N-NITROSAMINE RISK ASSESSMENT

Introduction

According to the discovery of N-Nitrosamine impurities in Angiotensin II Receptor Blockers (ARBs), Ranitidine, Metformin and other Drug Products (DPs), EMA and FDA recommend API and DP manufacturers to conduct risk assessment on approved or marketed products and product with pending applications and to take appropriate actions in case a potential risk for N-Nitrosamine presence is assessed.

MAHs are required to perform risk evaluation on their medicinal products according to ICH Q9 and ICH M7 principles (Step 1 Risk evaluation) and, in case a risk of presence of N-Nitrosamines is identified, to carry out confirmatory testing (Step 2 Confirmatory testing).
Finally if the presence of N-Nitrosamines is confirmed by analytical testing, in Step 3 MAHs are called to mitigate the risk by means of proper changes to the Marketing Authorization (MA).

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N-Nitrosamine
Risk Assessment

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N-NITROSAMINE RISK ASSESSMENT
Criteria

Manufacturers may prioritize evaluation according to **factors** such as maximum daily dose, duration of treatment, therapeutic indications and number of treated patients. The Risk evaluation activity is then addressed to all chemical synthetized APIs and, as a consequence, it is addressed to Drug Products (DPs) containing synthetized APIs. Moreover, EMA has recently extended the evaluation to all biological medicinal products with specific identified risk factors: containing chemically synthetized fragments or packaged in certain primary packaging such as blisters or manufactured using processes where nitrosating agents are added.

REGULATORY REQUIREMENTS & DUE DATES

Complete indications of the steps to be followed by MAHs are reported in EMA documentations, which have recently been updated (EMA/369136/2020 and EMA/409815/2020 came into force on 25 June 2020 and 03 August 2020 respectively), and in FDA guidance "Control of N-Nitrosamines Impurities in human Drugs" (issued in September 2020).

EMA

1. MAHs should conclude Risk Assessment on marketed/approved DPs containing **CHEMICALLY SYNTHETIZED APIs** within 31st March 2021 and confirmatory testing and submit any changes required within 26th September 2022.
2. For product containing **BIOLOGICAL APIs**, Step 1 Risk Evaluation should be concluded within 01st July 2021 and Step2 and Step3 activities within 01st July 2023.

FDA

1. Marketing Authorization Holders (MAHs) should conclude a Risk Assessment on their marketed/approved DPs containing **CHEMICALLY SYNTHETIZED APIs** within 6 months of the date of publication of the guidance (within 01st March 2021) and conclude confirmatory testing, if required, within 3 years of the date of publication of the guidance (within 01st September 2023).

N-NITROSAMINE RISK ASSESSMENT

PTM Consulting Approach

With the experience gained in QRM through the years and, in particular, in performing Product Prioritization and Risk Assessment on N-Nitrosamines to fulfill EMA directives, PTM consulting can actively manage information collection and N-Nitrosamine activity execution using its well-grounded methodology and experience in N-Nitrosamine topic.

PTM CONSULTING SUPPORT

From September 2019 onwards, date of first issue of the "Information on nitrosamines for MAHs" by EMA, PTM consulting has supported DP and API manufacturers as well as MAHs in Step 1 activities:

1. **IDENTIFY DP PRIORITY STARTING FROM THE EMA AND FDA RECOMMENDATIONS** considering criteria such as maximum daily dose (MDD), duration of treatment, number of treated patient and therapeutic indication and developing a suitable risk tool able to objectively prioritize DP for evaluation.
2. **ASSESS THE POTENTIAL RISK OF N-NITROSAMINE PRESENCE** and/or formation in finished products according to ICH Q9 and ICH M7 principles EMA directives and FDA guidance on N-Nitrosamines.