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Regulatory Aspects in Assessment and Control of DNA Reactive (Mutagenic) Impurities in API's and Final Products to Limit Potential Cancer Risk as Per ICH M7

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Abstract
The ICH M7 guidelines for DNA reactive (mutagenic) impurities elaborate on the assessment and control of genetically damage-causing impurities in API and finished products. This suggested adopting the in-sillico (Q) SAR models and bacterial mutagenicity assays by industries and regulatory agencies for evaluation, as well as the acceptance of various control strategies to lower the risk of carcinogenic properties of substances. This paper discusses principles for evaluating and assessing such impurities that will support the path of regulatory submissions.

1. Introduction

Drug substance synthesis involves the use of reagents, solvents, catalysts, and other processing aids in addition to reactive molecules. All drug ingredients and related drug products contain impurities due to chemical reactions or subsequent degradation. While the bulk of impurities are qualified and controlled by ICH Q3A (R2): Impurities in New Drug Substances. The aim of this study is to reduce the possibility of cancer through practical qualification and control of these mutagenic impurities. [3]

1.1. MATERIAL AND METHODS:

The drug substance manufacturing process is expected to use one of the four procedures listed in the ICH M7 guidance document for the management of mutagenic and possibly mutagenic impurities (MI and PMIs). [1]

Software for computation. Computational study and modeling of the Leadscope were used to gather data on chemical structure. Version 3.0 of enterprise software is available at www.leadscope.com.Dublin, Ohio, Inc. with the aid of Leadscope Model Applier. QSAR models were run with certain technologies and software (version 1.3). The programme was accessible to the FDA/CDER via a research collaboration agreement that has been authorized by the agency. [1]

Database for drug impurities. For this study, a fresh database of well-known drug impurities was created in order to compare its chemical properties to those of the 3575 compounds used in the QSAR model. Gathered data is available on 1094 drug impurities from various public and private data sources. These data are from FDA from submitted Investigational New Drug and New Drug Applications, which include 561 proprietary drug impurities. The contaminants were collected and computationally examined by CDER within CDER/FDA. Impurities were unbiasedly and randomly acquired from FDA databases. [1]

Statistics. The statistical parameters for evaluating the QSAR model are estimates for validation. [2]

1.2. SCOPE

The focus of this article is on substances that can directly harm DNA when present in low concentrations, which can result in mutations and ultimately, cancer. The article aims to serve as an overview of the assessment and control of new pharmacological substances during their clinical development and subsequent marketing application processes. Additionally, it applies to post-approval submissions of marketed products and to fresh marketing submissions for APIs and

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products containing previously approved products, in both circumstances where [3]:

- New impurities are produced by changes in the drug substance's manufacture, or old impurities are accepted with certain standards;
- Degradation products originate from modifications to the formulation, composition, or manufacturing method, or old degradation products are accepted with certain standards.
- The acceptable cancer risk level is considerably impacted by changes in the indication or dose regimen.

In these circumstances, the drug substance's cancer risk would be increased by exposure to mutagenic impurities. Such Impurities could therefore be kept under control at non-mutagenic impurity levels at which they are acceptable. For impurities in chemically synthesized excipients used for the first time in a drug product, the safety risk assessment concepts can also be performed if required. [3]

2. Methodology

The substances that can directly harm DNA when present in low concentrations, can result in mutations and, ultimately, cancer. A bacterial reverse mutation (mutagenicity) assay is typically used to identify this sort of mutagenic carcinogen. Other kinds of Geno-toxicants that aren't mutagenic frequently have threshold mechanisms and don't typically pose a risk of cancer in people at the amount typically present as impurities. Thus, the bacterial mutagenicity assay is used to evaluate the mutagenic potential and need for controls in order to reduce any potential human cancer risk linked with exposure to potentially mutagenic contaminants. [3]

Based on the existing knowledge, structure-based assessments are beneficial for forecasting the results of bacterial mutagenicity. To identify an acceptable intake for any unstudied substance that carries a minimal risk of carcinogenicity or other harmful consequences, the Threshold of Toxicological Concern (TTC) idea was created. It was found that several structural groups had such high potencies that, potentially, intakes even below the TTC could be linked to a significant risk of cancer. Aflatoxin-like, N-nitroso, and alkyl azoxy chemicals make up this "cohort of concern" of highly potent mutagenic carcinogens. [3]

2.1. DRUG SUBSTANCE AND DRUG PRODUCT IMPURITY ASSESSMENT

Impurities that could actually occur in the synthesis as well as in the storage of a new drug molecule, as well as during the production and preservation of a new drug product, should be evaluated. Impurity evaluation is a two-step procedure [3]:

- It is crucial to take into consideration the mutagenic potential of identified impurities.
- A potential impurity's likelihood of being present in the finished drug substance is evaluated to see if more investigation of its carcinogenic potential is necessary.

