Quest Journals
Journal of Research in Pharmaceutical Science
Volume 7 ~ Issue 8 (2021) pp: 14-20
ISSN(Online) : 2347-2995
www.questjournals.org

Research Paper

Genotoxic Impurity in Pharmaceutical Products: A Growing Concern

Sheetu*[1], Sagar Garg[2], Muskan Wadhwa[3], Manish Kumar[4], Mohit Dadwal[5]
1 Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, INDIA
2 Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, INDIA
3 Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, INDIA
4 Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, INDIA
5 Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, INDIA

ABSTRACT
The term "genotoxic substances" refers to chemical compounds that can cause genetic mutations and contribute to the growth of tumours. Genotoxic impurities in the pharmaceutical industry are a major challenge. The development and regulation of genotoxic sulfonate esters have received a lot of regulatory attention recently. This is to abnormal levels of ethyl-methane-sulfonate (EMS) in pharmaceutical industry. This resulted in an assessment of the impurity in the pharmaceutical industry and to ensure the safety of the people. The impurity is limited to TTC-based limits for all products but other techniques that can evaluate the impurity. In addition, this review article also consists of the different class as per ICH guidelines and the management and future prospective of the impurity.

KEYWORDS: *Active pharmaceutical ingredients (API), Threshold Toxicological Concern (TTC), Limit of Quantitation (LOQ), European guidelines, ICH.*

Received 24 July, 2021; Revised: 07 August, 2021; Accepted 09 August, 2021 © The author(s) 2021. Published with open access at www.questjournals.org

I. INTRODUCTION

Impurities detected in APIs are gaining popularity. The purity profile and the impurity profile have lately become another regulatory criterion as a result of numerous regulatory requirements. An impurity of any other organic product emerging from synthesis is defined in the pharmaceutical industry, other than drug substances, ingredients, and other undesirable chemicals with the use of APIs. Impurity can form during the formulation process or the aging of both APIs and formulated APIs in medicines. One example of this principle is the identification of impurities of APIs with a multidisciplinary method, which can affect the efficacy and protection of these undesirable chemicals, even in trace quantities. Profiles on impurities (identification and quantification of impurities in pharmaceuticals) are now being given critical attention from regulatory pharmacopeia authorities, such as the British Pharmacopeia (BP), the United States Pharmacopoeia (USP), and Indian Pharmacopoeia (IP) [1]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) also issued guidance for the validation of impurity analysis for new drug ingredients, medicinal products, residual solvents, and microbiological impurities [2].

Chemical agents' genotoxicity is determined by their electrophilic capacity to attach to nuclear sites in cellular macromolecules, such as Deoxyribonucleic acid (DNA), the bearer of hereditary material The toxicity thus expressed in the cell's genetic material is genotoxicity. Genotoxicity involves the direct and indirect effects in DNA: (1) mutations that are close to events known to occur in carcinogenesis at the molecular level, (2) indirect surrogate events linked to mutagenesis, or (3) DNA damage [3]. Increasing evidence of mutagenicity thresholds (MMS, EMS, etc.) is available for impurities. Although not all mutations result in cancer, oncogenes and tumour suppressors both have a role in cancer. Factors of mitigation - ADME, detoxifier, repair of the DNA, apoptosis, autophagy, anoikis to cell removal. The reaction of the solvent ethanol and the mesyl group removed in the epoxide formation reaction will result in the formation of ethyl methane sulphonate in the final step of the synthesis of the starting material that causes genotoxic impurity in the formulation [4]. The ICH M7 standard allows for compound-specific permissible intakes of mutagenic impurities with proven carcinogenic potency (as defined in figure 1). [5]

