**Questionnaire for Risk Assessment of the Presence of Nitrosamine in Raw Materials Used in the Manufacture of Medicines**

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| --- | --- |
| **Material Comercial Name** | **Click here to enter text.** |
| **Material Type / Generic Name** | **Click here to enter text.** |
| **Manufacturer Name** | **Click here to enter text.** |
| **Production Site Address** | **Click here to enter text.** |
|  | |
| **Nitrosamines are substances classified as probable cancer-causing agents in humans. In 2018, the presence of these substances was detected in various blood pressure medicines known as "sartans" and, in 2019, impurities of the same type were detected in batches of the active pharmaceutical ingredient ranitidine.**  **Therefore, in alignment with health authorities of several countries, ANVISA (Brazilian Health Authority) recommends a reassessment of the synthesis routes of raw materials used in the manufacture of medicines to ensure that the amounts of nitrosamines in pharmaceutical products do not present risks to patients.**  **This questionnaire must be answered by a qualified person of the manufacturers of raw materials and has the objective of knowing the manufacturing processes of these materials and to identify possible sources of contamination by nitrosamines.**  **Please, answer the following questions according to the manufacturing process of the material identified above:** | |

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| 1) Please tick the applicable category based on structure and origin of the raw material in support to evaluate the risk of formation of nitrosamines in the excipient: | | | | | | | | | | | | |
| Nitrogen Containing? | Yes → | **Proteins, enzymes,**  **products of fermentation or**  **extraction of biologic sources, ...** | | | | | **Synthetic origin and**  **nitrogen containing** | | | | | |
| No → | **Mined raw material, N-free products of fermentation or natural origin, ...** | | | | | **N-free mineral acids or bases, organic solvents, polymers, inorganic salts, small organic N-free entities, …** | | | | | |
|  | | ↑  No | | | | ↑  Yes | | | | | | |
| Chemical Synthetic Manufacturing Process?  Including processes to introduce chemically synthesized fragments to biological products or substances of natural origin. | | | | | | | | | | |
| 2) Is Sodium Nitrite (NaNO2) or any other nitrite or nitrosating agent: | | | | |  | | |  | | |  | |
| - Used in any steps in the manufacturing process as reagents / catalyst? | | | | | **YES** | | | **NO** | | |  | |
| - Known to be used in the preparation of raw materials or intermediates used in the manufacturing process? | | | | | **YES** | | | **NO** | | | **Unavailable information** | |
| - Known to be used in the preparation of reagents / catalysts / processing aids used in the manufacturing process? | | | | | **YES** | | | **NO** | | | **Unavailable information** | |
| - Known or likely to be generated as impurities during the manufacturing process? | | | | | **YES** | | | **NO** | | | **Unavailable information** | |
| - Deliberately added to the process, including components of cell culture media or for fermentation? | | | | | **YES** | | | **NO** | | | **Unavailable information** | |
| 3) Have your company analysed the material for identification and quantification of: | | | |  | | | | |  |  | | |
| * Nitrites? | | | | **YES** | | | | | **NO** |  | | |
| * Nitrates? | | | | **YES** | | | | | **NO** |  | | |
| * Nitrosamines? | | | | **YES** | | | | | **NO** |  | | |
| If any answer in this section is **YES**, please inform the results, test methodology and if the tests were performed in-house or by a third-party contractor.  **Click here to enter text.** | | | | | | | | | | | | |
| 4) Does the manufacturing process of the material use water? | | | | **YES** | | | | | **NO** | | |  |
| If so, is this water prepared by distillation, ion exchange or reverse osmosis? | | | | **YES** | | | | | **NO** | | | **Not applicable** |
| If this water is not prepared using one of the processes mentioned above. Inform (in ppm) the maximum level permitted for: | | | |  | | | | |  | | |  |
| * Nitrites | | | **Click here to enter text.** | | | | | | | Not Specified | | |
| * Nitrates | | | **Click here to enter text.** | | | | | | | Not Specified | | |
| 5) Is there any secondary and/or tertiary amine present in the material manufacturing process as: | | | |  | | | | |  | | |  |
| * Raw material? | | | | **YES** | | | | | **NO** | | |  |
| * Package material? | | | | **YES** | | | | | **NO** | | |
| * Intermediate? | | | | **YES** | | | | | **NO** | | |  |
| * Reagent? | | | | **YES** | | | | | **NO** | | |  |
| * Processing aids? | | | | **YES** | | | | | **NO** | | |  |
| * Catalyst / Base? | | | | **YES** | | | | | **NO** | | |  |
| * Solvent? | | | | **YES** | | | | | **NO** | | |  |
| If **YES**, are those amines present in which step of the manufacturing process? | | | | **BEFORE** the step on which any nitrosating agent mentioned in section 1 is added. | | | | | | | | |
|  | | | | The **SAME** step on which any nitrosating agent mentioned in section 1 is added. | | | | | | | | |
|  | | | | **AFTER** the step on which any nitrosating agent mentioned in section 1 is added. | | | | | | | | |
| Please, inform below the chemical name / structure of the amine (s):  **Click here to enter text.** | | | | **Not applicable** | | | | | | | | |
| 6) Is there any amide, primary amine or ammonium salt used or present in the material manufacturing process as: | | | |  | | | | |  | | |  |
| * Raw material? | | | | **YES** | | | | | **NO** | | |  |
| * Package material? | | | | **YES** | | | | | **NO** | | |
| * Intermediate? | | | | **YES** | | | | | **NO** | | |  |
| * Reagent? | | | | **YES** | | | | | **NO** | | |  |
| * Processing aids? | | | | **YES** | | | | | **NO** | | |  |
| * Catalyst / Base? | | | | **YES** | | | | | **NO** | | |  |
| * Solvent? | | | | **YES** | | | | | **NO** | | |  |
| * Washing fluid? | | | | **YES** | | | | | **NO** | | |  |
| Please, inform below the chemical name / structure of the substances:  **Click here to enter text.** | | | | **Not applicable** | | | | | | | |  |
| 7) Routinely, are tested new solvents for nitrosamines? | | | | **YES** | | | | | **NO** | | |  |
| Are recycled and / or recovered nitrogen containing solvents used in the manufacturing process of the material? | | | | **YES** | | | | | **NO** | | |  |
| Routinely, are tested recycled and / or recovered solvents for nitrosamines? | | | | **YES** | | | | | **NO** | | | **Not applicable** |
| 8) Are the equipment used in the maufacturing process of the material dedicated? | | | | **YES** | | | | | **NO** | | |  |
| If **NO**, are the equipment used to manufacture any other products that require nitrites, nitrosating agents or material with identified risk of formatting nitrosamines? | | | | **YES** | | | | | **NO** | | | **Not applicable** |
| 9) Conclusion  Please use this field to draw a conclusion about the overall likelihood of the presence of nitrosamines and nitrosating agents.  **Click here to enter text.**  If “unavailable information” has been ticked to any option in question 2), please include any additional comments here.  **Click here to enter text.** | | | | | | | | | | | | |

**Issued by:**

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| Name | **Click here to enter text.** |
| Job title | **Click here to enter text.** |
| Signature |  |