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An Overview and Discussion of Azido Impurities and their Risk Assessments in Drug Substances and Drug Products

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Azido impurities are known to be mutagenic and carcinogenic. A small exposure to these impurities may lead to cancer. These impurities may be formed and get incorporated into drug substances or drug products through reagents, catalysts, solvents, or raw materials used in the process of manufacturing drug substances. Various regulatory authorities have published press releases and notices regarding the control of these impurities with the interim limit. Azido impurities can be avoided by taking precautions during the manufacturing of drug substances and products. The methods used to identify and quantify these impurities require highly sensitive instruments such as LCMS/MS or GCMS, which can detect these impurities to a trace level within the given interim limit. These methods are validated according to various regulatory guidelines. Liquid chromatography, along with a mass detector, is mostly used for their determination.

Keywords: Impurities; Azido; classification; guidelines; drug substances; drug product.

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1. INTRODUCTION

"The European Directorate for the Quality of Medicines and Health Care (EDQM) first reported in April 2021 that they had received information about the possible presence of potentially mutagenic azido impurities in certain angiotensin II receptor blockers (ARBs) or 'Sartans' class medicines, which are used to treat patients with hypertension (high blood pressure) and heart failure. This announcement leads to the voluntary recall of hundreds of batches of these generic versions by pharmaceutical companies distributed worldwide" [1]. Similarly, in May 2021, Health Canada alerted the public that multiple drugmakers were recalling Irbesartan, Losartan, and Valsartan lots after tests found an azido impurity above the acceptable limit [2-4].

Azido impuriteis compounds have an azide functional group, which is a linear, polyatomic anion consisting of three nitrogen atoms with the formula N_3. Its structure can be represented as $^{-}N{=}N^{+}{=}N^{-}$. Organic azides are organic compounds having the azido functional group attached to the organic compound (R) which is represented as RN_3. This R may be alky, alkene, acetyl, aryl, cyclic or any other organic compound (Fig. 1).

1.1 Classification

Azido impurities may be mutagens, which are chemical substances that can impact genetic material through mutations caused by chromosomal breaks, rearrangements, covalent binding, or insertion into DNA during replication. Long-term exposure to azido impurities above the TTC (Threshold of Toxicological Concern) level also has the potential to increase the risk of cancer. Studies have confirmed that azido impurities are mutagenic. However, initial toxicological assessments indicate that they pose a significantly lower health risk compared to nitrosamines. As azido impurities are mutagenic, they can be classified in Class 3 as per ICH M7 (R2) and should be controlled at or below the acceptable TTC limit [5]. Therefore, it is important to identify azido impurities in drugs at very trace levels to ensure drug safety.

1.2 Metabolism

Azide compounds are metabolized in the body through highly reactive intermediate nitrene, which can add across double bonds to form aziridine (Fig. 2). The International Agency for Research on Cancer (IARC) has classified aziridine as a Group 1 carcinogen, meaning that it is a known human carcinogen. Thus, azide can lead to cancer by causing DNA damage. Azide compounds have been shown to react with DNA molecules, leading to mutations and other types of damage. This can disrupt the normal functioning of cells and lead to uncontrolled growth, which is a hallmark of cancer. Additionally, some azide compounds have been shown to interfere with the activity of enzymes that are important for DNA repair. This can result in the accumulation of DNA damage and increase the risk of cancer. Finally, some azide compounds can act as mutagens, meaning that they can increase the rate of mutations in DNA and thus increase the risk of cancer [6].