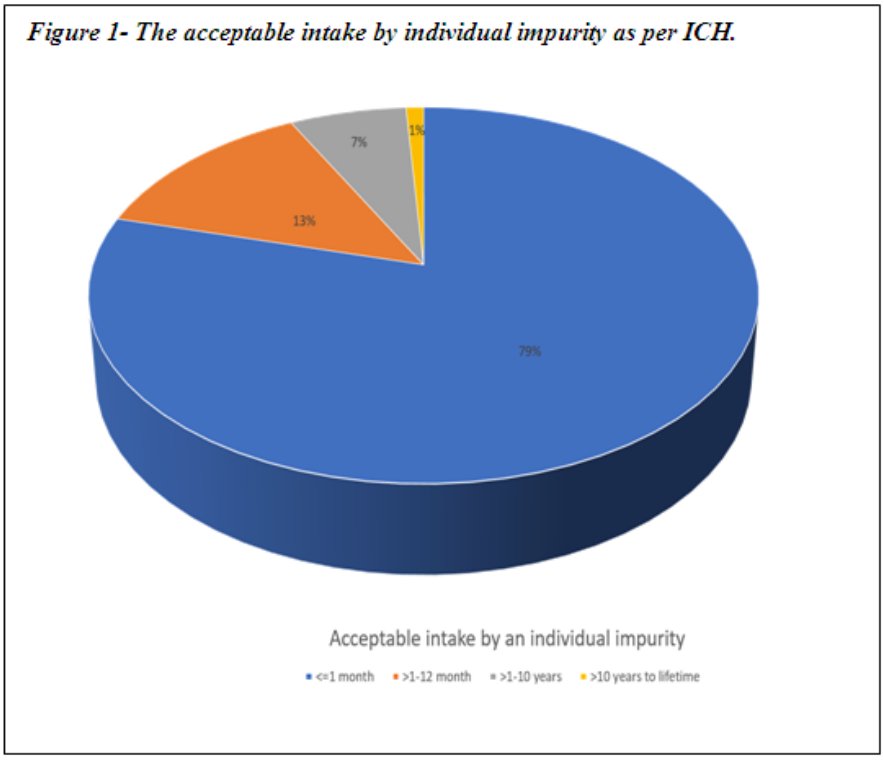


Figure 1- The acceptable intake by individual impurity as per ICH.

ETHYL-METHANE-SULFONATE

Ethyl-methane-sulfonate (EMS) with molecular formula $C_3H_8O_3S$ is a mutagenic and carcinogenic volatile organic solvent. It causes random mutations in DNA and RNA, especially guanine alkylation, by nucleotide substitution [6]. This hazardous substance was successfully used in random mutagenicity by Methanobacterium ivanovii and Methanococci. The EMS is a possible cancer compound that causes nucleotide substitution which only produces point mutations in DNA [7]. In the EMEA Guideline on GTIs with uncertain carcinogenic content or potential, of threshold toxicological concern (TTC) is specified. The TTC is focused on an approach to set a human exposure threshold value for all of the substances below which the risk for human health is very low. This definition focuses on toxicity data extrapolation from one or more bases available to a chemical compound that has a given chemical structure, but has no or restricted toxicity and would support customers, industry, and the regulatory authorities in developing and applying the generally accepted TTC principles [8]. The guidelines for reducing the risk of possible lifetime cancer associated with exposure of patients to genotoxic and carcinogenic impurities. These guidelines recommend a maximum daily exposure target of 1.5 µg per day [9].

European Guidelines

The guideline proposes new methods to promote acceptance of upcoming and current molecular moieties with synthetic routes or other modifications that could lead to higher levels of genotoxic impurities. Genotoxic impurities should be defined as a structural assessment and the route that including starting products, complex, catalysts and solvents should be taken into account. The EMA Guideline focuses primarily on the "DNA reactive substances which could have direct harm to DNA" [10]. An acceptable degree under class II solvents classified in the impurity guidance note Q3C: residual solvents for those with sufficient proof of threshold mechanism can be calculated. A reasonable limit based on a substance-specific estimate is possible for those without adequate proof of a threshold-related process where carcinogenicity data exist; a dosage consistent with the estimated risk amount of an added cancer mortality of 1 in 100000 people. The Guidance sets out "1.5 µg/d genotoxic impurity intake is considered an acceptable risk for most drugs". Based on the above consideration the amount specified by is equivalent to a 10^{-5} lifetime cancer chance. The TTC solution does not involve special high-performance case compounds. Alternatively, certain conditions such as short-term exposures, short lifetimes, life-threatening care for a living disease, and other common exposures to impurity may require a higher degree of TTC [11].

As per the current genotoxicity/carcinogenicity data it can be analyzed to test the genotoxic ability of an impurity. If no warning components are present, the impurity may be classified as non-genotoxic; nevertheless, if a structural alarm is present, either impurity picking should be done.

