

# GENOTOXIC IMPURITY (GTI) ASSESSMENT

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## ABSTRACT

This article is intended to provide a general overview of the issues surrounding genotoxic impurities and their potential resources. Here we shall focus on general and regulatory aspects review the toxicological issues.

Keywords Geotoxic impurity pharmaceutical Drug GTI

## INTRODUCTION

In pharmaceutical industry, the impurities can be defined as the substances which provide no therapeutic benefits but have the potential to harm. Therefore the level of these impurities need to be under control and we need to have a basis for its allowed levels in human to check on adverse effects.

As the pharma industry is facing a threat against the safety and development time of medicinal products from these impurities.

The impurities in drug substances can be classified in three categories according to ICH guideline:

Organic, Inorganic impurities and residual solvents. Under these categories, the genotoxic impurities form a special case which is of great potential for health risks, even at lower concentration in medicinal products. They are highly mutagenic and have the potential to damage the DNA at various levels.

As mentioned above that these genotoxic impurities poses threat and health risk, hence here I would draw the attention in its sources during the drug development life:

- 1: Starting materials and their probable contaminants
- 2: Reagents and catalysts
- 3: Solvents
- 4: Intermediates
- 5: Excipients and their contaminants
- 6: Leachables
- 7: Degradation products

The level of impurities in drugs must be reduced to acceptable safety limits to ensure the patient health. There are various regulatory guidelines and position papers focused on controlling the amount of impurities in drug manufacturing using specified limits. The guidelines for impurities control have mainly been developed by the International Conference on Harmonization (ICH). For example, ICH Q3A regulates impurities in new drug substances, ICH Q3B16 is the equivalent guideline for impurities in new drugs development.

### Regulation and guideline

The levels of impurities in drugs must be reduced to adequate safety limits to ensure the good health of patients. Additionally, reliable and accurate data measured in pharmaceutical laboratories are equally important to ensure product safety. Several organisations from industry and regulatory authorities have developed guidelines specifically addressing genotoxic impurities. As per the International Council for Harmonization (ICH) S2 (R1) Guideline,

The table given below is an overview of the guidelines and topics addressed (Souces-<https://www.ema.europa.eu/>):

Key Topics	Title
Guidelines for the control of genotoxic impurities	PhRMA position paper: A Rationale for Determining, Testing and Controlling Specific Impurities in Pharmaceuticals that Possess Potential for Genotoxicity (2006). 3 Introduced important concepts, e.g., five impurity classifications and the staged impurity threshold for short term exposure
	EMA: Guideline on the Limits of Genotoxic Impurities.19 Draft releases for consultation in 2002 and 2004, and final version released in 2006. Together with the related Q & A documents,20 this is the most complete regulatory document. It also introduced the concept and values for the threshold of toxicological concern (TTC).
	EMA, Safety Working Party (SWP): Questions and answers on the Guideline on the Limits of Genotoxic Impurities, 20 published in 2008, 2009, 2010, and 2012
	FDA Guidance for Industry (Draft): Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008).22 Generally aligned with the EMA guideline.
Guidelines for genotoxicity testing	ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Business Plan (2010), Position Paper.18 This document is under development and may replace existing EMA and FDA guidelines.
	ICH S2: Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use.1 This document combines previous guidelines ICH S2A (1996) and ICH S2B (2007), and is the global document for genotoxicity testing.
Risk assessment for genotoxic and carcinogenic substances	EMA: Guideline on the Assessment of Genotoxicity of Herbal Substances/Preparations (2008).21 This guideline describes a general framework and practical approaches for testing the potential genotoxicity of herbal substances/preparations, as well as how to interpret the results.
Risk assessment for genotoxic and carcinogenic substances	European Commission Health & Consumer Protection Directorate: General Risk Assessment

**Table 1. Guidelines for genotoxic impurities: control, testing, and risk assessment.**

The guidelines for genotoxic impurities broadly address the control of genotoxic impurities, genotoxic testing and risk assessment for genotoxic and carcinogenic substances.