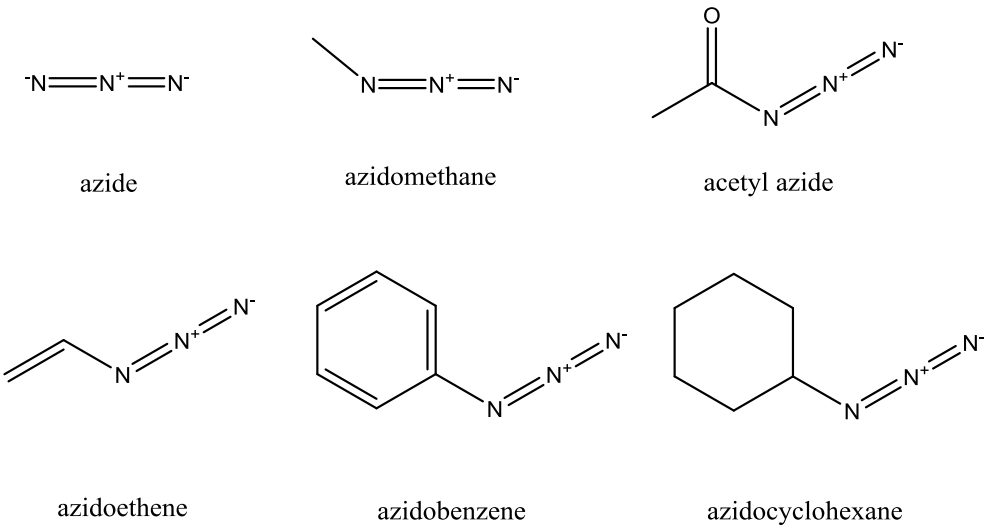


Fig. 1. Structures of some azido compounds

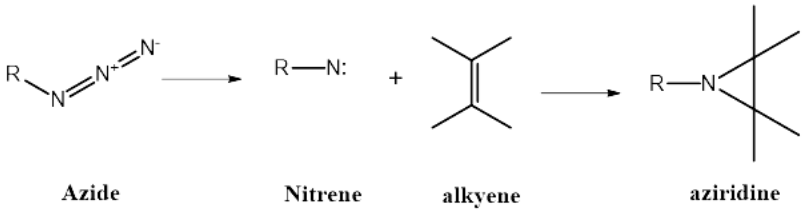


Fig. 2. Metabolism of Azido impurities

2. SOURCES OF AZIDO IMPURITIES

"Azido impurities can be incorporated into the drug substance and drug product through various pathways, including process formation, direct introduction, degradation, or cross-contamination. The manufacturing of drug substances involves the use of raw materials, intermediates, solvents, chemicals, and reagents" [7]. During these stages, if azido impurities are formed or present, they may get incorporated and carried forward into drug substances and drug products (Fig. 3). The following are some potential sources of azido impurities.

2.1 Starting Material, Reagents and Catalyst

Azides are highly reactive compounds that have been used for a long time in the synthesis of heterocycles that are building blocks of drug substances, especially triazole rings in sartan drugs. Hence, the use of these organic azides can introduce azido impurities into drugs. Examples of such azides include Methyl azide, Benzyl azide, Tosyl azide, Phenyl azide, Cinnamoyl azide, Azidotrimethylsilane, Benzenesulfonyl azide, and Diphenyl phosphoryl azide. In addition to this, inorganic azides such as Sodium azide (NaN_3), Potassium azide (KN_3), Lithium azide, and Hydrazoic acid (HN_3) are used as reagents or catalysts in the synthesis of organic compounds, which may get contaminated with azido impurities. These impurities, present in the starting materials, can affect their reactivity and safety [8].

2.2 Intermediates

Azides are versatile intermediates in organic synthesis and can be used to synthesize a wide range of compounds. Azides can be reduced to primary amines, which are important building blocks for many organic compounds. They can also be used to form amides, which are important components of peptides and proteins. Azides can also undergo cycloaddition reactions with alkynes to form 1,2,3-triazoles, which are important building blocks for the synthesis of many pharmaceuticals. Additionally, azides can be used to synthesize heterocyclic compounds, such as quinolones, pyridines, and azoles, which have a wide range of biological activities.