US Guidelines

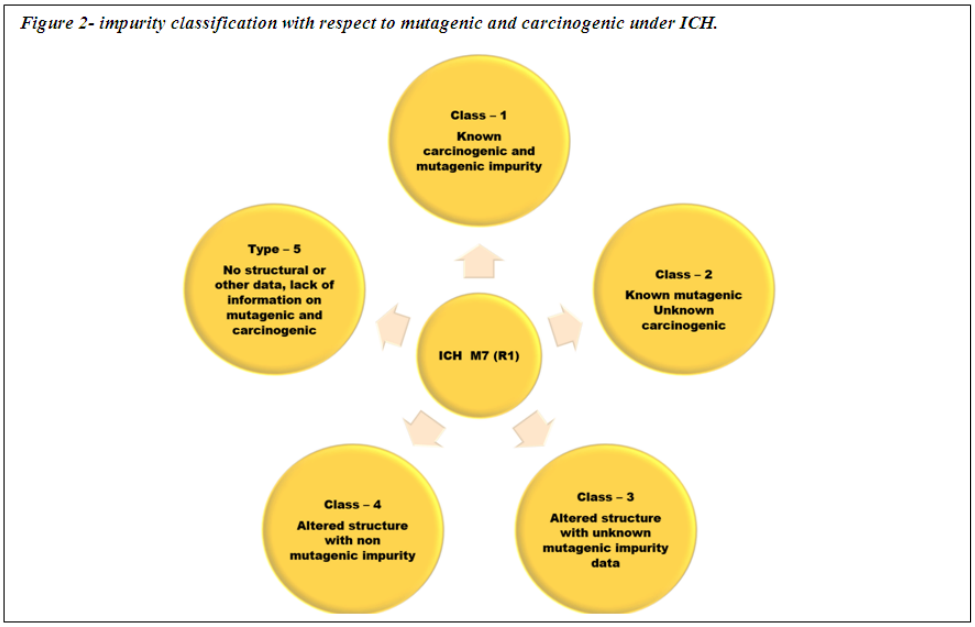
The USFDA recommendations tend to be close to the EMA Guideline, including the variety, proposed methods, and appropriate thresholds to diagnose and deal with these impurities. The guideline seeks to resolve defined and predicted API-related impurities and synthetic processes in clinical development and the marketing of new pharmaceutical products. The concern of impurities in NDA submissions that are arising by reformulating or incorporating new synthetic routes to create new impurities or comparatively high amounts of impurities. To detect significant impurities at an appropriate level, analytical approaches are recommended to compare the measured impurity level to the qualifying limits indicated in the related ICH Guideline [12]. Once the impurity is determined, the existence of warning structures or known implications should be tested for a genotoxic potential. If the warning structure is present, the link between impurities and the API should be regarded as regards the alert structure; common alert structures, in combination with negative genotoxicity results, will ordinarily be adequate for alleviating concern regarding impurity. However, it is understood that complete removal is often not possible and new synthetic routes can induce new impurities. An alternative way to eliminate impurity is to use process purification processes. Efforts to further decrease impurity levels should be continued during development, with significant increases in cancer risk depending on the stage of clinical development [13].

Various methods are available to provide adequate knowledge of potential or known genotoxic or carcinogenic impurities in safety qualifications. If carcinogenicity data can be collected, a risk evaluation can be carried out so that the conditions for approving the carcinogenic solvent are determined; ICH Guideline Q3C Annex 3 advises that this strategy should refer to Class 1 carcinogenic solvents. The testing should be carried out preferably with an isolated impurity to assess the genotoxic potential of impurity. However, testing for impurities that contain the contaminant load spiked APIs cannot meet product specifications before the tests have been conducted. The results of this evaluation pose a potential problem, as addressed in the US Federal Foreign Relations and Development Directive, concerning the proof of a threshold-related mechanism. As the guideline was intended to test the API, the same criteria could apply to impurity. To approve the marketing application compatible with the regular TTC intake, the threshold for impurity approvals can be decreased from 1.5 µg/day, where the dosage is expected to present a substantial carcinogenic or toxicological danger. The latest USFDA draft guideline, however, does include the suggested clinical development limits [14].

ICH Guidelines

Genotoxic and carcinogenic impurities can be widely defined as impurities which, regardless of the mechanism, have proved to cause deleterious modifications to genetic material (as defined in figure 2).

