propharma

case study

identify at-risk drug products and ensure compliance with a successful risk assessment ahead of nitrosamines deadline

ProPharma successfully supported a client by conducting a timely risk assessment of nitrosamines for applicable products ahead of the regulatory deadline to proactively ensure product safety.

Marketing Authorization Holders (MAHs) must perform a risk evaluation of their medicinal products containing chemically synthesized Active Pharmaceutical Ingredients (APIs) to assess adherence of nitrosamine regulations. The risk evaluation of all products must be concluded by 31 March 2021, at the latest.

ProPharma experts expediently satisfied this client's request for a risk assessment essential to meeting nitrosamine regulatory requirements. Through close collaboration, control of nitrosamine impurities in medicinal products for human use was safeguarded in a timely manner.

The keys to success are timely communication with all providers of external materials (excipients, packages, equipment, etc.) or facilities (CMOs or CROs),efficient utilization of the multidisciplinary team for performing the tailored risk assessment, and strong diligence with analytical method development and validation.

challenge

Both EMA and FDA are requiring that all human medicines, irrespective of marketing status, be assessed for the possible presence of nitrosamines and require completion of the risk assessment for chemical products before the end of the first quarter of 2021.

FDA requires the completion of a risk assessment for chemical products by February 28, 2021 and EMA by 31 March 2021, with EMA providing an additional three months for biological products.

The client wanted to immediately undertake the risk evaluation of their products. This came to 67 commercial drug products containing 62 drug substances of their newly filed, approved and marketed products.

The risk assessment covered potential formation, contamination by, and carry-over of nitrosamine impurities in the investigated drug substances and drug products, including the identification of sources of these impurities.

solution

Based on the high-level guidance related to nitrosamine issues available, the ProPharma team prioritized the medicines in the scope of the assessment. **The team identified and gathered relevant information from external suppliers, background quality documents, and registration documents.** This included information from impacted CMOs as well.

In cases where there was insufficient information, the team performed a risk assessment based on literature, general knowledge and practical expertise from comparable manufacturing processes and medicinal products.

The main categories of potential sources of nitrosamine impurities are starting materials, equipment, manufacturing process steps, presence of nitrosamines precursors, manpower and environment.

All aspects were evaluated and summarized in tailored risk assessment reports, as per requirements of the ICH Q9 guideline on "Quality Risk Management" and ICH M7 guideline on "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk". Findings from CHMP's review of sartans and other related guidance were also considered.

results

ProPharma supported the client with the development and implementation of the approach and tools for their successful risk assessment related to nitrosamine impurities. This in response to the call for review of the European Medicines Agency (EMA) requirements (EMA/189634/2019 from 19th of September 2019).

Utilizing the knowledge of our multidisciplinary scientific and drug manufacturing experts, combined with efficient project management, t**he assessment of 62 drug substances and 67 commercial drug products, containing both chemically synthesized and biological APIs, was successfully completed.** In total 12 drug substances and 31 drug products were found to be at risk.

Having successfully identified the at-risk drug substances and commercial products, the client could immediately develop a remediation plan to ensure compliance and patient safety going forward.

For the products at risk of nitrosamine impurities, candidates were proposed to enable targeted analytical method development, validation, and testing.

Whenever possible, risk mitigation activities were suggested, related to the testing strategy, adjustment of the synthesis route, or the drug product formulation process. This allowed the MAH to plan for the follow-up steps and resolve nitrosamine issues in their products.

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