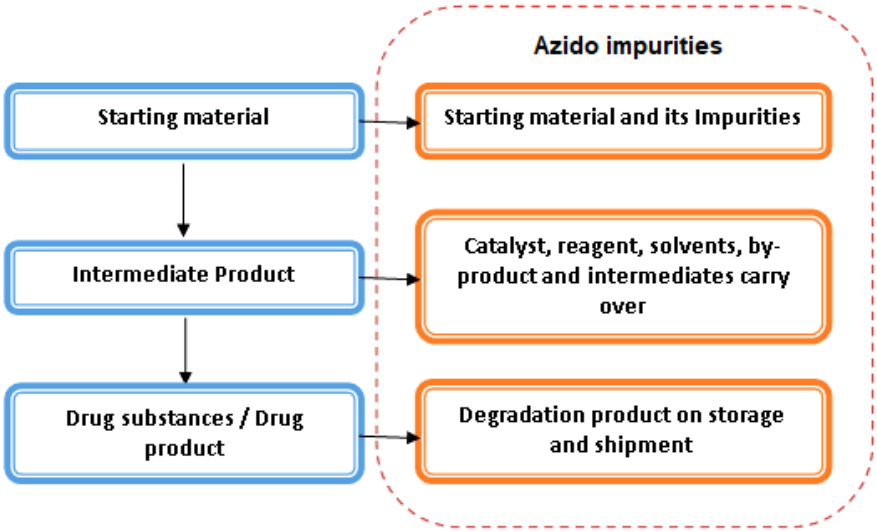


Fig. 3. Sources of Azido impurities

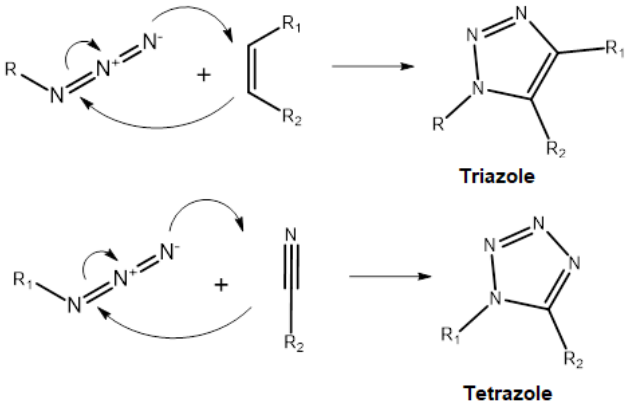


Fig. 4. Formation of triazole and tetrazole rings from azides

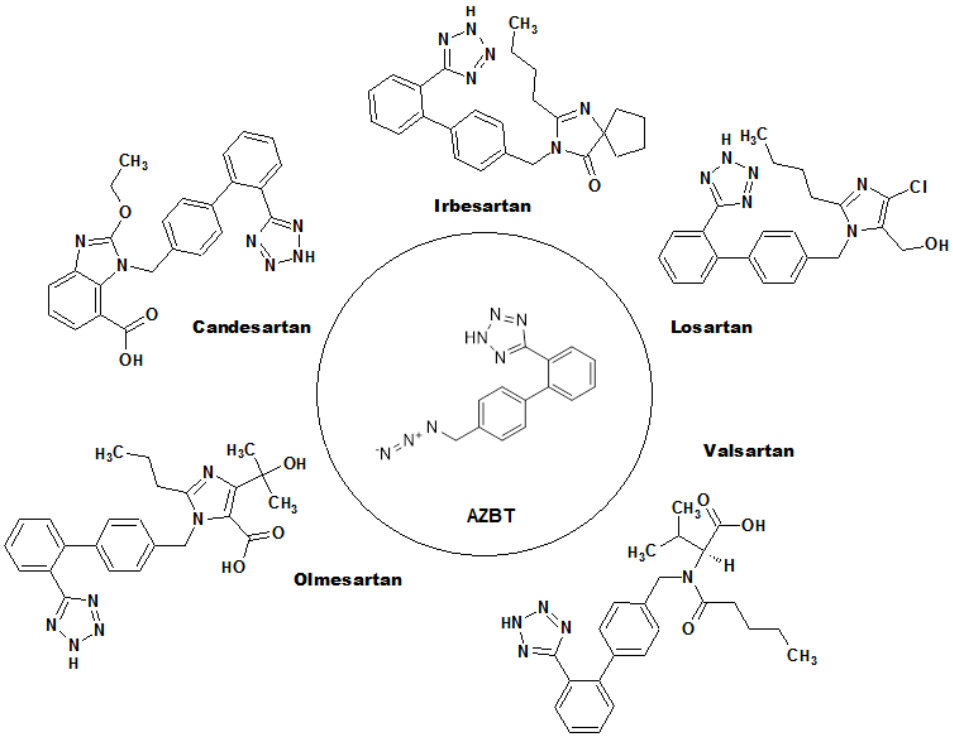


Fig. 5. Structure of sartan drug and AZBT impurity

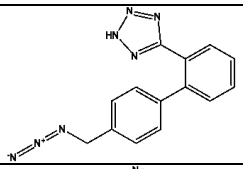
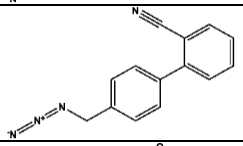
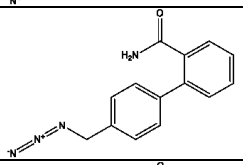
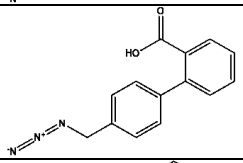
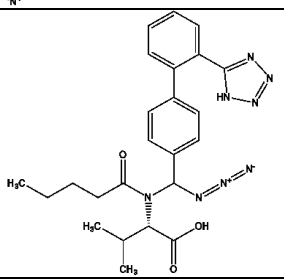
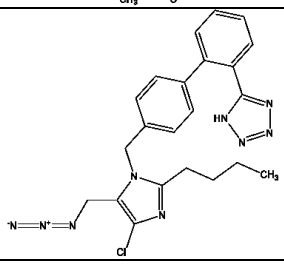
Due to dipolar character of organic azides, they are mostly used in the preparation of triazole and tetrazole rings through the Huisgen cycloaddition reaction, also known as click chemistry reactions, where azide reacts with unsaturated bonds such as alkene, alkyne, or nitriles to form triazolines, triazoles, and tetrazole rings (Fig. 4). This is