Figure 2- impurity classification with respect to mutagenic and carcinogenic under ICH.

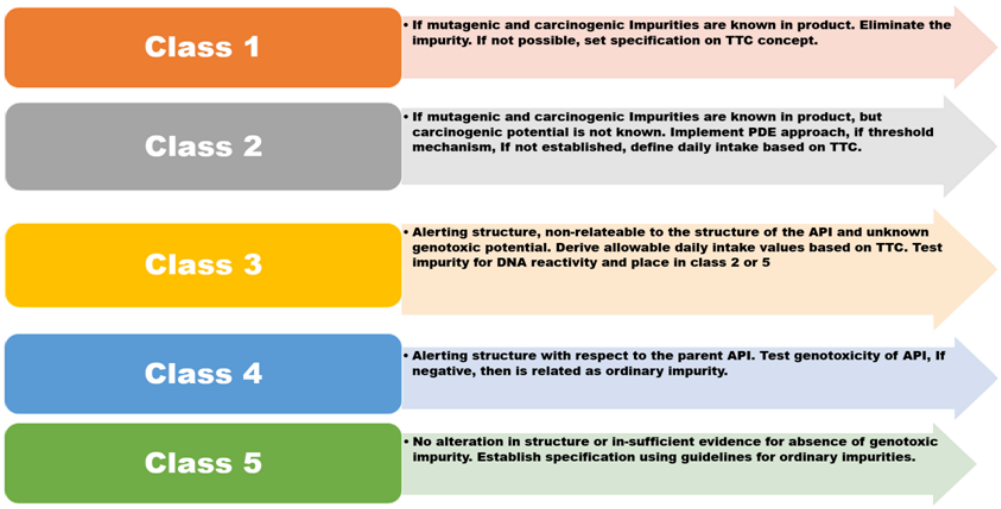


The major problem with genotoxic impurities is the synthesis of an active component, which often involves reactive raw materials which have the potential to interact with human DNA, even at the lowest level, to cause mutations and cancer. Genotoxic and carcinogenic impurities should therefore be avoided and reduced below a defined threshold if not possible. Genotoxic impurities guidelines broadly cover genotoxic impurity control, genotoxic testing and genotoxic and carcinogenic substance risk assessment [15].

PhRMA

Pharmaceutical Research and the American Manufactory (PhRMA) have introduced important concepts like five classifications and the step-by-step impurity threshold for short-term exposure in pharmaceuticals that have the potential for genotoxicity (as described in figure 3). A strategy for impurity assessment has been put forward by the classification system from PhRMA [16].

Figure 3 -The classification of five classes of impurity under PhRMA.



IDENTIFICATION, CLASSIFICATION, AND QUANTIFICATION OF IMPURITY

Identification of impurities in pharmaceutical industry are addressed from two prospective one is chemical which includes classification and identification of impurities and other is safety aspects it includes guidance and quantify the impurity. Impurities may occur due to various factors i.e., undesirable element, structural or unidentified. Impurities can be classified as organic, inorganic and residual. The below steps are defined for impurity identification.

Step 1: Examines the synthetic method for possible impurities in drugs and products, i.e., synthetic materials, reagents, intermediates, impurities, drug substances, and product degradants.

Step 2: Entails conducting a SAR assessment using in silico methods.

Step 3: Entails searching for structural warnings. If it is not detected, it is called a general impurity, and if it is found, it is moved on to the next level.