The Pharmaceutical Research and Manufacturers of America's (PhRMA's) position paper published in the year 2006, A justification for assessment, Testing and Controlling Specific impurities in Pharmaceuticals that possess potential for Genotoxicity have introduced important concepts for example, five impurity classifications and the staged impurity threshold for short-term exposure. Similarly, the European Medicines Agency (EMA) formulated related official guidelines, Guideline on Limits of Genotoxic Impurities, and thus there is an overlap of approaches. The key distinction between the documents is their importance on implementation, with PhRMA's paper having more details for implementation than the official EMA guidelines. The classification system from PhRMA became the key to proposition a strategy for impurity assessment. Handling of genotoxic impurities was detailed in the guidelines by the EMA, especially to close the gaps on the control of impurities with genotoxic potential from ICH Q3A and Q3B guidance. The EMA published the final guideline on the limits of genotoxic impurities in June 2006

### Calculating limits for exposure to genotoxic impurities

If genotoxic impurities are identified from assays, it is important to calculate the permissible daily exposure (PDE). In cases where the genotoxic dose cannot be determined, a toxicological threshold of concern can be used. If there is toxicological data that is available with a No Observable Effect Level (NOEL), then a calculation can be performed using the following equation, as referenced in ICHQ3C(R4):

$$PDE = (\text{NOEL weight adjustment}) / (F1 \times F2 \times F3 \times F4 \times F5)$$

Where



- F1 is a factor used to adjust for animal extrapolation to humans, based on allometric scaling
- F2 is a factor to account for variability between individuals
- F3 is a factor used for adjustment in study duration
- F4 is an adjustment factor, depending on the severity of the observed toxic effects
- F5 is a variable factor if the NOEL was not established.

## A FIVE-CLASS SYSTEM FOR CLASSIFYING GENOTOXIC IMPURITIES.

Class 1- Known to be genotoxic and carcinogenic. This includes known animal carcinogens with reliable data for a genotoxic mechanism, and human carcinogens. The genotoxic nature of the impurity is then demonstrated using published data on the chemical structure.

Class 2- known to be genotoxic , but with unknown carcinogenic potential. This impurity group includes impurities with demonstrated mutagenicity based on testing of the impurity in conventional genotoxicity.

Class 3- The class 3 group includes impurities with functional moieties that can be linked to genotoxicity based on structure. Though, these moieties have not been tested as isolated compounds and are recognized based on chemistry and using knowledge based expert systems for structure activity relationships (SAR).

Class 4- With an alerting structure impurities related to the API and contain an alerting functional moiety that is shared with the structure of the API.

Class 5- This class deals with 'No indication or alerting structure of genotoxic potential'. Based on this classification system, a strategy for impurity control and assessment was proposed. This strategy has basically used for most genotoxic impurity related risk assessments norms across the industry. The article recommends to adapt the ICH qualification of impurities according to the five class model. The proposal can be implemented as below in three steps described in Table 2.

Step	Action	Comments
1	Identify structural alerts in the parent compound and expected impurities, and classify the impurities into one of the five classes.	This requires a scientific review of the synthetic route to identify compounds of potential concern including process impurities, reagents, and intermediates.
2	Establish a qualification strategy for the impurities based upon the classification. This defines the genotoxic potential of each impurity or establishes permitted specification limits for the impurity in the drug product.	Information on the carcinogenic potential is based on literature supported by experimental data obtained in genotoxicity tests, such as the Ames test. The paper has detailed information for the qualification of each class.
3	Establish limits of the impurity based on the acceptable daily intake (ADI) and the TTC concept (see below).	The determination of acceptable amounts in drug substance and drug products is based on the qualification and risk assessment.

