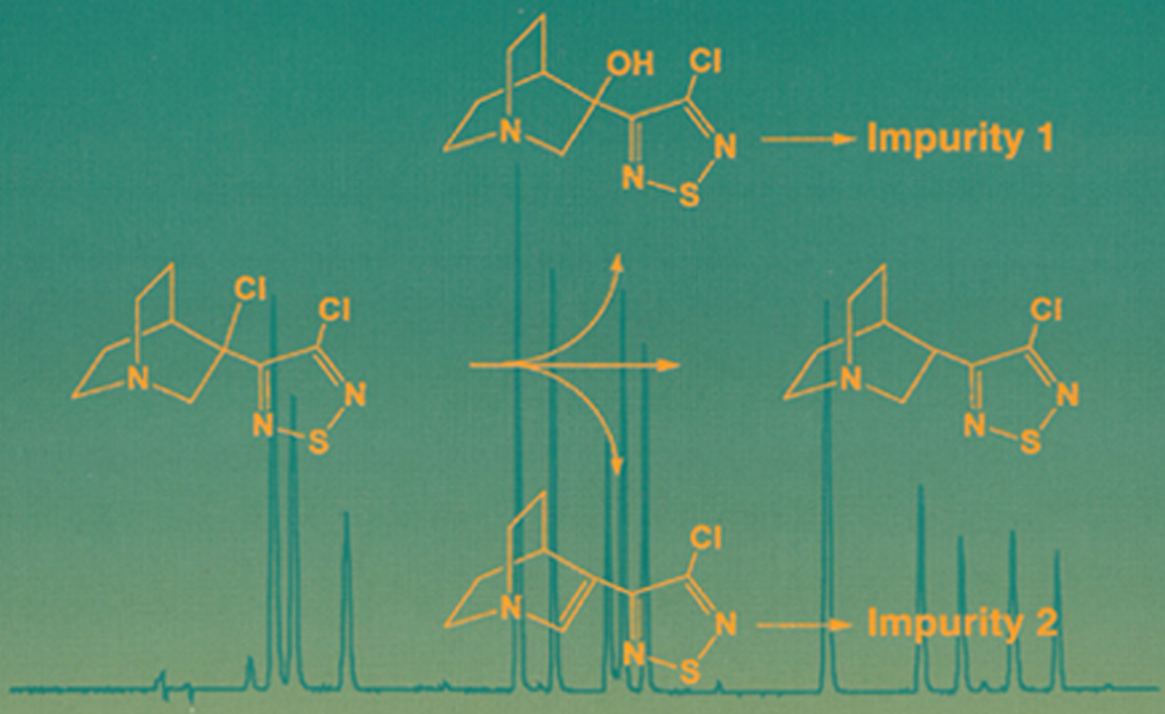
HANDBOOK OF ISOLATION AND CHARACTERIZATION OF IMPURITIES IN PHARMACEUTICALS

Edited by
Satinder Ahuja
Karen Mills Alsante



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HANDBOOK OF ISOLATION AND CHARACTERIZATION OF IMPURITIES IN PHARMACEUTICALS

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PREFACE

The pharmaceutical industry is required by the Food, Drug, and Cosmetic Act to establish the identity and purity of all marketed drug products. The United States Food and Drug Administration (FDA) and other regulatory bodies around the world require that impurities in drug substance and drug product when present at threshold levels recommended by the International Conference on Harmonisation (ICH) be isolated and characterized. This book fills the need for a text on the complex process of isolation and characterization of process-related (synthesis and formulation) impurities and degradation products to meet critical regulatory requirements. The identification of process-related impurities and degradation products can provide an understanding on production of impurities and define degradation mechanisms. When this process is performed at an early stage of drug development, there is ample time to address various aspects of drug development to prevent or control the production of impurities and degradation products well before the regulatory filing and thus assure production of a high-quality drug product.

The chapters in this book have been organized in a logical sequence to reflect the process used for the isolation and characterization of impurities. Chapter 1 points out that there are ethical, economic, and persuasive regulatory reasons to isolate and characterize impurities and degradation products. It provides an understanding of various sources of impurities and degradation products, the process and methodologies involved in separation, isolation, and characterization of impurities. Chiral impurities are also discussed from the standpoint of their origin, analytical methodology, and regulatory perspective for controlling them.