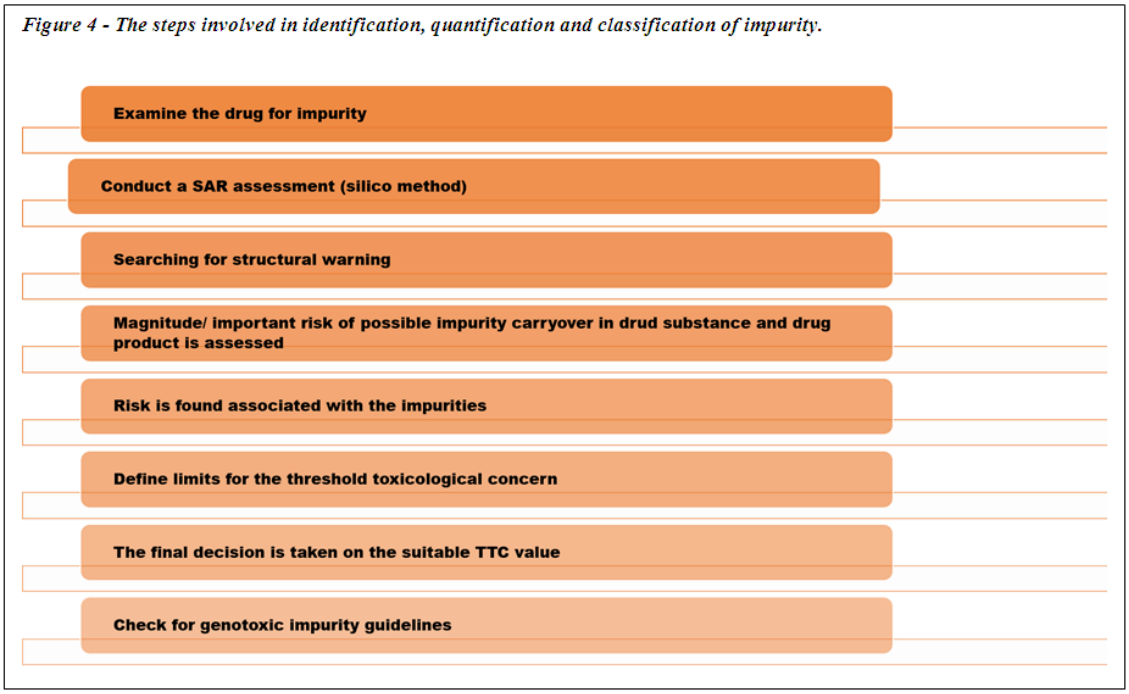
Step 4: In this step, the magnitude/importance of the risk of possible impurity carryover in drug substances and drug products is assessed. If insignificance is determined, no action is taken.

Step 5: If the risk is found to be important in step 4, quantification of the level of impurity is performed, or test safety testing is performed.

Step 6: The risk assessment is completed here based on the defined limits for the Threshold of Toxicological concern (TTC) in the guidelines. If it is determined that the substance is not genotoxic, it is classified as an impurity.

Step 7: The final decision is taken based on the suitable TTC values as defined by the genotoxic impurity guidelines (as described in Figure 4) [17].

Figure 4 - The steps involved in identification, quantification and classification of impurity.



Thus, if the level of genotoxic impurity is less than the TTC value, it is deemed appropriate for clinical use; if the level is greater, the technique is modified to achieve reasonable limits by alteration of the synthetic pathway and in vivo genotoxicity testing. Also, this strict multi-step rule has several exceptions, such as accepting higher TTC values for systemic warnings in cases of short-term exposure, life expectancy, or greater exposure from sources such as food. Thus, the existence of structural warnings is not the only determining factor for drug product elimination; we must also consider their reactivity profile, which categorizes them into three groups - (1) Extremely reactive. Epoxides, aldehydes, sulfonate esters, acyl halides, aziridines, and hydrazine are some examples. (2) Reactive in a moderate way. N or S, reactive acceptors, halo-alkenes, and primary halides are a few examples. (3) It is less reactive. Amino aryls, nitro compounds, purines or pyrimidines, and carbamates are some examples. The highly reactive class, which is vulnerable to attack by a diverse range of nucleophiles, deserves special consideration.

ANALYTICAL TECHNIQUES FOR DETECTION OF GTIS (GENOTOXIC IMPURITIES)

By splitting GTIs into two categories according to their volatility, analytical methodologies may be chosen. Because of the ease and availability of the technologies, nonvolatile GTIs ought to be analysed using high-performance liquid chromatography (HPLC) with UV detection. HPLC, on the other hand, may not be sensitive enough for some GTIs in low-level analysis. Because ultraperformance or ultrafast liquid chromatography (UPLC or UFLC) have increased UV-detector sensitivity, they can be employed if GTIs provide insufficient UV response Alternate detectors in HPLC include evaporative light scattering detector and conductivity detector. While establishing low-quantitation limits is difficult, connecting HPLC or UPLC with mass spectrometers (MS) enhances technique selectivity and accuracy dramatically. These detectors are sensitive, reducing interference difficulties in the sample matrix and thereby enhancing data quality. The use of multiple mass spectrometry (MS) detectors has provided a significant advancement in genotoxic impurity analysis. Due to their high high sensitivity and specificity, MS-based approaches often give more durability and ruggedness than techniques like UV alone [18].

