasdale stresses that the intention is to compile data on excipients, not suppliers, and the identity of the manufacturer of a particular excipient will be blinded. The database will show the excipient name, the method used to test for elemental impurities and the results, with the supplier and batch information present but hidden from the user.

No 'smoking gun'

"*The aim is to see where the real risk before formulation development starts*," said Teasdale, who believes that data amassed to date suggest "*there is most likely not the 'smoking gun' that was perhaps anticipated before ICH Q3D*."

The overall risk of reaching ICH Q3D limits is low, providing GMP processes are followed and the compatibility of different materials and risk associated with each component understood.

There may however be a risk in some extreme cases, for instance if a product has an unusually high daily intake. Hypothetically, a solid oral dosage form taken at a 10g or more daily dose that includes mined excipients, or a large volume liquid product that has a low pH and is held in a metal container for a long time, might be examples.

"*The more data we can generate and share, the more this will help with a practical, rational implementation of ICH Q3D,*" he said, noting that the EIPC is open to other companies who may wish to participate in the data-sharing exercise.

It's worth noting that the data that is being collated by the EIPC and in the FDA study are invaluable, but still only represent a small sample of the range of excipients being used around the world. A lot more work on impurity levels and variability is needed to understand what can be considered 'normal' for excipients in use today.

At the moment, work is underway at the European, US and other pharmacopoeias to work out how to incorporate ICH Q3D into their respective compendia, with the aim of coming into alignment shortly after the deadline for established products at the end of 2017.