CHAPTER-1

Impurity introduction

1.1Impurity introduction

There is no precise definition for "impurity," because of the apparent negativity attached to this word in the pharmaceutical sciences . Webster's dictionary defines impurity as something that is impure or makes something else impure A better definition of an impure substance may be as follows: a substance of interest mixed or impregnated with an extraneous or usually inferior substance. Simple definition for an impurity, that is, any material that affects the purity of the material of interest, viz., active ingredient or drug substance. The impurities are not necessarily always inferior. From the standpoint of its usage, the drug substance is compromised in terms of purity even if it contains another material with superior pharmacological or toxicological properties. At first pass this may not be readily clear; however, on further thought it would become apparent that if we are to ensure that an accurate amount of the drug substance is being administered to the patient, then we must assess its purity independently from the extraneous materials. Therefore any extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties.

A number of terms have been commonly used to describe an impurity or impurities·

Intermediate

Penultimate intermediate

By-products Transformation products

Interaction product

Related products

Degradation products

1.1.1 Intermediates: The compounds produced during synthesis of the desired material are called intermediates, especially if they have been isolated and characterized The most important criterion is characterization, i e , they cannot be just potential reaction products theorized to occur. The theorized compounds are best designated as potential intermediates.

1.1.2 Penultimate Intermediate: As the name suggests, this is the last compound in the synthesis chain prior to the production of the final desired compound. Sometimes confusion arises when the desired material is a salt of a free base or acid. It is inappropriate to label the free acid or base as the penultimate intermediate if the drug substance is a salt.

1.1.3 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 thorny problem to the analytical chemist. Produced in the reaction. Transformation products are very similar to by-products, except the term tends to connote that more is known about the reaction products.

1.1.4 Interaction Products: This term is slightly more comprehensive and more difficult to evaluate than the two described above, i.e., by-products and transformation products, in that it considers interactions that could occur between various involved chemicals--intentionally or unintentionally.

1.1.5 Related Products: As mentioned, 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. These products can have similar chemical structure and potentially similar biological activity.

1.1.6 Degradation Products: The compounds produced due to decomposition of the material of interest or active ingredients are often referred to as degradation products. We also need to concern ourselves with the products produced from degradation of other compounds that may be present as impurities in the drug substance

1.1.7 Miscellaneous Impurities: Other sources of impurities are the materials that may be present in the starting material that can be potentially carried into the active ingredient of interest. And the impurities that relate to inert ingredients (excipients) and solvents used during synthesis must also be considered. Impurities can be produced during various drug product formulation steps. These impurities have the potential of being present in the final drug product Potential reaction products must also be evaluated. [1]

1.2 Compendial Terminology

United States Pharmacopeia (USP 29, 2006 edition) deals with impurities under several sections: [2]

Impurities in Official Articles

Ordinary Impurities

Organic Volatile Impurities

The pharmacopeia 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, biochemical, isomeric, or polymeric components can all be considered impurities. The following terms have been used to describe impurities:

1.2.1 Foreign Substances: The materials that are introduced by contamination or adulteration, and not as consequences of synthesis or preparation, are labeled foreign substances, e.g., pesticides in oral analgesics.

1.2.2 Toxic Impurities: These impurities have significant undesirable biological activity, even as minor components, and require individual identification and quantitation by specific tests.

1.2.3 Concomitant Components: Bulk pharmaceutical chemicals may contain concomitant components, e.g., geometric and optical isomers and antibiotics that are mixtures.

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

1.2.5 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.

1.2.6 Organic Volatile Impurities: This term relates to residual solvents Organic volatile impurities are the solvents that may be found in the drug substance

1.2.7 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

1.2.8 Chiral Impurities: Compounds having similar chemical structure but different spatial orientation, leading to different optical rotation, are of great importance.

1.3 Chromatography is a frequently used analytical technique for the separation and quantitative determination of various compounds such as pharmaceuticals, pesticides and other environmental pollutants, food ingredients and additives, toxic substances, drugs, etc Chromatography has been developed as a powerful and rapid technique with the unique objective of separating compounds with highly similar molecular characteristics even from complicated matrices. The rapid progress of various chromatographic methods and the increasing range of applications quickly revealed that chromatography is more than a very effective separation method based on empirical or semi empirical principles. Chromatographic techniques have reached the point where the average chromatographer can achieve standard spectacular results using empirical rules and experiences However, it is more and more obvious that successful separation of various solutes (selection of the best separation technique, stationary and mobile phase composition, etc.) requires a profound knowledge of the effects of molecular parameters of solutes, supports, and mobile phases and their possible interactions on retention. The rational design of an optimal separation process involves the expert application of such knowledge. Over the past few years major advances have been made not only in practice, but also in the theory of chromatography Many excellent papers have been published on the influence of molecular structure on the retention behavior of solutes using both theoretical and

practical approximations. In this study the influence of molecular structure on the retention and separation capacity is discussed and a thorough study of the special field of research is offered.