Furthermore, volatile GTIs may be quantified using gas chromatography (GC) with a flame ionization detector (FID). The recommended approach for sample injection methods for GC–FID are split injection, splitless injection, direct injection, on-column injection. When GTIs include halogens, an electron-capture detector (ECD) can be utilized. NPDs (nitrogen–phosphorus detectors) is a new instrument for GTIs with nitrogen or phosphorus atoms. ECD and NPD, on the other hand, have restricted applicability. For low-level GTI analysis, the most sensitive and selective detection, as well as the lowest background noise, is provided by GC–MS, this approach is also less susceptible to interferences. If the GTIs are unstable, lack chromophores, and contain reactive functional groups, they can be solubilized to produce detectable species (hydrazine derivatizes with benzaldehyde to produce 1,2-dibenzylidenehydrazine, for example). The solubilizing reagent should be chosen based on the analyte's functional groups. *Gas Chromatography (GC) and GC-MS* for the investigation of a variety of genotoxic contaminants, such as sulfonates (Ethyl methane-sulfonate), halides, and epoxides, static

headspace gas chromatography and GC-MS are usually regarded to be the ideal approaches. Because it closely follows ICH Q3C criteria, the GC headspace technique is widely used in quality control laboratories across the world for residual solvent analysis. *Nuclear Magnetic Resonance (NMR)* offers extensive data on bonding and stereochemistry inside a molecule and has a wide range of applications. This is particularly imperative in the structural characterization of genotoxic contaminants and degradants, which are typically present in extremely small concentrations. NMR spectroscopy is a great method for the characterization of contaminants and degradants present at extremely low levels since it is non-destructive and non-invasive. NMR can also offer quantitative results, which is a crucial part of the process of profiling impurities [19]. *Inductively-Coupled Plasma Optical Emission Spectroscopy (ICP-OES) and Inductively-Coupled Plasma Mass Spectrometry (ICP-MS)* Metal contaminants may induce DNA mutations, and ICP-OES and ICP-MS are strong multi-element methods for analyzing them. The new draught elemental impurities process (USP<233>) stipulates those elemental impurities must be determined using an instrument-based approach, with reference techniques based on ICP-MS or ICP-OES. Sample analysis may be done in three different ways using both methods: immediately (unsolved), after sample preparation by solubilization in an aqueous or organic solvent, or after acid digestion utilizing a closed-vessel microwave system [20].

MANAGEMENT OF IMPURITIES

The formation, fate, and purge of impurities can be controlled through the production process. They can also be controlled by establishing appropriate controls at places where the substances or drugs are entered or formed during the manufacturing process. As set by ICH Q3A(R2) requirements, any type of API impurity at an identification threshold level higher than the identifying threshold must perform structural characterization studies, whether shown in any batch of the commercial process or any product of degradation observed in stability studies under the recommended conditions of storage. The impurities specified shall be listed with the unidentified impurities specified which are estimated to be present at a level greater than the threshold for identification. [21]

Following Methods Can Be Seen For Management Of Impurity

a. Confirm the degradation of the product's impurities, mostly impurities arise during synthesis, purification or due to storage.
b. Monitor and/or indicate the quantity of all product degradation.
c. Complete all manufacturing and stability studies of degradation products. Stress testing (ICH-Q1(A) on stability) are used ti identify impurity due to storage.
d. Evaluate and justify a rational evaluation or interaction with excipient or container closure systems of a potential degradation pathway of a drug product.
e. Specify all degradation products with the acceptable criterion not to exceed (to) identified, specified unidentified, specified degradation product (total quantity of) identified in Q3B (R2).
f. The method used in determining the degradation product specified and unspecified is validated by selectivity.
g. The European Medicine Agency (EMA, 2006), the FDA (2008), and the ICH (2017) have published and revised their regulations concerning genotoxic, mutagenic, and carcinogenic impurities.
h. Demonstrate DTI threshold mechanism above TTC level. Any impurity level greater than the threshold should be identified [22].

