Journal of Liquid Chromatography & Related Technologies®, 30: 877–935, 2007

ISSN 1082-6076 print/1520-572X online
DOI: 10.1080/10826070701191151

Identification of Pharmaceutical Impurities

Fenghe Qiu and Daniel L. Norwood
Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, USA

Abstract: Identification of pharmaceutical impurities is a critical analytical activity in the drug development process whose goal is to fully elucidate the chemical structures of unknown pharmaceutical impurities present in either drug substances or drug products above a particular threshold. Knowledge of the chemical structure of an impurity is essential to assess its toxicological implications and to gain an understanding of its formation mechanism. Knowledge of the formation mechanism is critical for improving the synthetic chemical processes and optimizing the drug formulation to reduce or eliminate the impurity. This article reviews the current regulatory requirements for impurity identification and the chemical origins of various impurities, particularly those derived from degradation of drugs. Strategies for identification of pharmaceutical impurities are discussed followed by an overview of the critical steps and the roles of various analytical techniques, such as HPLC-DAD, LC-MS, LC-NMR, GC-MS, and NMR, in pharmaceutical impurity identification, with an emphasis on applications of mass spectrometry based hyphenated techniques. Carefully selected examples are included to demonstrate key points in impurity formation and the appropriate application of various analytical techniques.

Keywords: Pharmaceutical impurities, Hyphenated techniques, Impurity identification

INTRODUCTION

Impurity profiling and control is one of the most regulated areas in the pharmaceutical industry.[1–7] According to ICH Q3A (R) "Impurities in the New Drug Substance."[1] and ICH Q3B (R) "Impurities in the New Drug Product",[2] a drug substance impurity is "any component of the new drug substance that is not the chemical entity defined as the new drug

Address correspondence to Fenghe Qiu, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Rd., Ridgefield, CT 06877, USA. E-mail: fqiu@rdg.boehringer-ingelheim.com

substance," and a drug product impurity is "any component of the new drug product that is not the drug substance or an excipient in the drug product." In a pharmaceutical product, an impurity is first and foremost a quality issue, since it could potentially compromise the efficacy of the drug product. Secondly, impurities also cause safety concerns.[9–12] Hence, any impurity present in a drug product must be fully understood, both qualitatively (chemically) and quantitatively, and qualified, if necessary, through toxicological assessment. From a chemical perspective, pharmaceutical impurities are inevitable because no chemical reaction has 100% selectivity and no chemical compound is "rock" stable. Nonetheless, it is possible to reduce impurities via synthetic process improvement and appropriate preformulation/formulation studies. Knowing the structure of an impurity is essential for allowing assessment of its toxicological implications and for understanding its formation mechanisms, which is critical knowledge for improving the synthetic chemical process and optimizing the formulation. Impurity identification is a specialized field in the pharmaceutical industry which requires specialized analytical facilities and expertise.[13–21] The goal of this review is to provide an overview of the current regulatory requirements on impurity identification, the chemical origins of various impurities, and the strategies and roles of various analytical techniques in pharmaceutical impurity identification, with an emphasis on mass spectrometry based hyphenated techniques. The examples presented in this review are used to illustrate key points in impurity formation chemistry and applications of various analytical techniques, particularly mass spectrometry based hyphenated techniques.

REGULATORY REQUIREMENTS FOR PHARMACEUTICAL IMPURITY IDENTIFICATION

ICH guidelines[1–3] classify impurities into three categories: organic impurities, inorganic impurities, and residual solvents. These impurities can be from a variety of sources, as given in Table 1. Organic impurities are derived from drug substance synthetic processes and degradation reactions in drug substances

Table 1. Impurity classification based on ICH guidelines Q3A(R),[1] Q3B (R),[2] and Q3C[3]

Organic impurities	Starting materials
	Intermediates
	By-products
	Degradation products
	Reagents, ligands and catalysts
Inorganic impurities	Reagents, ligands and catalysts
	Heavy metals or other residual metals
	Inorganic salts
Residual solvents	Inorganic or organic liquids

Table 2. ICH reporting, identification and qualification threshold for organic impurities in drug substance[1]

Maximum daily dose[a]	Reporting threshold	Identification threshold	Qualification threshold
≤2 g/day	0.05%	0.1% or 1.0 mg TDI[b], which ever is lower	0.15% or 1.0 mg TDI, which ever is lower
>2 g/day	0.03%	0.05%	0.05%

[a]The amount of drug substance administered per day.
[b]TDI: Total daily intake of the impurity.

and drug products. Synthetic process related impurities can be derived from starting materials, intermediates, reagents, ligands, and catalysts used in the chemical synthesis, as well as by-products from the side-reactions of the chemical synthesis. Degradation products are derived from the chemical degradation of drug substances and drug products under storage or stress conditions.

