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US FDA backlog holding up revamp of inactive ingredients database

By Phil Taylor, 07-Mar-2016

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The process of sorting out problems with the US FDA's controversial Inactive Ingredients Database (IID) is shaping up to be a huge task, particularly as the agency is working through a backlog of missing updates extending back several years.

The IID is a listing of inactive ingredients found in FDA-approved drug products, and is meant to be updated in a consistent manner as new medicines and their excipients are given the go-ahead by the regulator.

However, it emerged recently that - from around 2005 - FDA resource constraints meant that the IID was not being updated at all with new excipient listings, and was left in hiatus for around a decade.

If the database is not reliable, the review times for new medicines can be extended and may lead to applications being refused, according to excipient trade body IPEC-Americas .

Once listed in the IID, an excipient is no longer considered new, and later products using it can cite the database and potentially lead to a less extensive review. Inclusion in the IID comes after a review, looking for example at whether the excipient is novel or is being delivered at a higher potency than normal or via a different route or dosage form.

The agency is now working hard to work through the backlog of applications - which amounted to around 4,000 formulations - and launched a clean-up project towards the end of 2014.

In the meantime, FDA researchers have been able to update the IID master database with all the New Drug Applications (NDAs) approved between 2008 and 2015, and all the Abbreviated New Drug Applications (ANDAs) for generic drugs approved since 2013. At the moment the agency is working through ANDAs approved between 2008 and 2012.

There are still major concerns about the quality of the data in the IID, however, according to IPEC-Americas' vice chair of scientific and regulatory affairs Dave Schoneker, who gave an update on the IID at the recent IPEC Europe Excipients Forum in Nice, France.

Over the years, the IID has become peppered with inaccurate information that has compromised its integrity, including inaccurate ingredient names and potencies and ingredients listed as a percentage with no indication of basis units.

There is also a disconnect between the structure and toxicology data for excipients - even though that data would have been submitted as part of marketing applications - which is further undermined by the lack of an effective search engine.

Last year, the FDA started work on standardising and correcting potency units, another big task that requires manual sifting through historic NDAs and ANDAs, and has been consulting both internally and externally on other changes that might improve matters.

Schoneker acknowledged that the FDA has made "*significant progress in 2015 to add missing NDA and ANDA backlog entries*".

However, there are examples where the clean-up process has resulted in worrying changes, including the removal of some excipient listings and the reduction of permissible levels for other including simethicone and magnesium stearate, amongst others.

IPEC-Americas submitted comments to the FDA on the discrepancies last summer but as of last month had not received a formal response to the concerns raised.

The database also refers to unit doses instead of maximum daily intake (MDI), which is also poorly understood. For example, it raises the potential for an FDA reviewer to ask for scientific evidence to back up the safety of an excipient whose daily exposure exceeds the unit dose level listed - and for now there is no database of MDI data available anywhere, according to Schoneker.

"*MDI is in fact the only piece of information that really matter*s" when assessing whether the amount of excipient used in a medicine is appropriate, he added.

IPEC-Americas is pushing for the database to include MDI as standard, and while the FDA is on board with that idea there is still deliberation about how this can be achieved in practice.

Overall, the FDA says it is aiming to transform the IID into a complete, fully-searchable database that will link into other databases on nomenclature, toxicology etc and accommodate electronic submissions, to eliminate data entry errors and potentially allow it to be updated in real time.