1.4 Chromatography today is a proven method for separating complex samples into their constituent parts, and it is undoubtedly the most important procedure for isolating and purifying chemicals. Using data from the first half of 2003, Ryan estimated that nearly 5% of all chemical research in 2003 would involve chromatography.

In addition, most chromatographic instrumentation is equipped with detectors, making chromatographs true instruments, devices capable of making measurements. Consequently, this monograph will deal not only with the principles of chromatography but also with the practice of quantitative analysis. It is this latter subject that has been greatly influenced by both industry and the federal government because of the need for standards and standardization that go hand-in-hand with governmental regulation In the modern world, these issues extend to foreign countries as well and have given rise to international organizations and guidance's/regulations that need to be recognized by chromatographers worldwide. Since much important information is available on the Internet, all scientists need to be knowledgeable about its retrieval and its impact on their work. In addition, much effort is being made internationally to provide a cooperative and harmonized approach to analysis and analytical method development written from the perspective of chromatographers in the United States, the principles are applicable internationally, and scientists would be well advised to recognize that fact and become aware of the developments outside their own countries.

Fortunately, the fundamental principles of chromatography and analytical chemistry in general are the same in academia, industry, and government, of course. Their common objective is to perform laboratory tests and procedures that are based on sound scientific principles. However, some industries operate under more stringent controls than others For example, the pharmaceutical industry in the United States is regulated by the Food and Drug Administration (FDA), which enforces federal regulations known as the Current Good Manufacturing Practices (CGMPs). These regulations were promulgated to

ensure the safety and efficacy of drugs by setting forth minimum standards for manufacturing and testing. The GMPs are not prescriptive and, therefore, they have been supplemented by FDA guidance documents that provide more specific details on complying with the regulations. This guidance's provide insight for the practice of good chromatography in all venues where analytical chemistry is performed, in the United States and abroad. While it is true that European and Asian counterparts are similarly regulated by their respective agencies, the fundamental analytical principles are the same and are becoming internationally codified.

1.5 Locus of Chromatography in Chemical Industry: Chemical companies and related industries such as pharmaceutical companies and the petroleum industry more than ever need to have laboratories devoted to analysis methods and characterization, including in most cases a section well trained in chromatography. Those that produce and sell chemicals have a laboratory function called quality control (QC) that monitors the quality of incoming raw materials, evaluates in-process intermediates, and tests the purity of final products. Assurance of the quality of manufactured products, referred to as quality assurance (QA) and carried out in conjunction with manufacturing, is a related function. Both functions may be combined, and the laboratory may be called a QC/QA laboratory. This laboratory usually performs both qualitative (identity) analyses and quantitative analyses The latter are often performed by gas chromatography (GC) or liquid chromatography (LC). Usually, these laboratories are situated close to, or within, the manufacturing site Typical of many companies hiring B.S chemists, large pharmaceutical firms hire recent bachelor's chemists as analytical chemists into their QC laboratories.

Depending on the size of the company, another laboratory may be responsible for developing the methods for the QC laboratories. This function may be in the Research and Development (R&D) Department. The chromatographers in this laboratory are usually responsible for keeping up with the latest developments in chromatography and searching for and evaluating new improved methods of analysis, as well as developing methods for the QC laboratory. Instrument companies manufacturing chromatographs

may also have their own instrumental R&D groups that often provide technical support. Generally, R&D groups are staffed by degree chemists at several levels with some Ph.D.s at the highest levels.

Another analytical need is for a group to perform general analytical services to support the chemical activities of the company (synthesis, pilot plant, product support, etc) These services most often include chromatography, spectroscopy, and micro analytical (elemental) analysis. Often this is a separate group of scientists and engineers and may include a small group of experts that advises and consults with technicians in the other areas who do their own analytical work Separate groups may exist to support the sales and marketing department or the patent and law department, for analysis of competitor's samples or evaluation of patent infringement, for example Within a chemical corporation, these various laboratories are responsible for providing accurate and reliable analytical methodology. Latest developments in bio analysis and development of various chiral stationary phases are described below to give flavor of advancements in the analysis area how ever this part of literature is just an update on current trends.