the most popular tool in drug synthesis due to its high efficiency, mild reaction conditions, and tolerance of a wide range of functional groups. The use of azide reactants, may lead to azide process impurities in intermediate and drug substances [9].

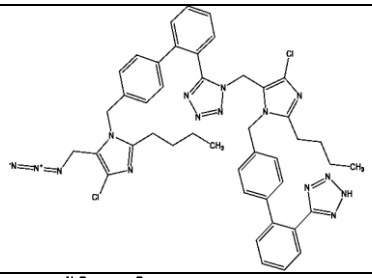
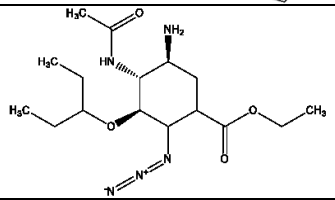
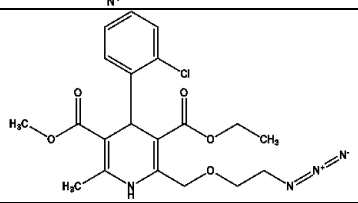
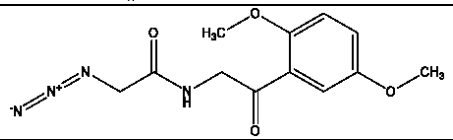
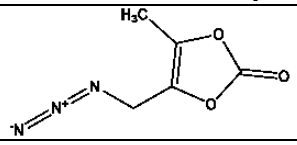
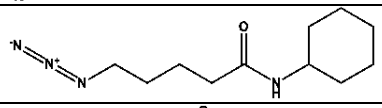
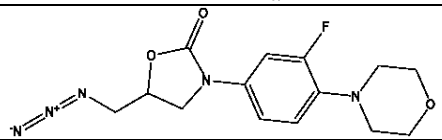
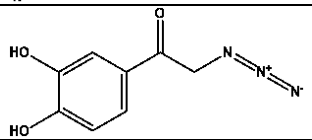
One of the azido impurities, 5-[4'-(Azidomethyl)[1,1'-biphenyl]-2-yl]-2H-tetrazole, also known as azidomethyl-biphenyl-tetrazole (AZBT), can form during the manufacturing of the active ingredient in some sartan drugs such as olmesartan, Losartan, Irbesartan, Valsartan, and Candesartan (Fig. 5).

