|  |  |  |
| --- | --- | --- |
| **Currently identified risk factors for presence of nitrosamines (Q4 of EMA/409815/2020)** | **Evaluated?****(Yes / No)** | **Reference to annexed background documents** |
|  |  | **DS manuf. 1** | **DS manuf. 2** | **DS manuf. …..** | **DP manuf. 1** | **DP manuf. 2** | **DP manuf. …..** |
|  | ***Risk factors related to the manufacture of the active substance:*** |
| **1** | Use of nitrite salts and esters (e.g. NaNO2, alkyl nitrites), or other nitrosating agents (e.g. nitroso halides, nitrosonium salts, nitrogen oxides, nitro alkanes, halogenated nitro alkanes, Fremy’s salt, nitroso sulfonamides), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process. Sources for secondary or tertiary amines can also be starting materials, intermediates, reagents, solvents (e.g. DMF, DMAc and NMP) and catalysts, which contain amine functionality, amine impurities (e.g. quaternary ammonium salts) or which are susceptible to degradation to reveal amines. |  |  |  | NA | NA | NA |  |
| **2** | Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process (see 1). |  |  |  | NA | NA | NA |  |
| **3** | Use of disinfected water (chlorination, chloro-amination, ozonisation) in the presence secondary or tertiary amines within the same or different steps of the manufacturing process (see 1). |  |  |  | NA | NA | NA |  |
| **4** | Oxidation of hydrazines, hydrazides and hydrazones by hypochlorite, air, oxygen, ozone and peroxides in the manufacturing process or during storage. Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts). |  |  |  | NA | NA | NA |  |
| **5** | Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts). |  |  |  | NA | NA | NA |  |
| **6** | Use of contaminated starting materials and intermediates supplied by vendors who use processes or raw materials which may contain residual nitrosamines or nitrosating agents. |  |  |  | NA | NA | NA |  |
| **7** | Carry-over of nitrosamines deliberately generated (e.g. as starting materials or intermediates) during the manufacturing process. |  |  |  | NA | NA | NA |  |
|  | ***Risk factors also related to the finished product:*** |
| **8** | Reaction of nitrosatable nitrogen functionality in APIs or their impurities/degradants with nitrosating agents present in components of the FP during formulation or storage. A particular risk of formation of nitrosamines should be noted for active substances that contain a nitrosatable amine functional group. Several examples have been reported where the amine functionality was shown to be vulnerable to nitrosation and formation of the corresponding N-nitroso impurity (i.e. NO-API). Secondary amines appear particularly vulnerable to this reaction although some cases with tertiary amines have also been observed. Vulnerable amines could also be formed by degradation (e.g. hydrolysis) during formulation or storage. Nitrites have been identified as impurities in many common excipients. MAHs and/or applicants should be aware that N-nitroso API impurities can form at levels exceeding the AI even if nitrite levels in the excipients are very low. The overall nitrite content will also depend on the relative composition in terms of the excipients. As it has been reported that N-nitroso impurities can form from APIs or their impurities/degradants (containing amine functionality or susceptible to degradation to reveal amines) during manufacture of the finished product, as well as during storage, MAHs should give consideration to the stability of the finished product and should ensure that the AI of any N-nitrosamine impurity is not exceeded until the end of shelf life of the FP. For further information, please refer to the assessment report of the CHMP’s Article 5(3) opinion on nitrosamine impurities in human medicinal products. |
| **8a** | Does the API, or one of its known impurities, have a nitrosatable nitrogen functionality? |  |  |  | NA | NA | NA |  |
| **8b** | May nitrites be present in one of the used excipients? | NA | NA | NA |  |  |  |  |
| **9** | Degradation processes of active substances, including those induced by inherent reactivity (e.g. presence of nitro-alkyl, oxime, or other functionality) or by the presence of an exogenous nitrosating agent. This could potentially occur during both active substance and finished product manufacturing processes or during storage and could be influenced by crystal structure, crystal habit and storage conditions (temperature, humidity etc.). For more details, refer to page 6 of Referral under Article 31 of Directive 2001/83/EC for ranitidine and published literature. |  |  |  |  |  |  |  |
| **10** | Oxidation of hydrazine or other amine-containing functional groups present in active substances or their impurities/degradants (e.g. from hydrazones and hydrazides), either in active substance manufacturing processes or during storage. This root cause has also been observed during manufacture and storage of finished products containing such functional groups. Potential oxidants include oxygen and peroxides (common impurities in some excipients). |  |  |  |  |  |  |  |
| **11** | Use of certain packaging materials. Relevant nitrosamine contamination has been observed in primary packaging of finished products in blister with lidding foil containing nitrocellulose. During the blister heat-sealing process, nitrogen oxides can be generated thermally from nitrocellulose. Under these conditions, nitrosamines have been shown to form from low molecular weight amines present either in printing ink or in the finished product and to transfer to the product and/or to the cavity via evaporation and condensation. |  |  |  |  |  |  |  |
| **12** | Reaction of amines leaching from quaternary ammonium anion exchange resins (e.g. used for purification steps) with nitrosating agents present in the liquid phase. A recent example of this was in the production of water for injections where residual chloramine used to disinfect incoming water reacted with dimethylamine leaching from the anion exchange resin used in the demineralisation step to form NDMA. In addition, disinfection procedures such as e.g. chlorination, chloro-amination and ozonisation can lead to significant N-nitrosamine generation as by-products in case vulnerable amines are present. Given the source of contamination, risk is related to the concentration of the reactive agent(s) and thus to the volume of water in or used to dilute a particular product. The same risks could be associated with active substances or finished products manufactured using water purified using similar resins. |  |  |  |  |  |  |  |
|  | ***Risk factors related to GMP aspects:*** |
| **13** | Cross-contamination due to different processes being run successively on the same manufacturing line. |  |  |  |  |  |  |  |
| **14** | Carry-over of impurities between process steps due to operator-related errors or insufficiently detailed batch records such as inadequate phase separations during work-up procedures. |  |  |  |  |  |  |  |
| **15** | Use of contaminated recovered or recycled materials (e.g. solvents, reagents and catalysts) where the recovery is outsourced to third parties who are not aware of the content of the materials they are processing. Recovery processes carried out in non-dedicated equipment should also be considered. |  |  |  |  |  |  |  |
|  | ***Any other risk factors identified:*** |
| **16** |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
|  |
| **Overall conclusion of Applicant:** |  |

**DS manuf. – drug substance manufacturer**

**DP manuf. – drug product manufacturer**

**NA – not applicable**