II. FUTURE OUTCOMES

In regulatory terms, the preclinical safety test must be carried out in every country according to the regulatory guidelines of that country. These processes are time-consuming, contain intensive processes, and require a large number of experimental animals. Most guidelines in the country are insufficient to conclude the new chemical entity's (NCE) genotoxic potential with a final exact conclusion. The delayed regulatory approval of NCE results in different pharmaceuticals, various designs, protocols, and critical experimental evaluation, and different directives of various regulatory agencies. There are no recommendations on specific test systems and test protocols and no guidelines for compounds that are genotoxic, however seemingly act according to non-DNA targets. There are no specific recommendations on the threshold and the organ-specific effects of the different genotoxic and tumorigenic compounds [23].

III. CONCLUSION

Nowadays, knowing the impurities present in APIs is a prerequisite in many pharmacopeia's. Impurities are to be isolated and characterized for the acquisition and evaluation of data providing biological security which demonstrates the need to profile medicinal impurities in pharmaceutical research and their scope. In contrast to the International Harmonization Conference Q3A/Q3B, genotoxic impurities may not be

necessary to prove drug-use safety by the genotoxicity test used to certify the product. While the main components of GTI regulatory guidelines have been in effect for many years, there is still significant scientific uncertainty on several important toxicological issues. Furthermore, the implementation of in silico techniques into the regulatory arena raises many crucial issues concerning the sufficient number of independent systems, data integrity, and the importance of expert interpretation. There are a variety of risk evaluation methods available for non-genotoxic and genotoxic carcinogens, and it is currently unknown which are more or less suitable. It is hoped that future ICH, USFDA, EMA, PhRMA guidelines will recognize such issues and allow for a variety of approaches as long as they are scientifically justified. Furthermore, the implementation of in silico techniques into the regulatory arena raises many crucial issues concerning the sufficient number of independent systems, data integrity, and the importance of expert interpretation. There are a variety of risk evaluation methods available for non-genotoxic and genotoxic carcinogens, and it is currently unknown which are more or less suitable. It is hoped that future guidelines will recognize such issues and allow for a variety of approaches as long as they are scientifically justified. Various instrumental analytical methods are widely used to isolate and measure impurities.

REFERENCE

[1]. D. Nath and B. Sharma, "Impurity Profiling-A Significant Approach in Pharmaceuticals," CPA, vol. 15, no. 7, pp. 669–680, Oct. 2019, doi: 10.2174/1573412914666181024150632.

[2]. M. N. Salunkhe, S. D. Gite, and R. N. Kachave, "Recent trends in impurity profiling and forced degradation of antihypertensive drugs," Journal of Liquid Chromatography & Related Technologies, vol. 40, no. 16, pp. 813–831, Oct. 2017, doi: 10.1080/10826076.2017.1373670.

[3]. Hartwig et al., "Mode of action-based risk assessment of genotoxic carcinogens," Arch Toxicol, vol. 94, no. 6, pp. 1787–1877, Jun. 2020, doi: 10.1007/s00204-020-02733-2.

[4]. M. Batke et al., "Threshold of Toxicological Concern—An Update for Non-Genotoxic Carcinogens," Front. Toxicol., vol. 3, Jun. 2021, doi: 10.3389/ftox.2021.688321.

[5]. D. H. Atha, E. Coskun, O. Erdem, A. Tona, V. Reipa, and B. C. Nelson, "Genotoxic Effects of Etoposide, Bleomycin, and Ethyl Methanesulfonate on Cultured CHO Cells: Analysis by GC-MS/MS and Comet Assay," Journal of Nucleic Acids, vol. 2020, pp. 1–10, Jul. 2020, doi: 10.1155/2020/8810105.

[6]. F. B. Sarmiento, J. A. Leigh, and W. B. Whitman, "Genetic Systems for Hydrogenotrophic Methanogens," in Methods in Methane Metabolism, Part A, Elsevier, 2011, pp. 43–73. doi: 10.1016/b978-0-12-385112-3.00003-2.

[7]. L. L. Pham, S. J. Borghoff, and C. M. Thompson, "Comparison of threshold of toxicological concern (TTC) values to oral reference dose (RfD) values," Regulatory Toxicology and Pharmacology, vol. 113, p. 104651, Jun. 2020, doi: 10.1016/j.yrtph.2020.104651.