2.3 Drug Substance and Drug Products

Starting materials, reagents, catalysts, and side products are major sources of azido impurities in drug substances. Besides this, azide impurities that can also be formed as a result of the degradation or decomposition of a substance during storage or handling also pose a risk in drug substances. Azido compounds are used as cross-linking agents in the manufacturing of certain polymers, such as polyethylene and polypropylene, which are used as packaging materials; hence, these impurities may get incorporated from packing materials into drug substances or drug products. Inks, dyes, and colours used in the manufacture of drug products should be free from azido compounds. Azides may be present in plasticizers or other additives that are used in the production of pharmaceutical packaging materials. Azide impurities can originate from the use of azide-containing chemicals in the production of packaging materials such as rubber stoppers, gaskets, and seals. For example, azide-containing blowing agents may be used in the production of rubber stoppers and gaskets to create the desired properties, such as elasticity and flexibility. If these azides are not fully removed during the manufacturing process, they can contaminate the final product and cause potential safety issues.

Table 1. Drugs and corresponding azido impurities

Azido impurity (Drugs)	Structure
5-[4'-(Azidomethyl)[1,1'-biphenyl]-2-yl]-2H-tetrazole (AZBT) **(Sartans)**	
4'-(azidomethyl)-[1,1'-biphenyl]-2-carbonitrile (AZBC) **(Sartans)**	
4'-(azidomethyl)-[1,1'-biphenyl]-2-carboxamide (AZBX) **(Sartans)**	
4'-(azidomethyl)-[1,1'-biphenyl]-2-metanoic acid (AZBA) **(Sartans)**	
N-((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)(azido)methyl)-N-pentanoyl-L-valine **(Valsartan)**	
5-[4'-[(5-(azidomethyl)-2-butyl-4-chloro-1H-imidazol-1-yl)methyl]-[1,1'-biphenyl]2-yl]-1H-tetrazole **(Losartan)**	

Azido impurity (Drugs)	Structure
1-((1-((2'-(2H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methyl)-5-(4'-((5-(azidomethyl)-2-butyl-4-chloro-1H-imidazol-1-yl)methyl)-[1, 1'-biphenyl]-2-yl)-1H-tetrazole (Dimer azido impurity) **(Losartan)**	
(3S,4R,5S)-Ethyl 4-acetamido-5-amino-2-azido-3-(pentan-3-yloxy)cyclohexanecarboxylate **(Oseltamivir)**	
2-[(2-Azidoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl)-6-methyl-1,4-dihydropyridine **(Amlodipine)**	
2-azido-N-(2-(2,5-dimethoxyphenyl)-2-oxoethyl)acetamide **(Midodrine)**	
4-(azidomethyl)-5-methyl-1,3-dioxol-2-one (**Olmesartan**)	
5-azido-N-cyclohexylpentanamide **Cilostazol**	
5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one **(Linezolid)**	
2-azido-1-(3,4-dihydroxyphenyl)ethan-1-one **(Norepinephrine)**	

3. REGULATORY PERSPECTIVE

3.1 Food Drug Administration (FDA)

The US Food and Drug Administration (FDA) has not yet issued any guidelines regarding acceptable levels of azido impurities in pharmaceuticals. The FDA requires that the level of mutagenic impurities in pharmaceuticals be controlled to levels below the acceptable daily intake (ADI). The FDA has also stated that manufacturers of pharmaceuticals should take steps to minimize the presence of azido impurities in their products.

