Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 59 (2007) 3 – 11
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Assuring quality of drugs by monitoring impurities☆

Satinder (Sut) Ahuja *

Ahuja Consulting, 1061 Rutledge Court, Calabash, NC 28467, USA

Received 14 January 2006; accepted 25 October 2006
Available online 16 November 2006

Abstract

To assure the quality of drugs, impurities must be monitored carefully. It is important to understand what constitutes an impurity and to identify potential sources of such impurities. Selective analytical methods need to be developed to monitor them. It is generally desirable to profile impurities to provide a yardstick for comparative purposes. New impurities may be observed as changes are made in the synthesis, formulation, or production procedures, albeit for improving them. At times it is necessary to isolate and characterize an impurity when hyphenated methods do not yield the structure or when confirmation is necessary with an authentic material. Availability of an authentic material can also allow toxicological studies and provide a standard for routine monitoring of the drug product.
© 2007 Published by Elsevier B.V.

Keywords: Characterization; Chiral impurity; Degradation product; Drug product; Drug substance; Isolation; Profiling; Selective analytical methodologies; Terbutaline

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Pharmaceutical Impurities: Analytical, Toxicological and Regulatory Perspectives".

* Corresponding author. Tel.: +1 910 287 7565.
E-mail address: sutahuja@atmc.net.

0169-409X/$ - see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.addr.2006.10.003

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

1. Introduction

Webster's dictionary defines impurity as something that is impure or makes something else impure. An impure substance may be defined as follows: a substance of interest mixed or impregnated with an extraneous or usually inferior substance. These definitions can help generate a more concise definition of an impurity: any material that affects the purity of the material of interest, viz., an active pharmaceutical ingredient (API) or drug substance [1–4]. The purity of a drug product is in turn determined on the basis of the percentage of the labeled amount of API found in it by a suitable analytical method. Later discussion will also reveal that a drug product can have impurities that need to be monitored even though they do not affect the labeled content. The presence of some impurities may not deleteriously impact on drug quality if they have therapeutic efficacy that is similar to or greater than the drug substance itself. Nevertheless, a drug substance can be considered as compromised with respect to purity even if it contains an impurity with superior pharmacological or toxicological properties. Consequently, in order to ensure that an accurate amount of the drug substance is being administered to the patient, drug substance purity must be assessed independently from these undesirable extraneous materials (e.g., inert, toxic, or pharmacologically superior impurities).

2. Terminology

A large number of terms have been used to describe the materials that can affect purity of the API. For the purpose of this discussion, they are all considered impurities. To better acquaint the reader with advantages and limitations of the use of various terms, a brief description of these terms is given below, followed by some comments.

2.1. Commonly used terms

A number of terms have been commonly used in the pharmaceutical industry to describe organic impurities:

- Starting material(s)
- Intermediates
- Penultimate intermediate (Final intermediate)
- By-products
- Transformation products
- Interaction products
- Related products
- Degradation products

Some of these terms denote potential sources of impurities, e.g., intermediates; others tend to de-emphasize the negativity, e.g., related products. Let us review them individually.

2.1.1. Starting material(s)

These are the materials that are used to begin the synthesis of an API.

2.1.2. Intermediates

The compounds produced during synthesis of the desired material are called intermediates, especially when they have

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

been isolated and characterized. The most important criterion is characterization, i.e., they cannot be just theorized potential reaction products (see by-products below). The theorized compounds are best designated as potential intermediates.

2.1.3. Penultimate intermediate

As the name suggests, this is the last compound in the synthesis chain prior to the production of the final desired compound. It is more appropriate to call it *Final Intermediate*. Sometimes confusion arises when the desired material is a salt of a free base or a free acid. In the opinion of this author, it is inappropriate to label the free acid or base as the penultimate intermediate if the drug substance is a salt.

2.1.4. By-products

The unplanned compounds produced in the reaction are generally called by-products. It may or may not be possible to theorize all of them. Hence, they present a challenging problem to the analytical chemist in that a methodology cannot be optimally planned if it is not known what needs to be excluded from evaluations.

2.1.5. Transformation products

This is a relatively nondescript term that relates to theorized and non-theorized products that may be produced in the reaction, which can include synthetic derivatives of by-products. Transformation products are very similar to by-products, except this term tends to connote that more is known about the reaction products.

2.1.6. Interaction products

Interaction products is a slightly more comprehensive term than the two described above (by-products and transformation products); however, it is more difficult to evaluate in that it considers interactions that could occur between various involved chemicals — intentionally or unintentionally. Two types of interaction products that can be commonly encountered are drug substance–excipient interactions and drug substance–container/closure interactions.

2.1.7. Related products

As mentioned before, the term related products tends to suggest that the impurity is similar to the drug substance and thus tends to play down the negativity frequently attached to the term impurity. Clearly these products generally have similar chemical structures as the API and may exhibit potentially similar biological activity; however, as discussed later, this by itself does not provide any guarantee to that effect.

