Stability Programs Need to be Re-invented

One has to sympathize with Johnson & Johnson. A volatile residue on wooden storage pallets, purportedly tribromoanisole a breakdown product of a chemical used to treat wood, was adsorbed on to Tylenol Caplets and other OTC products, leading to complaints of a moldy odor, nausea/pain and product recalls.
http://www.reuters.com/article/idUSTRE5BS2L820091229

A "one-in-a-million" occurrence that conventional stability programs would rarely, if ever detect!. J&J's announcements and recall seem to have been exemplary, in the light of the single-digit level of complaints of GI disturbance. A "when to recall" decision is notoriously difficult if the volume of complaints is around "noise level", particularly as low levels of complaints of "nausea and stomach pain" are not unusual with many products. If organizations recalled product following each such report (many of which can be outlandish) there would be few medicines left to treat patients.

The incident may raise wider issues. Pallets, like those used at the J&J facility are probably used by many other organizations to stack food, nutritional products, beverages etc. Can the same volatile residues contaminate such products? Foods contain carbohydrates and other components that are also used as excipients. These probably have the same adsorptive capability for volatiles as materials in medicinal products. Packaging may be equally permeable to vapors. Nutritionals utilise the same excipients, containers, packaging accessories as Ethical Drugs. It would be good if a collaborative program were to consider the implications for such products. J&J have probably now accumulated expertise in detecting and quantitating such contaminants, as well as acumen in associated "root cause" investigations. Co operation and sharing such expertise could be initiated and spearheaded by the organization whose mission is to improve the health of all Americans *viz* the FDA.

But that has not happened. Instead, the Agency defaults to "blame game" mode and issues the usual "warning letter".
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm197811.htm.

Investigations to establish the cause of the contamination were probably long and arduous. Scientists and other personnel must have spent many long days establishing root cause. The reward?: a warning letter !. One can be cynical and think that earlier notification by J&J would have elicited similar castigation that "root cause had not been established". Will there now be a knee-jerk "pallet stability" requirement for future filings? Don't bet against it.

What are the take-home messages?:

- Drug product stability and component interactions will never fail to surprise and require constant diligence and excellent science to predict and control.
- Mandated stability requirements, largely tabulations of data, generated over many months and years rarely if ever mitigate the risk of such surprises.

It is time to redefine what constitutes good stability assessment. Good stability studies should get to know the drug in terms of its chemical and physical propensities for degradation and interaction (particularly in the state it takes in the dosage form: not just mechanistic and kinetic evaluations in solution). Comparable knowledge of the materials with which the drug is compounded is also vital (numbers of excipients are relatively small). We also need to "know" the packaging materials (and yes, even the pallets, the volatiles that may emanate from lacquers and coatings in warehouses etc etc). For too long the focus on packaging materials has concerned capability to protect (with meaningless WVTR requirements in pharmacopoeias): too little attention is paid to capability to "contaminate" being a source of agents that can interact with components or residues in the dosage form or delivery device.

"Stability" evokes images of multiple table of "all the same data" among Regulatory Affairs professionals and of testing that most probably will produce "the same" results among laboratory scientists. In a word "boring" (and who mandates the generation of such data?). Paradoxically stability is seen as only becoming interesting when an incident mandates in-depth studies and creative chemistry.

It's time to re-assign "good science" status to stability studies so that organizations (and academic institutions) can once again study behaviors in depth and use the accumulated knowledge to creatively assign use periods, storage cautions and appropriate packaging to safeguard the quality of medicinal products.

Allocating blame post-the-event is all very well but at times we need to see the mote in our own eye. It's time to re-think approaches to stability and incorporate genuine "QbD" in our stability programs!.

Are you listening ICH?

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Jan 12th 2010