3.2 European Medicines Agency (EMA)

EMA (European Medicines Agency) and EDQM (European Directorate for the Quality of Medicines) are regulatory bodies responsible for the evaluation and supervision of medicines in Europe. The general information on the possible presence of azido impurities was made public in April 2021. Since then, various measures have been taken to ensure that any drug substance

containing azido impurities above the acceptable level will not be released into the market. EMA states that CEP holders should provide the appropriate information relating to the risk identification they have performed for their CEP to their customers. The marketing authorization holders will then be able to use this information to fulfil their legal responsibilities. CEP holders were requested to take corrective action. In the absence of additional information from in vivo studies for azido impurities, the EDQM stresses the necessity to ensure that this mutagenic azido impurity is controlled at or below the threshold of toxicological concern (TTC) as outlined in ICH M7 for known mutagens with unknown carcinogenic potential (class 2) via a suitable control strategy.

3.3 Other Regulatory Agency

Therapeutic Goods Administration (TGA) of Australia: Manufacturers are required to follow these guidelines when developing and manufacturing drugs. They must demonstrate that their products are within acceptable limits for azido impurities before they can be approved for use in Australia. If a drug is found to have excessive levels of azido impurities, the TGA may take regulatory action, such as issuing warnings, recalling the product, or revoking its approval. TGA also had a database called the System for Australian Recall Actions (SARA), which provides information related to recall actions occurring in Australia for azido impurities.

ANVISA is the Brazilian regulatory agency responsible for the regulation and supervision of pharmaceutical drugs in Brazil. It requires that pharmaceutical companies conduct tests to identify and quantify azido impurities in their products, and pharmaceutical companies are required to meet these standards. ANVISA also requires that pharmaceutical companies report any detected impurities to the agency, including azido impurities, and take appropriate corrective measures to ensure the safety and efficacy of their products.

Health Canada holds manufacturers responsible for the safety and effectiveness of drugs sold in the Canadian market and has taken several actions to mitigate the risk to Canadians. According to Health Canada, manufacturers should take appropriate steps to minimize the presence of azido impurities in their drug products. This includes identifying potential sources of azido impurities in raw materials, intermediates, and final products, and implementing appropriate control measures to prevent their formation or remove them if they are present.

4. LIMITS AND ACCEPTABLE INTAKE

Azido impurities are classified as Class-2 impurities as per the ICH guideline due to their known mutagenicity and unknown carcinogenicity data. In the absence of additional information from in vivo studies, azido impurities should be controlled at or below the threshold of toxicological concern (TTC), according to which 1.5 µg per day intake is acceptable for a mutagenic impurity according to the ICH M7 guideline [10]. Considering the maximum daily doses for various sartan drugs, limits for AZBT impurity are calculated and tabulated below (Table 2).

Table 2. Limit for AZBT in sartans drugs

Active substance	AZBT	
	Maximum daily dose	Limit
Candesartan	32 mg	46.8 ppm
Irbesartan	300 mg	5.0 ppm
Losartan	150 mg	10.0 ppm
Olmesartan	40 mg	37.5 ppm
Valsartan	320 mg	4.68 ppm

5. REVIEW OF THE MANUFACTURING PROCESS

Presently, there is no template for evaluation, but most manufacturers are following the same template as that for nitrosamine issued by the European Medicines Agency (EMA) for marketing authorization holders. The following steps are required by the manufacturer to control the assessment of azido impurities in human medicinal products [1].