2.1.8. Degradation products

These are the compounds produced because of decomposition of the material of interest or active ingredient. This term can also include those products produced from degradation of other compounds that may be present as impurities in the drug substance.

2.2. Compendial terminology

The United States Pharmacopoeia (USP) deals with impurities in several sections:

Impurities in official articles
Ordinary impurities
Organic volatile impurities

The USP acknowledges that concepts about purity are susceptible to change with time, and purity is intimately related to the developments in analytical chemistry. What we consider pure today may be considered impure at some future date if methods are found that can resolve other components contained in a particular compound. Inorganic, organic, or polymeric components can all be considered impurities. The following terms have been used by the USP to describe impurities:

- Foreign substances
- Toxic impurities
- Concomitant components
- Signal impurities
- Ordinary impurities
- Organic volatile impurities (OVIs)

2.2.1. Foreign substances

The materials that are introduced by contamination or adulteration, not as a consequence of synthesis or preparation, are labeled foreign substances, e.g., pesticides in oral analgesics.

2.2.2. Toxic impurities

These impurities have significant undesirable biological activity, even as minor components; and they require individual identification and quantification by specific tests.

2.2.3. Concomitant components

Bulk pharmaceutical chemicals may contain concomitant components, e.g., antibiotics that are mixtures and are geometric and optical isomers (see Section 2.4.1).

2.2.4. Signal impurities

These are distinguished from ordinary impurities discussed below in that they require individual identification and quantification by specific tests. These impurities include some process-related impurities or degradation products that provide key information about the process.

2.2.5. Ordinary impurities

The species of impurities in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant undesirable biological activity in the amounts present are called ordinary impurities.

2.2.6. Organic volatile impurities (OVIs)

This term relates to residual solvents that may be found in the drug substance. OVIs are generally solvents used in the

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

synthesis or during formulation of the drug product. The solvents have been classified as follows by ICH.

Class I (to be avoided): benzene, carbon tetrachloride, 1,2-dichloromethane, 1,1-dichloroethane, and 1,1,1-trichloroethane.
Class II (should be limited): acetonitrile, chloroform, methylene chloride, 1,1,2-trichloroethane, 1,4-dioxane, and pyridine.
Class III: low toxic potential and permitted daily exposure (PDE) of 50 mg or more.
Class IV: solvents for which adequate toxic data are not available.

2.3. ICH terminology

2.3.1. Organic impurities
Starting materials
Process-related impurities
Intermediates
Degradation products.

2.3.2. Inorganic impurities
Salts
Catalysts
Ligands
Heavy metals or other residual metals.

2.3.3. Other materials
Filter aids
Charcoal.

2.3.4. Residual solvents
Organic and inorganic liquids used during production and/or crystallization.

2.4. Comments on various terminologies

The impurities that may be present in the starting material(s) can potentially be carried into the active ingredient of interest. And the impurities that relate to the solvents used during synthesis and the inert ingredients (excipients) used for formulation must also be considered potential impurities that may be found in API or drug product. Inorganic impurities may also be found in compendial articles. These impurities may be as simple as common salt or other compounds that are controlled, such as heavy metals, arsenic, etc., which can be introduced during various synthetic steps. Potential reaction by-products, degradation products, and drug substance–excipient interactions must also be evaluated. All of these impurities have the potential of being present in the final drug product.

Of the various terminologies described above, the International Conference on Harmonisation (ICH) provides a simple classification to adequately address various impurities that may be present in pharmaceutical products. However, all of these terminologies fail to adequately highlight that enantiomeric (chiral) impurities might warrant additional considerations.

2.4.1. Chiral impurities
Chiral impurities have the identical molecular formula and the same connectivity between various atoms, and they differ only in the arrangement of their atoms in three-dimensional space. The differences in pharmacological/toxicological profiles have been observed with chiral impurities *in vivo* [4,5]. This suggests that chiral impurities should be monitored carefully.

3. Identification and qualification thresholds of impurities

The International Conference on Harmonisation addresses questions relating to impurities as follows [6]:

Q1A (R) stability testing of new drug substances and products
Q3A (R) impurities in drug substances
Q3B (R) impurities in drug products
Q3C impurities: residual solvents
Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products; chemical substances

ICH guidelines for the identification and qualification threshold of impurities and degradation products are provided in Table 1.

As can be seen from the data in Table 2, ICH treats the degradation products slightly differently than impurities even though for all intents and purposes the degradation products are impurities.

4. Sources of impurities

Discussed below are three important sources of impurities.

4.1. Synthesis-related impurities

Impurities in a drug substance or a new chemical entity (NCE) originate mainly during the synthetic process from raw materials, solvents, intermediates, and by-products. The raw materials are generally manufactured to much lower purity requirements than a drug substance. Hence, it is easy to understand why they can contain a number of components that can in turn affect the purity of the drug substance.

