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Case History-The Control of Impurities-A Critical Issue to The Active Pharmaceutical Ingredient

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Abstract

The ICH guidelines on impurity have clearly defined the levels of toxic impurities and have become benchmark in establishing impurities in pharmaceutical drug products. The present article summarizes the concept of impurity profiling and presents a case study on impurity profiling of quantification of active pharmaceutical ingredient and impurities in sildenafil citrate purchased via internet and its relative outcomes.

Keywords: Aflatoxin; Contamination; Lethal dose

Introduction

Case study on quantification of active pharmaceutical ingredient and impurities in sildenafil citrate obtained from the Internet

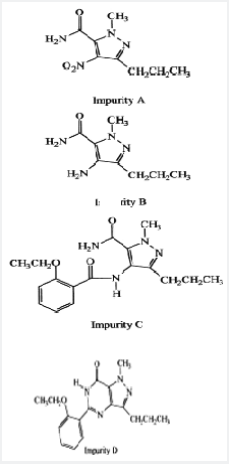

Figure 1

Consumers can obtain prescription drugs via the Internet without any difficulty and professional oversight. The accessibility of prescription drugs produced outside of the United States, most notably sildenafil citrate (innovator product, Viagra®), has been made much easier by the Internet. Clinicians and policymakers are more concern to product quality and patient safety. The US Food and Drug Administration (FDA) has issued warnings to potential buyers that the safety of drugs purchased from the Internet cannot be guaranteed and may present a health risk to consumers from substandard products (Figure 1).

Discussion

A study was conducted to determine whether generic sildenafil citrate tablets from international markets obtained via the Internet are equivalent to the US innovator product regarding major aspects of pharmaceutical quality: potency, accuracy of labelling, and presence and level of impurities. As in case a total of 15 sildenafil citrate tablets were taken for pharmaceutical analysis out of which 14 generic samples from international Internet pharmacy websites and one was innovator product. According to US Pharmacopeial guidelines, tablet samples were tested using high performance liquid chromatography for potency of active pharmaceutical ingredient (API) and levels of impurities (impurities A, B, C, and D). 1- methyl-4-nitro-3-n-propyl-5-pyrazole carboxamide (Impurity A); 4-amino-1-methyl-3-n-propyl5-pyrazole carboxamide (Impurity B); 4-(2-ethoxybenzoylamino) -1-methyl - 3 - n - propyl - 5 - pyrazole carboxamide (Impurity C); 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-pyrazole [4,3-d] pyrimidine-7-1 (Impurity D). Impurity levels were compared with International Conference on Harmonisation (ICH) limits. As outcome of among 15 samples, 4 samples possessed higher impurity B levels than the ICH qualification threshold, 8 samples possessed higher impurity C levels than the ICH qualification threshold, and 4 samples possessed more than 1% impurity quantity of maximum daily dose (MDD). For API, 6 of the samples failed to fall within the 5% assay limit [1-3].

Outcomes of study revealed that in that manufacturing standards for sildenafil citrate generic drug products compared with the US innovator product are not equivalent with regards to potency and levels of impurities. They have implications for safety and effectiveness that should be addressed by clinicians to safeguard consumers who choose to purchase sildenafil citrate and foreign-manufactured drugs, via the Internet. In the present era, there is a tremendous upsurge for impurity profiling of pharmaceutical products. Presence of impurities in trace quantity in drug substance or drug product is inevitable. Therefore, their level should be controlled and monitored. They can reinforce or diminish the pharmacological efficacy of the Active Pharmaceutical Ingredient (API). Sometimes, the effect produced by impurities can be teratogenic, mutagenic or carcinogenic. This can jeopardize the human health by affecting quality, safety and efficacy (QSE) of the product [4]. Therefore, there is an ever-increasing interest in controlling and monitoring impurities present in API / pharmaceutical products. Hence, API impurity profiling (identification, isolation and characterization) is required. Their limits and threshold values should comply with the limits set and specified by official bodies and legislation (Pharmacopoeias and International Conference on Harmonization (ICH) guidelines).

This is very important when company files Investigational New Drug Application (IND) or Abbreviated New Drug Application (ANDA). However, monitoring and controlling of impurity is different for different people. Therefore, there must be unified system to ensure that everyone speaks the same language when addressing "Issues related to impurities" ICH has published guidelines for validation of methods for analysis of impurities in new drug substances, new drug products, residual solvents and microbiological impurities for registration of pharmaceuticals for human use [5]. ICH defines impurities as "substances in the API that are not the API itself". For pharmaceutical products, impurities are defined as "substances in the product that are not the API itself or the excipients used to manufacture it" i.e. impurities are unwanted chemicals that remain within the formulation or API in small amounts which can influence QSE, thereby causing serious health hazards. According to ICH guidelines on impurities in new drug substances and new drug products, identification of impurities below the 0.1% level is not necessary unless the potential impurities expected to be unusually potent or toxic. In all cases, impurities should be qualified. If data related to qualification of the proposed specification level of an impurity is not available, then studies were required to obtain such data. According to ICH, the maximum daily dose qualification threshold is as follows: <2g/ day 0. 1% or 1 mg/ day intake and >2g/ day 0.05% As impurity profile received a critical attention from regulatory authorities, different Pharmacopoeias such as British Pharmacopoeia (BP), United States of Pharmacopoeia (USP), European Pharmacopoeia (EP) and Indian Pharmacopoeia (IP) are slowly incorporating limits to allowable levels of impurities present in new drug substances or APIs and formulations. Moreover, several articles have stated guidelines and designed approach for isolation and identification of process related impurities and degradation products using Mass spectroscopy (MS), Nuclear Magnetic Resonance (NMR), High Performance Liquid Chromatography (HPLC), FT-Ion Cyclotron Resonance MS (FT-ICR-MS) and Tandem MS for pharmaceutical substances. Impurity profiling is a major concern in drug developing and processing [6,7]. Identification of impurities is very important task during the synthesis of drug substances and manufacture of dosage forms. It can provide crucial data regarding the toxicity, safety, various limits of detection and limits of quantitation of several organic and inorganic impurities, usually accompany with APIs and finished products. ICH has outlined guidelines about impurities but much more need to be required. There is strong requirement to have unified specifications/standards about impurities.

Conclusion

Pharmaceutical impurities are the organic and inorganic unwanted chemicals which are found in active pharmaceutical ingredient after synthesis or develop during formulation development. These impurities severely affect the safety and efficacy of developed pharmaceutical product [8]. Impurity profiling detects and quantifies the levels of organic and inorganic impurities and thereby helps in better monitoring of quality, stability and safety of pharmaceutical products. Regulatory bodies worldwide are serious towards presence of impurities and impurity profiling has thus become an important step in filling drug dossiers.

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