Table 2. Implementing the five-class impurity model

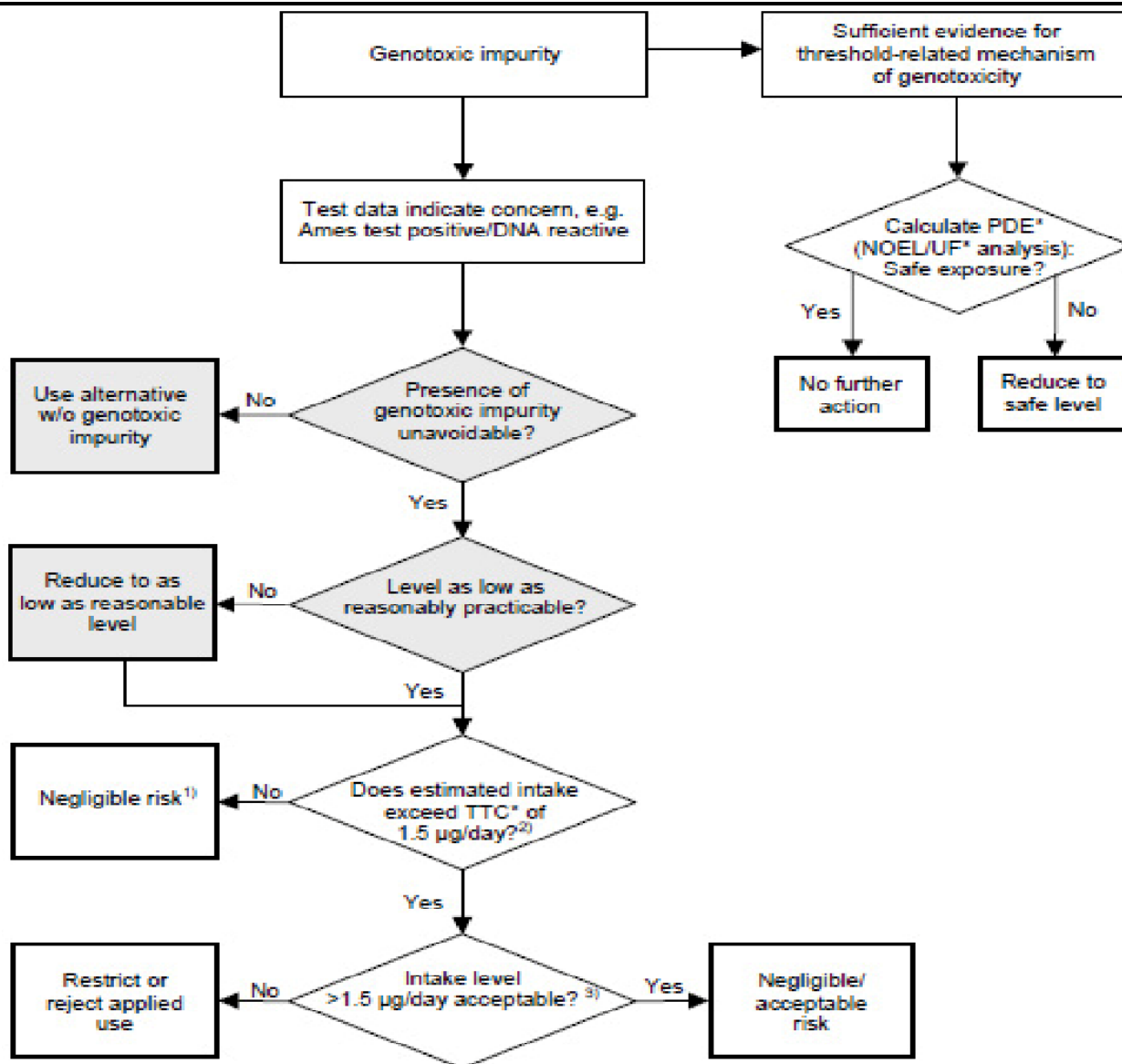


Figure 1. Decision tree for assessment of acceptability for GTI (EMEA,2006).

The analysis of pharmaceutical impurities is a very rigorous job involving method development, impurity synthesis, impurity isolation and many analytical procedures to identify the impurity. It involves the identification of structural alerts acting as impurity in a drug substance which are above the prescribed threshold limits. The chemical structure and the mechanism of how the impurity is formed need to be identified which helps for toxicological assessment, thus improving the synthesis to reduce or prevent the impurities in final drug. Hence, many analytical methods are emerging for quality assessment of new drugs getting manufactured. According to the Regulations, Impurity profiling needs a high resolution chromatography technique which is capable of giving reproducibly, separating and detecting the impurities present in pharmaceuticals

## Summary

Overall, the current regulatory and pharmacopeial approaches are considered to exhibit a reasonable level of pragmatism, but some of the underlying principles often appear to lack clarity and precision, for example, regarding ‘common mechanisms of toxicity’, analysis of structurally alike GTIs and Ames negative compounds with one or more positive results in mammalian-cell genotoxicity assays. It is to be hoped that a discussion will be established around ICH M7 leading ultimately to a guideline that is acceptable to Industry and regulatory authorities alike.

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