Similarly, solvents used in the synthesis are likely to contain a number of impurities that may range from trace levels to significant amounts that can react with various chemicals used

Table 1
Thresholds for reporting impurities

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Less or equal to 2 g/day	0.05%	0.10% or 1.0 mg/day (whichever is lower)	0.15% or 1.0 mg/day (whichever is lower)
>2 g/day	0.03%	0.05%	0.05%

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

Table 2
Threshold for reporting degradation products in a new drug product

Maximum daily dose	Threshold
1 g	0.1%
>1 g	0.05%

in the synthesis to produce other impurities. Intermediates are also not generally held to the purity level of the drug substance—hence the remarks made for the raw materials apply. It is not reasonably possible to theorize all by-products; as a result, any such products that may be produced in the synthesis would be hard to monitor. The "pot reactions," i.e., when the intermediates are not isolated, are convenient, economical, and timesaving; however, they raise havoc in terms of the generation of impurities because a number of reactions can occur simultaneously. Incidentally, this problem of numerous reactions occurring simultaneously can be also encountered in single reactions where intermediate is isolated.

The final intermediate is generally controlled in the pharmaceutical synthesis by conducting regulatory impurity testing. This typically entails residual solvents (that are not used in further downstream processing) or process impurities (in cases where they conclusively demonstrate that these moieties are not also degradation products). It is important to remember that this step is the last major source of potential impurities, therefore, it is very desirable that the methods used for analysis at this stage be rigorous. It should be remembered that base-to-salt or acid-to-salt conversions could also generate new impurities. Furthermore, thermally labile compounds can undergo decomposition if any further processing involves heating.

4.2. Formulation-related impurities

A number of impurities in a drug product can arise out of interactions with excipients used to formulate a drug product. Furthermore, in the process of formulation, a drug substance is subjected to a variety of conditions that can lead to its degradation or other deleterious reactions. For example, if heat is used for drying or for other reasons, it can facilitate degradation of thermally labile drug substances.

Solutions and suspensions are potentially prone to degradation that is due to hydrolysis or solvolysis (see kinetic studies discussed below). These reactions can also occur in the dosage form in a solid state, such as in the case of capsules and tablets, when water or another solvent has been used for granulation. Not only can the water used in the formulation contribute its own impurities, it can also provide a ripe situation for hydrolysis and metal catalysis. Similar reactions are possible in other solvents that may be used.

Oxidation is possible for easily oxidized materials if no precautions are taken. Similarly, light-sensitive materials can undergo photochemical reactions. Details are provided in Chapter 6 of reference [1] regarding how various excipients can contribute to degradation and the resulting impurities.

4.3. Degradation-related impurities

A number of impurities can be produced because of API degradation or other interactions on storage. Therefore, it is very important to conduct stability studies to predict, evaluate, and ensure drug product safety [7]. Stability studies include evaluation of stability of API, preformulation studies to evaluate compatibility of API with the excipients to determine its stability in the formulation matrix, accelerated stability evaluations of the test or final drug product, stability evaluation via kinetic studies and projection of expiration date, routine stability studies of drug products in marketed, sample or dispensed package under various conditions of temperature light, and humidity.

The stability studies under various exaggerated conditions of temperature, humidity, and light can help us determine what potential impurities can be produced by degradation reactions (for details see Chapter 8 of reference [1]). It is important to establish a viable stability program to evaluate impurities. A good stability program integrates well the scientific considerations with regulatory requirements. The importance of kinetic studies in monitoring and evaluating impurities is discussed below.

4.3.1. Kinetic studies

Most of the degradation reactions of pharmaceuticals occur at finite rates and are chemical in nature. These reactions are affected by conditions such as solvent, concentration of reactants, temperature, pH of the medium, radiation energy, and the presence of catalysts. The order of the reaction is described by the manner in which the reaction rate depends on the concentration of reactant. The degradation of most pharmaceuticals can be classified as zero order, first order, or pseudo-first order, even though they may degrade by complicated mechanisms, and the true expression may be of higher order or be complex and noninteger.

An understanding of the limitations of experimentally obtained heat of activation values is critical in stability predictions. For example, the apparent heat of activation of a pH value where two or more mechanisms of degradation are involved is not necessarily constant with temperature. Also, the ion product of water, pKw, is temperature-dependent, and $-\Delta Ha$ is approximately 12 kcal, a frequently overlooked factor that must be considered when calculating hydroxide concentration. Therefore, it is necessary to obtain the heat of activation for all bimolecular rate constants involved in a rate–pH profile to predict degradation rates at all pH values for various temperatures.

It is incumbent upon the chemist to perform some kinetic studies to predict stability of a drug substance and to evaluate degradation products. However, it is also important to recognize the limitations of such predictions. The importance of kinetic studies and the effect of various additives on the reaction rates are discussed at some length in Chapter 7 of reference [1].

5. Selective analytical methodologies

Development of a new drug mandates that meaningful and reliable analytical data be generated at various steps of the new

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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.