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GENEVOLUTION and DELSART REGULATORY CONSULTING (DRC) have joined forces to offer a comprehensive solution for nitrosamines risk management in pharmaceutical products

Nitrosamines are a class of compounds that have raised significant concerns in the pharmaceutical industry due to their potential carcinogenicity. Effective risk management for nitrosamines in pharmaceutical products involves the following strategy:

1. **Step 1: Perform a risk assessment:**
   - Evaluation of ingredients characteristics: chemical formulae
   - Evaluation of the documentation submitted by ingredient suppliers on the risk of presence of:
     - ✓ Nitrosamines (direct contamination)
     - ✓ Nitrosamines precursors such as secondary amines and nitrosating agents.
   - Evaluation of the scientific literature to predict the pathways for N-nitroso compound formation and confirmation through lab testing (NAP)
   - Evaluation of the contribution from the utilities (water) and cleaning agents
   - Evaluation of the contribution from the drug product manufacturing and packaging processes
   - Synthesis of nitroso-impurities and qualification (for toxicological characterization and confirmatory analysis)
   - Estimation of the Acceptable Intake using the Carcinogenic Potency Categorization Approach (CPCA)
   - Confirmation of the Acceptable Intake by running an in vitro genotoxicity study, under GLP conditions:
     - ✓ In vitro mutagenicity tests in bacteria: Enhanced Ames Test (EAT)
     - ✓ In vitro mammalian cell mutagenicity assay: Mousse Lymphoma Assay (MLA)
     - ✓ Metabolism studies

2. **Step 2: Confirmatory testing:**
   - Method development (LC-MS/MS, LC-HRMS, GC-MS/MS)
   - Exploratory analysis (non-GMP) with method verification: first result not validated
   - If nitrosamine is detected during exploratory analysis: method validation and regulatory assay (GMP)

3. **Step 3: Risk mitigating plan and Benefit/Risk assessment:**
   - Evaluation of the results of confirmatory testing
   - Benefit/risk assessment
   - Definition of the risk mitigating plan (CAPA plan)
     - ✓ Implementation of skip testing or routine testing
     - ✓ Carrying out additional analyses (e.g. nitrites in excipients)
     - ✓ Modification of the drug formula (e.g., addition of antioxidant)
     - ✓ Changing the API manufacturing process
     - ✓ Change of ingredient suppliers
     - ✓ Definition of the regulatory strategy

In addition, GENEVOLUTION and DRC provide training on the risks associated with nitrosamines and the importance of adhering to risk management protocols. We believe in fostering a culture of awareness and responsibility regarding nitrosamine risks.

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By leveraging their expertise, GENEVOLUTION and DRC help pharmaceutical companies navigate the complexities of nitrosamine risk management effectively, ensuring product safety and regulatory compliance.

"As the pharmaceutical industry faces increasing scrutiny regarding nitrosamines, GENEVOLUTION is committed to leading the charge in risk management solutions through its partnership with DRC. Our combine expertise enables us to provide comprehensive assessments and innovative strategies that not only ensure regulatory compliance but also prioritize patient safety. We believe that proactive measures in understanding and mitigating nitrosamine risks are essential for building trust and integrity in the pharmaceutical sector", says Isabelle Mouche, co-founder and CEO of GENEVOLUTION.

"*In a context where regulations related to nitrosamines have dramatically evolved since 2020, reaching a high level of complexity, DRC is committed, together with GENEVOLUTION, to providing comprehensive solutions and pragmatic approaches to MAHs to comply with health authorities' expectations. We are convinced that our partnership enables MAHs to manage, in an integrated way, regulatory requirements related to nitrosamines, and notably the emerging concerns of authorities related to Nitrosamine Drug Substance-Related Impurities (NDSRIs). "*, says Guillaume Delsart, founder and CEO of DRC.

For more information about our comprehensive offering on nitrosamines risk management in your drug products, please contact Gautier Decock at gautier.decock@genevolution.fr or Guillaume Delsart at g.delsart@delsartrc.com and visit our website at www.genevolution.fr.

About GENEVOLUTION:

GenEvolutioN is an expert CRO dedicated to In-Vitro Genetic toxicology and toxicology expertise using new Human cell models combined to advanced analytical technologies to anticipate tomorrow challenges and predict the risk of cancer. Hosted within the Seqens'Lab, GenEvolutioN offers a broad portfolio of GLP compliance in-vitro toxicity and genotoxicity test for the pharmaceutical, cosmetic, medical device and food industry. The mission of GenEvolutioN is to contribute to a safer world by providing our customers with innovative and high-quality laboratory, research and advisory services whilst creating opportunities for our employees and generating sustainable value to further enhanced innovation. Driven by an entrepreneurial and innovative spirit, our employees are committed to providing our customers with the highest level of service and quality.

About DRC:

DRC is a consulting firm providing Regulatory Affairs expertise and advice services, both to pharmaceutical and medical devices industries, having a particular experience in managing some highly specific topics like nitrosamines. Having worked in the field of nitrosamines regarding pharmaceutical products since the publication of the first regulation on this topic, DRC offers comprehensive support services to MAHs and CDMOs, by assessing the risk of presence of nitrosamines, managing confirmatory testing and building strategies to comply with regulatory requirements. DRC also provides Regulatory Affairs support services for medical devices, notably the management of MDR certification, and for pharmaceutical products (CMC). The mission of DRC is to help its customers differentiating key regulatory endpoints from minor ones. Always having in mind the overall picture when finding solutions to operational issues, DRC is committed to providing pragmatic tailored services to its customers.

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