The procedures applied to synthetic and degradation products are given as follows:

1) Synthetic Impurities :

Starting materials, reagents, and intermediates along the synthetic pathway from the starting material to the drug substance are all possible sources of impurities in the drug substance. For predictable impurities which are present in raw material and intermediates, as well as impurities that have been reasonably expected by-products in the mode of synthesis, its potential of carryover into the drug substance must be evaluated. A risk-based justification could be offered for the stage in the synthesis after which these types of impurities should be assessed for mutagenic potential because the risk of carryover may be negligible for some impurities. [3]

2) Degradation Products :

In addition to impurities that develop during the drug product's manufacturing process, actual degradation products in the drug product also include those that were seen during storage of the drug product above the ICH Q3B reporting threshold and during primary and secondary packaging. When the levels exceeds the identification limits specified by ICH Q3A/Q3B, detection of actual degradation products is expected. The drug substance and drug product's potential degradation products are those that could theoretically arise under long-term storage conditions. Products that arise above the ICH Q3A/B identification threshold in accelerated stability investigations under long-term storage circumstances in the primary packaging are possible examples of degradation products. (For

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example, 40°C/75% relative humidity for 6 months) and confirmatory photo-stability studies as described in ICH Q1B must be performed. [3]

2.2. HAZARD ASSESSMENT ELEMENTS

To designate impurities as Class 1, Class 2, or Class 5 according to Table 1, the initial examination of actual and probable impurities entails searching databases and literature for information on bacterial mutagenicity and carcinogenicity. An evaluation of Structure-Activity Relationships (SAR) which concentrates on predictions of bacterial mutagenicity should be carried out. This can result in classification as Class 3, 4, or 5. [3]

Table.1: Classification of Impurities Considering Carcinogenic Potential and Corresponding Control Measures [3]

Class	Definition	Proposed action for control
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

2.3. RISK CHARACTERIZATION

Each impurity will be categorized into one of the five classes in Table as a result of the hazard assessment, which are as given below:

2.3.1. TTC-based Acceptable Intakes

The TTC-based acceptable intake of a mutagenic impurity of 1.5 g per person per day is associated with a negligible risk (theoretical excess cancer risk of 1 in 100,000 over a lifetime of exposure) and can, in general, be used as a default for most pharmaceuticals to derive an acceptable limit for control. [3]

Table.2: Acceptable Intakes for an Individual Impurity [3]

Duration of treatment	< 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

2.3.2. Acceptable Intakes for Multiple Mutagenic Impurities

Total mutagenic impurities should be kept to a minimum for clinical development and marketed products when three or more Class 2 or Class 3 impurities are listed on the drug substance specification. Each active ingredient must be controlled individually for combination products. [3]

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Table.3. Acceptable Total Daily Intakes for Multiple Impurities [3]

Duration of treatment	< 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Total Daily intake [µg/day]	120	60	30	5

2.3.3. Marketed Products

In some instances, a portion of the patient population may get treatment for a longer period of time than the marketed drug's categorical upper limit (for example, treatment lasting more than ten years for an acceptable intake of 10 g/day, possibly 15 years of treatment). For the majority of patients who were treated for 10 years, this would result in a small increase (in the case given, a fractional increase to 1.5/1,00,000) in overall calculated risk. [3]

2.4. LIFECYCLE MANAGEMENT:

Over the lifecycle of a drug substance or product, development and improvement of the manufacturing process typically continue. The performance of the manufacturing process, particularly the efficiency of the control strategy, must be assessed on a regular basis. After any change in the manufacturing process of a drug substance, a proper assessment should be performed to check the product's mutagenicity. The structural characterization of an impurity may also result from advancements in analytical techniques. The revised structure would then be evaluated in those situations. The process must be tracked for better suitability and capability of the product. Even if that impurity is not regularly monitored, control of the statistical process can be based on process variables that affect impurity growth or clearance (e.g., Option 4). [4]