Regulatory guidance is provided in Chapter 2, which includes a significant discussion on ICH guidelines. Thresholds for identification, safely qualification, and reporting impurities have been set in these guidelines with

specific action levels reflective of the proposed daily dose of drugs under development. The rule of thumb for identifying impurities in drug substance and drug product is 0.1% (depending on the daily dose). Identification and control of toxic impurities present even well below the 0.1% level may be required.

Chapter 3 discusses polymorphic and solvatomorphic impurities. Since a major pharmaceutical manufacturing goal is to produce drug substance that is phase-pure and stable, the question of small amounts of polymorphic and solvatomorphic impurities in a bulk solid is of great importance. The drug substance should also remain phase-pure during drug product formulation and shelf life.

Chapter 4 specifically addresses impurities in drug product originating from formulation ingredients and processing that are likely to cause stability or performance issues in the drug product. The sources of the impurities as well as resulting drug stability issues are outlined in this chapter. Chapter 5 describes strategies for investigating process-related and degradation-related impurities in drug substances and drug products, with emphasis on a "chemistry-guided approach."

A critical component in the analytical quantification of impurity levels is reference standard materials. Chapter 6 provides useful information on the role of reference standards in monitoring impurities. It includes the qualification process and governance of reference standards. Chapter 7 reviews analytical method development for the quantification of impurities and degradation products present in drug substance and drug product. This process involves selecting the key impurities/degradation product sample set, screening of chromatographic conditions, and optimizing method parameters.

To assure the high quality of pharmaceutical products, it is of critical importance to carry out elucidation of structure of impurities and degradation products present in the drug substance and drug product throughout the drug development process. For low-level impurities/degradation products, this quite often involves isolation. The next three chapters detail the isolation of impurities and degradation products. Chapter 8 provides guidance on extraction and isolation techniques for successful sample preparation including specificity for the targeted material, homogeneity, and good recovery.

An excellent isolation technique is exemplified by thin-layer chromatography (TLC), discussed in Chapter 9. TLC is particularly useful when high-performance liquid chromatography (HPLC) fails to yield useful information because of retention on the head of column, early elution, or poor detection issues. It can be easily scaled up for preparative work.

The resolving power of HPLC is frequently needed for challenging isolation problems. Chapter 10 details the use of HPLC for the isolation of impurities and covers the various options that are available for stationary phases, detectors, and the preparative scaleup process.

Structure elucidation of impurities and degradation products at trace levels in complex matrices requires advanced instrumental techniques and collaborative efforts of scientists from various disciplines. Chapter 11 describes the fundamental of mass spectrometry-based techniques for ion

structure analysis, including aspects of ion formation, attributes of various mass analyzers, and scan modes used for collision-induced dissociation experiments and interpretation of mass spectra. It also discusses at some length LC-MS, the powerful combination of a versatile separation technique like HPLC with the universal detectability of MS. Chapter 12 focuses on nuclear magnetic resonance (NMR) spectroscopy, which provides key structural information and intramolecular interactions not readily available from other analytical methods. Vast improvements in NMR sensitivity limits have been made to assist with structural elucidation of impurities at low levels. Nondestructive NMR analysis allows additional characterization experiments to be performed with the same sample. Chapter 13 explains how hyphenated techniques have improved efficiency in structure elucidation of impurities and degradation products. Techniques discussed include HPLC-DAD, LC-MS, GC-MS, LC-IR, and LC-NMR.

Chapter 14 provides practical guidance with case studies on isolating and characterizing process-related impurities and degradation products for pharmaceutical drug candidates. The case studies utilize isolation or synthesis in conjunction with mass spectral and NMR characterizations. A collaborative multiple disciplinary strategy has been found to be the most efficient way to solve impurity/degradation product problems.

We sincerely believe that the detailed information provided by all authors, actively working with the pharmaceutical industry and FDA, will be of great value to various readers who are interested in the isolation and characterization of impurities and degradation products.

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