Control of the organic impurities in new drug substances is based on the Maximum Daily Dose and total daily intake (TDI) of the impurities. Table 2 provides the ICH threshold for control of the organic impurities in new drug substances.[1] Depending on whether the Maximum Daily Dose higher or lower than 2 g, organic impurities in a new drug substance at (or greater than) 0.05% or 0.1% require identification. Note that these thresholds do not apply to toxic impurities.[7,22,23] According to EMEA CHMP recommendations,[7] genotoxic impurities should be controlled based on compound-specific risk assessment. For an unstudied impurity (such risk assessment data do not exist), a threshold of toxicology concern (TTC) of 1.5 μg/day can be applied, with exceptions for aflatoxin-like, N-nitroso- and azoxy-compounds, which should be assessed based on compound-specific toxicity data.

Control of organic impurities in new drug products are outlined in Table 3 and Table 4.[2] Note that these thresholds are not the same as those for impurities in new drug substances given in Table 2. Based on the Maximum Daily Dose, the identification thresholds for organic impurities in new drug products are divided into 4 groups to give more consideration to low dose drug products. For most new drug products, the Maximum Daily Dose is between 10 mg–2 g/day, therefore, any impurities at 0.2% or greater would have to be identified.

Table 3. Reporting thresholds for impurities in new drug product[2]

Maximum daily dose	Reporting threshold
≤1 g	0.1%
>1 g	0.05%

Table 4. Identification thresholds for organic impurities in new drug product[2]

Maximum daily dose	Identification threshold
<1 mg	1.0% or 5μg TDI, which ever is lower
1–10 mg	0.5% or 20 μg TDI, which ever is lower
>10 mg-2 g	0.2% or 2 mg TDI, which ever is lower
>2 g	0.1%

Leachables are a separate class of drug product impurities, however, control of leachbales is not covered by ICH guidance.[2] Recently, the PQRI (Product Quality Research Institute) Leachables and Extractables Working Group proposed safety and qualification thresholds for leachables in OINDP (Orally Inhaled and Nasal Drug Products) to the regulatory authorities.[8] The proposed Safety concern threshold (SCT) is 0.15 μg/day, and the Qualification Threshold (QT) is 5 μg/day for an individual leachable in an OINDP. Note that proposed safety thresholds only apply to OINDP and not other drug product type (e.g., injectables, ophthalmic, etc.)

Inorganic impurities are, in most cases, introduced from the synthetic process of the drug substance (e.g., catalyst), or as impurities present in excipients. Analysis and control of inorganic impurities usually follows pharmacopoeial monographs or other appropriate procedures and will not be discussed further in this review.

Residual solvents are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products.[3] Residual solvents are divided by a risk assessment approach into three classes.

Class 1 solvents are known human carcinogens, strongly suspected human carcinogens, and environmental hazards; therefore, these solvents should be avoided in the production of drug substance, excipients, or drug products, unless their use can be strongly justified in a risk-benefit assessment. If unavoidable, the level of an individual Class 1 residual solvent should be strictly controlled below the concentration limits (for example the limit for benzene is 2 ppm).[3] Class 2 solvents are non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Class 2 solvents are controlled according to the PDEs (Permitted Daily Exposure) and Maximum Daily Dose (Option 1 and Option 2). ICH Q3C[3] provides PDEs of all Class 2 solvents. Class 3 solvents are solvents with low toxic potential to man. It is recommended that amounts of these residual solvents of 50 mg per day or less would be acceptable without justification.

For solvents for which no adequate toxicological data are available, manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

ORIGINS OF PHARMACEUTICAL IMPURITIES

Organic impurities can be originated from a variety of sources in both drug substances and drug products. Generally, the origins of impurities can be categorized into the following sources: synthetic process of the drug substance, degradation of the drug substance, container/closer and packing materials, and extraneous contaminants.

Impurities Originating from Drug Substance Synthetic Processes

Most small molecule drug substances are chemically synthesized. Chemical entities, other than the drug substance, that are involved or produced in the synthetic process can be carried over to the final drug substance as trace level impurities. These chemical entities include raw materials, intermediates, solvents, chemical reagents, catalysts, by-products, impurities present in the starting materials, and chemical entities formed from those starting material impurities (particularly those involved in the last steps of the synthesis). These impurities are usually referred to as process impurities. The goal of process impurity identification is to determine the structures and origins of these impurities. This knowledge is critical for improving the synthetic chemical process, in order to eliminate or minimize process impurities.

Process Impurities Originating from Starting Materials and Intermediates

Starting materials and intermediates are the chemical building blocks used to construct the final form of a drug substance molecule. Unreacted starting materials and intermediates, particularly those involved in the last a few steps of the synthesis, can potentially survive the synthetic and purification process and appear in the final product as impurities.[23] For example, in the synthesis of tipranavir drug substance, the "aniline" is the intermediate in the last step of the synthesis.[24] Because the similarity between the structures of the "aniline" and the final product, it is difficult to totally eliminate it in the subsequent purification step. Consequently, it appears in the drug substance at around 0.1%.

Process Impurities Originating from Impurities in the Starting Materials

Impurities present in the staring materials[25–27] could follow the same reaction pathways as the starting material itself, and the reaction products could carry over to the final product as process impurities. Knowledge of the impurities in starting materials helps to identify related impurities in the final product, and to understand the formation mechanisms of these related process impurities. An often encountered scenario involves starting

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.