2.5. DOCUMENTATION:

2.5.1. Clinical Trial Applications

A summary of steps taken to reduce the probability of mutagenic impurities with a focus on Class 1 and 2 impurities and those within the cohort of concern as described in ICH M7(Section 7) should be provided for Phase 1 trials lasting 14 days or less. Class 3 impurities with the need for analytical controls should also be included in Phase 1 clinical trials lasting more than 14 days and Phase 2a clinical trials. A list of the impurities evaluated by (Q) SAR should be included for Phase 2b and Phase 3 clinical trials, and any Class 1, class 2 or Class 3 actual or potential impurities must be documented together with strategies for control. It is important to describe the in-silico (Q) SAR studies that were used to conduct the evaluations. Results of actual impurity tests on bacterial mutagenicity should be presented. [4]

2.5.2. Common Technical Document (Marketing Application)

The classification of mutagenic impurities and the justification for this classification should be provided for actual and potential process-related impurities. This would comprise the outcomes and an explanation of the in-silico (Q) SAR systems that were applied, as well as any relevant supporting data, to reach the general conclusion for Class 4 and 5 impurities. When bacterial mutagenicity testing on impurities was conducted, study reports on bacterial mutagenicity assays for impurities should be submitted. [4]

Case examples of potential control approaches:

Case 1: Example of a Control Strategy for Option 3

Two steps away from the drug substance, an intermediate X is formed, and impurity A is frequently found in intermediate X. The drug material also contains this stable compound, impurity A. At the laboratory scale, a spike analysis of impurity A at various concentration levels in intermediate X was carried out. These experiments showed that even when impurity A was present at 1% in intermediate X, impurity A was consistently eliminated from the drug material to less than 30% of the TTC-based limit. [4]

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This intermediate X is formed only two steps away from the drug substance, and the impurity level in intermediate X is relatively high. The purging ability of the process has also been confirmed by determining impurity A in the drug substance in multiple pilot-scale batches, with results that were below 30% of the TTC-based limit. As a result, it is appropriate to manage impurity A in intermediate X with an acceptability limit of 1.0%, and no test for this impurity is required by the drug substance specification. [4]

Case 2: Example of a Control Strategy for Option 3 Based on a Spiking Study's Predicted Purge and Standard Analytical Techniques

A starting material Y is added in step 3 of a 5-step synthesis, and a standard analytical technique consistently detects an impurity B in the starting material Y at less than 0.1%. In a purge study at laboratory scale, impurity B was spiked into starting material Y at varying concentration levels up to 10%, and a purge factor of > 500 fold was calculated over the last three processing steps to establish whether the 0.1% specification in the starting material is acceptable. This purge factor would yield a predicted level of impurity B in the drug substance of lower than 2 parts per million (ppm) when applied to a 0.1% specification in starting material Y. The 0.1% specification of impurity B in starting material Y is justified since it is below the TTC-based limit of 50 ppm for this impurity in the drug substance, hence there is no need to provide batch data on pilot-scale or commercial-scale batches of the drug substance. [4]

Case 3: An example of a control strategy for Option 4: Extremely Reactive Impurity

Thionyl chloride is Mutagenic and extremely reactive substance. In the first stage of a five-stage synthesis, this reagent is introduced. Water is used in substantial volumes throughout the synthesis. There is no possibility of any residual thionyl chloride being present in the drug substance because thionyl chloride reacts with water instantly. Without any laboratory or pilot scale data, an Option 4 control strategy is suitable. [4]

3. Conclusion:

According to ICH M7 (R1), mutagenic impurities must be identified, evaluated, and controlled as a significant component of the overall impurities control strategies for pharmaceuticals produced through chemical synthesis. Depending on the stage in the synthesis where the mutagenic impurity is introduced, the quantity of MI observed, and purging tests that demonstrate the efficacy of Mutagenic impurity removal, a variety of control techniques are available in ICH M7 (R1). In order to ensure that current Mutagenic impurities are still regulated and new MIs are not introduced without proper controls, evaluations need to be done as changes to the synthetic route or process are made during the lifecycle management of the medications. Another area that will make progress is the incorporation of MI specifications in pharmacopeial standards. With all of these efforts, it is believed that risk-based assessments of patient safety will prevent the introduction of new MIs without the necessary controls.

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