[8]. U. B. R. Khandavilli, L. Keshavarz, E. Skořepová, R. R. E. Steendam, and P. J. Frawley, "Organic Salts of Pharmaceutical Impurity p-Aminophenol," Molecules, vol. 25, no. 8, p. 1910, Apr. 2020, doi: 10.3390/molecules25081910.

[9]. V. K. Ahirrao, R. A. Jadhav, V. P. Rane, H. R. Bhamare, and R. D. Yeole, "Time-dependent selected reaction monitoring-based GC-MS/MS method for estimation of genotoxic impurities in new antibacterial agent: alalevonadifloxacin mesylate," J Anal Sci Technol, vol. 11, no. 1, Jun. 2020, doi: 10.1186/s40543-020-00214-w.

[10]. European Medicines Agency guidelines for mutagenic impurities- Guidelines on assessment and control of DNA reactive.

[11]. P. Prajapati and Y. K. Agrawal, "Analysis and impurity identification in pharmaceuticals," Reviews in Analytical Chemistry, vol. 33, no. 2, Jan. 2014, doi: 10.1515/revac-2014-0001.

[12]. M. Kashoki et al., "A Comparison ofEMAandFDADecisions for New Drug Marketing Applications 2014–2016: Concordance, Discordance, and Why," Clin. Pharmacol. Ther., vol. 107, no. 1, pp. 195–202, Aug. 2019, doi: 10.1002/cpt.1565.

[13]. Feng et al., "Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis," Genes & Diseases, vol. 5, no. 2, pp. 77–106, Jun. 2018, doi: 10.1016/j.gendis.2018.05.001.

[14]. T. Nohmi, "Thresholds of Genotoxic and Non-Genotoxic Carcinogens," ToxicolRes, vol. 34, no. 4, pp. 281–290, Oct. 2018, doi: 10.5487/tr.2018.34.4.281.

[15]. Shaikh, "Genotoxic Impurities and Its Risk Assessment in Drug Compounds," DDIPIJ, vol. 2, no. 4, Oct. 2018, doi: 10.32474/ddipij.2018.02.000143.

[16]. P. Kushwaha, "Metallic Impurities in Pharmaceuticals: An Overview," CPA, vol. 17, no. 8, pp. 960–968, Jun. 2021, doi: 10.2174/1573412916999200711151147.

[17]. EFSA Scientific Committee et al., "Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment," EFS2, vol. 17, no. 6, Jun. 2019, doi: 10.2903/j.efsa.2019.5708.

[18]. W. C. Knol, B. W. J. Pirok, and R. A. H. Peters, "Detection challenges in quantitative polymer analysis by liquid chromatography," J. Sep. Sci., vol. 44, no. 1, pp. 63–87, Oct. 2020, doi: 10.1002/jssc.202000768.

[19]. E. E. Kwan and S. G. Huang, "Structural Elucidation with NMR Spectroscopy: Practical Strategies for Organic Chemists," Eur. J. Org. Chem., vol. 2008, no. 16, pp. 2671–2688, May 2008, doi: 10.1002/ejoc.200700966.

[20]. S. Wilschefski and M. Baxter, "Inductively Coupled Plasma Mass Spectrometry: Introduction to Analytical Aspects," CBR, vol. 40, no. 3, pp. 115–133, Aug. 2019, doi: 10.33176/aacb-19-00024.

[21]. M. Blessy, R. D. Patel, P. N. Prajapati, and Y. K. Agrawal, "Development of forced degradation and stability indicating studies of drugs—A review," Journal of Pharmaceutical Analysis, vol. 4, no. 3, pp. 159–165, Jun. 2014, doi: 10.1016/j.jpha.2013.09.003.

[22]. Amberg et al., "Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses," Regulatory Toxicology and Pharmacology, vol. 102, pp. 53–64, Mar. 2019, doi: 10.1016/j.yrtph.2018.12.007.

[23]. R POUNIKAR, M. J UMEKAR, and K. R GUPTA, "GENOTOXIC IMPURITIES: AN IMPORTANT REGULATORY ASPECT," Asian J Pharm Clin Res, pp. 10–25, Apr. 2020, doi: 10.22159/ajpcr.2020.v13i6.37370