Letters to the Editor

Genotoxic Impurities in Drug Substances

Dear Editor:

I believe that the recent paper by Pierson et al. (Approaches to Assessment, Testing Decisions, and Analytical Determination of Genotoxic Impurities in Drug Substances. *Org. Process Res. Dev.* **2009**, *13*, 285−291) makes a valuable contribution to developing strategies for controlling genotoxic impurities (GTIs) in drug substances (DSs). The need for an integrated assessment based on chemical processing and toxicological considerations is paramount, but unfortunately, this principle is not explicitly endorsed in the EU guideline[1] or the draft FDA guidance.[2] Whilst agreeing with the overall philosophy outlined by Pierson et al., I believe that there are three issues worthy of further comment:

Relating the Need for Specification Limits to Point of Introduction of GTI in API Synthesis

It is agreed that carryover to the DS of a reagent introduced three to four steps from the active pharmaceutical ingredient (API) is unlikely although some genotoxic starting materials (such as hydrazine) tend to be rather persistent and difficult to remove completely. Conversely, a genotoxic intermediate or reagent introduced in the final step of the synthesis can be completely removed. For example, based on its reactivity with water and short-chain alcohols, residues of ethyl chloroformate used for N-acylation in the final stage are likely to be eliminated if aqueous workup and/or alcohol recrystallisation are employed. During ethanol crystallisation of the crude product any residues of unreacted ethyl chloroformate would be converted to traces of nongenotoxic diethyl carbonate and HCl. Similarly, no residues of an acid chloride should remain following an ester formation reaction, provided that there is a slight excess of hydroxy compound present and appropriate workup procedures (e.g. sodium carbonate solution wash of a solution of the crude ester) followed by crystallisation in ethanol or methanol. Moreover, carboxylic acid chlorides are generally Ames-negative if tested in an aqueous system (both benzoyl and acetyl chlorides being reported as Ames-negative in HSDB).[3]

Need for a Comprehensive Toxicological Risk Assessment of All GTIs

Pierson et al. use formaldehyde as an example of a GTI introduced at step two of a five-stage synthesis and demonstrate how appropriate chemical processing can virtually eliminate all residues from the API. In fact formaldehyde should not be considered as a standard GTI since, although it is genotoxic *in vitro*, it was noncarcinogenic when administered to rats by the oral route in a lifetime bioassay.[4] Numerous independent expert assessments, for example by the U.S. Environmental Protection Agency,[5] the World Health Organization,[6] the Agency for Toxic Substances and Disease Registry,[7] and the German Institute for Risk Assessment,[8] reach the unanimous conclusion that an oral Permitted Daily Exposure (PDE) of at least 10 mg/day can be determined. This is not surprising since, in the body, formaldehyde is a metabolic intermediate in the conversion of methanol[9] (derived from food and metabolic processes) to formate (both methanol and formic acid being permitted solvents[10] with PDEs of 30 and 50 mg/day, respectively). The body reserve of formaldehyde is >100 mg, and turnover is 30−60 g/day.[11] Consequently, many if not all of the precautions mentioned in the paper to reduce formaldehyde levels are most probably unnecessary. The formaldehyde example supports the case for undertaking a detailed expert toxicological assessment of **all** compounds that might be regulated as potential or actual genotoxic impurities since compound-specific toxicological data or data on close analogues may enable a risk assessment that produces a PDE much higher than the current default limit of 1.5 μg/day.

Procedures for Setting Specification Limits and Need for Routine Tests

EU guidance on specification setting is available for some types of impurities including metal catalysts and reagents[12] and residual solvents.[13] In terms of residual solvents data need to be made available on at least six pilot batches or three production batches. Routine tests are not required if a solvent is present at ≤30% or 10% of the specified limit for Class 1 and Class 2 solvents,[10] respectively. Since Class 1 solvents are associated with significant toxicity (e.g. carcinogenicity), their treatment in terms of specification requirements appears to be a clear precedent for omitting routine tests for genotoxic impurities in drug substances.

No doubt issues related to genotoxic impurities will continue to stimulate considerable debate and discussion, and it is to be hoped that risk assessments based on integrated toxicological/pharmaceutical approaches will ultimately prevail.

Yours faithfully,

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(1) Guideline on the limits of genotoxic impurities: http://www.emea.europa.eu/pdfs/human/swp/519902en.pdf.
(2) Genotoxic and carcinogenic impurities in drug substances and products: recommended approaches: http://www.fda.gov/cder/guidance/7834dft.pdf.
(3) Hazardous Substances Database (HSDB): http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
(4) Til, H. P.; Woutersen, R. A.; Feron, V. J.; Hollanders, V. H.; Falke, H. E.; Clary, J. J. Two-year drinking-water study of formaldehyde in rats. *Food Chem. Toxicol.* **1989**, *2*, 77–87.
(5) EPA Integrated Risk Information System, Formaldehyde: http://www.epa.gov/iris/subst/0419.htm.
(6) Formaldehyde. Concise International Chemical Assessment Document 40: http://www.inchem.org/documents/cicads/cicads/cicad40.htm.
(7) Toxicological profile for formaldehyde. Agency for Toxic Substances and Disease Registry: http://www.atsdr.cdc.gov/toxprofiles/tp111.pdf.
(8) Assessment of the carcinogenicity of formaldehyde. Bundesinstitut für Risikoberwertung: http://www.bfr.bund.de/cm/238/assessment_of_the_carcinogenicity_of_formaldehyde.pdf.
(9) International Programme on Chemical Safety. Environmental Health Criteria 196. Methanol: http://www.inchem.org/documents/ehc/ehc/ehc196.htm.
(10) Impurities. Residual Solvents. ICH Topic Q3C(R3): http://www.emea.europa.eu/pdfs/human/ich/028395en.pdf.
(11) Dhareshwar, S. S.; Stella, V. J. Your prodrug releases formaldehyde: should you be concerned? No. *J. Pharm. Sci.* **2008**, *10*, 4184–4193.
(12) Guideline on the specification limits for residues of metal catalysts or metal reagents: http://www.emea.europa.eu/pdfs/human/swp/444600enfin.pdf.
(13) Specifications for Class 1 and Class 2 residual solvents in active substances: http://www.emea.europa.eu/pdfs/human/qwp/045003en.pdf.

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