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Evaluation of Genotoxic Impurities Risk in Pharmaceutical Compounds

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Why Genotoxic Impurities are Important?

An Active Pharmaceutical Ingredient (API) synthesis encompasses multiple reaction steps for conversion of basic starting materials to the products. Each reaction involves reactive intermediates, reagents, catalysts, byproducts, solvents, etc. Low-levels of reagents or by-products may therefore be present in the final API as impurities. Such chemically reactive impurities may have unwanted toxicities, including genotoxicity and carcinogenicity, and hence may react with DNA bases causing mutations. Mutations can be rearrangements, chromosomal breaks, covalent binding or insertion into DNA during replication. Mutations may also occur indirectly by a activating a cell to produce genotoxic substances. These changes to the genetic material, which can be caused by exposure to very low levels of a genotoxin, can lead to cancer [1]. Due to this, it is important to identify genotoxic substances followed by monitoring and control at very low levels to ensure safety to the public health.

An example of a case that contributed to the heightened awareness and potential dangers of genotoxic impurities in a pharmaceutical product was the viracept (neflinavir mesylate) contamination incident [2]. Various lots of this HIV drug were pulled out of the market in 2007 because of the high levels of ethyl mesylate which is an alkylating class that can covalently bind to DNA and enhance cancer risk.

The balance between appropriate control with minimal impact to the time and costs associated with developing life-improving drugs is the major challenge with genotoxic impurities in pharmaceuticals. Some may argue that setting such low limits for genotoxic impurities is not always practical and lacking solid scientific justification.

PGI Classification and Assessment

Genotoxic substances in pharmaceutics, known as PGI, are gaining more attention. These substances add risk without any benefit to pharmaceuticals. Genotoxic impurities can be identified by various methods: 1) as already know genotoxins, 2) possessing similar functional groups with known genotoxic, 3) testing positive by genotoxicity assays or 4) marked as a potential genotoxin by one of many computer-based structure-activity software programs.

Muller et al. [3] describes a genotoxic impurity assessment decision tree that includes the 5 impurity classes. Toxicology assessment identifies genotoxic compounds in a route that need to be addressed. Based on the structural alerts suggested by Muller et al., most of the key reactive intermediates which are usually employed to facilitate smooth chemical transformation are found to be PGIs and hence, it is a bitter pill to the synthetic chemist to avoid them during synthesis. Therefore, it is imperative to ensure its complete conversion during reaction sequence or reject them using proper work up method.

Regulatory Aspects and Guidelines

Nowadays, regulatory authorities generally expect sponsors of clinical trials and commercial marketing authorizations to demonstrate the removal of Potentially Genotoxic Impurities (PGIs) or control them to minute levels in the ppm range.

The European Medicines Agency´s (EMEA) was the pioneering regulatory body to impose detailed guidelines to handle PGIs at the beginning of 2008 [4]. The FDA subsequently released a draft guideline in December 2008 entitled "Genotoxic and Carcinogenic Impurities in Drug Substance and Products: Recommended Approaches" [5]. Moreover, ICH provides guidelines for impurities (Q3A, B and C) [6-8], but does not specifically provide acceptable levels for those genotoxic in nature. The intention of the FDA guideline was to be an adjunct to the ICH guideline.

Essentially all of these guidelines mention the recommended approaches to deal with PGIs, especially its control limits in the form of Threshold of Toxicological Concern (TTC) [4]. TTC represents a level at which a patient can be exposed to a genotoxic impurity in a pharmaceutical with minimal risk while balanced with the therapeutic benefits of the pharmaceutical. Currently, 1.5 μg per day daily intake of impurity is considered as virtually safe dosage, while low and high limits are case specific based on the toxic potential of a given compound, thus the PGI have to be controlled below the TTC limit.

Analytical Methods to Monitor Potential Genotoxic Impurities

Since the advent of the EMEA guideline relating to genotoxic impurities it has become necessary to monitor and control such impurities to very low levels. This has led to the development of a series of analytical methods.

Moreover, because of the low limits defined within the EMEA guideline [4], based on the TTC concept, such methods need to be able to quantify the potentially genotoxic impurities at trace level, sometimes around or below 1 ppm (1 μg/g), which is typically 500 times lower than for classical impurity analysis in pharmaceutical quality control.

There are excellent reviews and publications available on the topic of impurity analysis [9-14]. Briefly, in terms of the techniques employed, GC has been used in preference, combined with, where possible, static headspace. For a less volatile analytes, SPME and DHS could be used to extend the headspace extraction. Nonvolatile compounds are mostly analyzed by LC-MS. When analytes are poorly retained by RP-LC, precolumn derivatization could be successfully employed. Moreover, derivatization could be also found to be useful to increase detectability in MS.

The analytical method should be phase appropriate and evolving

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as the drug moves toward commercialization. The method should be robust, simple and run using standard equipment to ensure a smooth transfer from R&D to a regulated laboratory. Additional requirements to ensure the intended purposes are the validation of the instrumentation and the methods. Validation should cover sensitivity, specificity, accuracy, linearity and precision in order to prove the method is capable of its intended use.

Conclusion

In conclusion, there is a critical need for analytical methods to monitor genotoxic impurities. Most important, the analytical method needs to possess specificity and appropriate sensitivity. Genotoxic impurities have a broad range of chemical properties, and therefore, the handing and analysis of them will also vary.

Genotoxic impurity analysis is a challenging, complex aspect of the drug development process. Furthermore, an appropriate balance needs to be found that takes into account patients safely against the amount of time and resources to quickly get a pharmaceutical to market.

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