Organic Process Research & Development

BOOK REVIEW

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Genotoxic Impurities: Strategies for Identification and Control

Genotoxic Impurities: Strategies for Identification and Control. Edited by Andrew Teasdale . Wiley: Hoboken, NJ. 2011. $125. 444 pages. ISBN: 978-0-470-49919-1 (Hardcover).

The editor, Andrew Teasdale, is a key member of Astra Zeneca's toxicology group, chairing an internal advisory group on genotoxic impurities. He has also been extensively involved in external activities, leading two analytical groups, notably a group in the Product Quality Research Institute where a particular focus was studying the formation and control of sulfonate esters.

The book uses 24 authors plus the editor and, of those, 16 are from industry. Although there are multiple authors, the style throughout is easy to read and content readily digested, especially those chapters that resonated most closely to my own areas of work and experience (i.e., chemical process development and early-phase API development). For me, chapter 4 was rather too detailed, but that may well reflect my own interests.

I found this a very topical, relevant and interesting book to read.

The book contains 15 chapters and is arranged in four separate parts. Part one (chapters 1 and 2) discusses the development of the guidelines for genotoxic impurities and evolution of the currently applied threshold of toxicological concern: the so-called TTC approach and the now accepted staged approach wherein the allowed TTC level varies according to the duration of a human clinical trial. This was a nice introduction to the area for the non-expert and helped set the scene.

Part two (chapters 3−6) discusses the evaluation of genotoxic risk from a preclinical perspective. Chapter 3 describes test methods used. I found the section on test strategy particularly interesting as it outlined the position that a positive result in the typically applied Ames test does not in itself necessarily result in cessation of development of the drug, as further studies to understand the mechanism of action can establish that, in fact, there is a threshold below which the offending component is not genotoxic. This for instance is the case for ethyl mesylate. There are multiple repair systems in operation in mammals that means that the application of the TTC level is considered to be extremely conservative.

Chapters 4−6 discuss the in silico tools available to help identify likely components in the API, conducting compound-specific assessments such that one can justify the use of a permitted daily exposure (PDE) approach rather than the blanket TTC and the tricky issue of metabolites, which can be costly and time consuming.

Part three (chapters 7 and 8) further discusses the risks posed by genotoxic impurities. Chapter 7 uses various examples, including ethyl mesylate to explore the issue of toxicological thresholds and provides a nice overview of typical repair mechanisms for the uninitiated. Chapter 8 then presses home the point that the TTC approach is in many cases very conservative by discussing a range of endogenous chemicals, as well as others in the environment, that have known genotoxic activity, but which are tolerated without issue at levels far higher than that prescribed by the TTC approach. This is a subject area of significant current debate, and as the bank of data grows on the mechanisms of genotoxicity coupled with a knowledge of classes of compounds for which thresholds may be present, it is likely that more effective justifications for the PDE approach can be established and presented to regulatory authorities.

Part four of the book (chapters 9−15) considers assessment of genotoxic risk from a quality perspective. This section provides information about strategies used to select and develop the analytical methods relevant for the particular impurities identified in the earlier chapters about risk assessment. From a chemists' perspective, I found it very helpful to have some analytical methods outlined in the book and imagine it could provide a very good point of reference when aiming to identify a testing strategy with which to proceed. The final chapter then discusses the challenging issue of low-level degradants in the API and/or drug with some suggested strategies for their assessment and analysis, while keeping in mind the current ICH guidelines.

From a more practical point of view, the contents are well set out, and indexing appeared appropriate. Although essentially all diagrams are in black and white, they are clear, easy to follow, and located close to the relevant text. A glossary of terms may have been a useful addition. Granted, there *is* a glossary for chapter 3, but perhaps a book-wide glossary would be helpful for readers less familiar with the wide range of acronyms that occur.

Overall, a valuable addition to a pharmaceutical scientist's library. The topics covered are relevant and of interest to various 'stake-holders' in the drug development arena, including chemists, analysts, and programme managers. I can recommend it.

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