5.1 Step 1: Risk Evaluation

The marketing authorization holder, along with the drug substance and drug product manufacturer, should perform a risk evaluation of azido impurity as per ICH Q9 and ICH M7 guidelines The risk evaluation should be conducted in a priority manner, i.e., the highest probability of contamination should be evaluated first. Authorities must be informed about the evaluation results. If a risk of potential contamination has been detected, the marketing

authorization holder should proceed to step 2 as below.

5.2 Step 2: Confirmatory Testing

After risk evaluation, confirmatory testing activity should start immediately. A product with high risk must be analytically tested as soon as possible for azido impurities using validated methods that are appropriately sensitive. Similarly, confirmatory testing of all the concerned drug products should be concluded. If Azido impurities are detected, the competent authorities are to be informed immediately, irrespective of the amount detected.

5.3 Step 3: Changes to the Marketing Authorization

Changes to the marketing authorization, such as a change in the manufacturing process of a drug substance or drug product specifications, are to be applied for in a timely manner. If there is a risk to public health, the competent authorities must be informed immediately. All steps must be completed within three years in a prioritised manner.

6. CONTROL OF AZIDO IMPURITY

Thus, the following precautions may lead to minimizing these azido impurities in human medicinal products [11].

- Contaminated raw materials, intermediates, and reagents used in drug substance manufacturing may be potential sources of azido; hence, high-quality raw materials that are well-characterised and tested for possible azide impurities should be used.

- During the development of the process, reaction conditions should be optimized for parameters such as temperature, pressure, and reaction time for each step to minimize the formation of azido impurities.

- Monitor the process using chromatographic techniques such as HPLC or GC to detect and control azido impurities during the manufacturing process.

- Use a purification system during the manufacturing process so that azido impurities can be purge out.

- Azide reagents, are considered antecedents in the generation of azido impurities when they react with alkenes and alkynes used within the same or different steps in the manufacturing of drug substances. Thus, azide reagents and compounds need to be avoided in the manufacturing process.

- Recovered solvents should be avoided, as purged azido impurities may be reintroduced in the synthesis process.

- Similarly, recovered catalysts may contaminate the drug with azido impurities if reused.

- Equipment used for the manufacturing of drug substances may be cross-contaminated with azido impurities due to previous products. Equipment should be properly cleaned and checked for azido impurities contamination.

- Azido impurities, if present, should be controlled with a proper limit in intermediate stages or final drug substances or drug products as per the ICH M7 guideline.

- If Azido impurities observed are above the specified limit, the manufacturer should modify the process to purge out residual azide impurities at various stages.

- The degradation products of raw materials and intermediates in the presence of traces of azides on storage may lead to the formation of Azido impurities. Hence, these materials should be properly stored and tested for Azido impurities in stability samples.

Overall, it can be concluded that Azido impurities in finished products can be very effectively controlled by selecting the synthesis path that minimizes the formation of these impurities and also observing and implementing strict GMP requirements such as cleaning of equipment; Control of the recovery process for solvents may also lead to removing and limiting the Azido impurities in drug substances and drug products.

7. ANALYTICAL METHODS

"Similar to Nitrosamine, the development of analytical methods to determine azido impurities is a challenging task due to the very low levels of impurities present in the complex matrices. The basic task in the development of an analytical method for azido impurities is to develop methods that can detect and quantify these impurities at or below the acceptable limit. Advanced and sophisticated techniques such as LCMS/MS or GCMS are used for the detection of azido impurities. The developed analytical methods need to have less variability by conducting a series of controlled experiments to make quality and safe drug products. As regulatory requirements have become more stringent, analytical methods must be able to meet all the requirements. The developed methods also need to be validated to conform to GMP requirements. The developed analytical methods are validated with specificity, linearity, precision, accuracy, ruggedness, robustness, and forced degradation parameters in accordance with the ICH Harmonized Tripartite Guidelines" [12].

Several methods have been published by the instrument manufacturer to cover various azido impurities in in different 'sartans'. The EMA has indicated the extension of measures to include more azido along with various instrument manufacture such as Shimadzu, Thermo, Agilent and Waters.

Other regulatory authority Taiwan FDA have developed and published the analytical methods for testing azido in drug substances and drug products (Sartans) utilize chromatographic techniques such as reversed-phase liquid chromatography (LC) combined with mass spectrometry (MS) detector.

The German OMCL (Official Medicines Control Laboratories) at the LGL in Bavaria and the Swissmedic OMCL has developed and published analytical methods for determination of azido impurities [13-16].

Some of methods are tabulated below in Table 3.

These published testing methods serve as a starting point for the development and validation of analytical methods appropriate for other drug substances and drug products. The FDA says that these methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product or if the results are used in a regulatory submission.

Table 3. Published analytical methods for testing Azido impurities

Source	Technique	Ionisation	Impurity	Sample
Arabian Journal of Chemistry	LC-MS/MS	Triple quad	AZBC, AZBT, and AZTT	Losartan, Irbesartan &Olmesartan
Swissmedic	LC-MS/MS	Triple quad	AZBC & AZBT	Sartans drug substances
Thermo	LC-MS/MS	Triple quad	AZBT	Six sartan drug products
LGL	LC-MS/MS	Triple quad	AZBT	Valsartan, Irbesartan, Candesartan and Losartan
Taiwan FDA	LC-MS/MS	Triple quad	AZBT	Candesartan, Irbesartan, Losartan, Olmesartan, & Valsartan
Taiwan FDA	HPLC	UV/PDA	AMBBT	Losartan
Shimadzu	LC-MS/MS	Triple quad	AZBT & AMBBT	Olmesartan, Irbesartan, Candesartan, Valsartan, and Losartan
Shimadzu	LC-MS/MS	Triple quad	AZBT	Irbesartan, Valsartan, and Losartan
Shimadzu	LC-MS/MS	Triple quad	AMBBT, AZBC AZBT & AMBBC	Irbesartan

7.1 Analytical Method Validation

"A very general definition of validation is establishing documented evidence that provides a high degree of assurance that a specific procedure, process, equipment, activity, or system will consistently produce a product meeting its predetermined specifications and quality attributes. Validation is an important feature after the development of any analytical method because it is closely related to the quality of the results" [1]. "All analytical methods, whether qualitative or quantitative, are required to be validated. The degree of validation varies depending on the type of method and its application. For several years now, method validation studies, guidelines, and procedures have focused mainly on quantitative methods of analysis. Validation is an imperative activity in the process of impurity profiling where the developed analytical method used for the determination of genotoxic impurities in drug substances is validated in order to establish that the method is suitable for its intended purpose. The analytical methods are validated with specificity, linearity, precision, accuracy, ruggedness, robustness, and forced degradation parameters in accordance with the ICH Harmonised Tripartite Guidelines" [17-20].

8. CONCLUSION

Mutagenic and carcinogenic azido impurities need to be limited to the acceptable limit in drug substances and drug products. Potential sources of azido impurities such as raw materials, reagents, catalysts, solvents, and cross-contamination used in manufacture should be identified to control them in drug substances. Medicine regulatory authorities such as the FDA, EMA, TGA, and Health Canada need to have published several public notices to guide the manufacturer in controlling and limiting these impurities to acceptable intake levels. Regulatory authorities have also issued templates for marketing authorities to assess the azido impurities in human medicinal products. Azido impurity formation can be avoided by selecting proper reagents, catalysts, and solvents in the manufacturing of drug substances. The analytical method used for the determination and quantification of azido impurities is by LC or GC using mass spectroscopy. To determine these impurities at very low levels, these procedures must be thoroughly designed and validated in accordance with ICH requirements.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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