Table 26: Nitrosamine Risk Assessments – Implementation

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Scope:

The CHMP finalized its opinion on the evaluation of the risk presented by N-nitrosamine impurities in human medicines (EMA/341963/2020) to now include all biological medicinal products within scope. The implementation of a risk assessment for potential N-nitrosamine impurities being introduced into biological medicinal products will be discussed in this round table. The term 'biological medicinal products' is understood in accordance with Directive 2001/83/EC as a product containing a biological substance as the active component, where (with noted exceptions e.g. certain antibiotics) a biological substance is extracted from a biological source. Therefore, the scope of the risk assessment for the biologic medicinal product discussed in this roundtable includes monoclonal antibodies, vaccines, ADCs, RDA, DNA and recombinant therapeutic proteins.

The roundtable will discuss the risk assessment for: 1) active substance 2) chemically modified active biological substances 3) excipients (including water) 4) primary and secondary packaging/labelling

Questions for Discussion:

1. If there is no conjugation or synthetic step in the preparation of the drug substance, is there any risk of N-nitrosamines from the drug substance?
2. For a N-nitrosamine to form, a vulnerable amine and a nitrosating source must be present. For formulations that use excipients that do not contain vulnerable amines but may contain traces of nitrosating agents, is there any risk?
3. What efforts must be taken to demonstrate the container closure system (primary packaging/labelling) does not pose a risk to N-nitrosamine formation.
4. For a chemically/synthetically (conjugates) modified biologic medicinal drug substance, where should the risk assessment start?
5. For biologic medicinal products that have the potential to contain N-nitrosamines, how will this be evaluated.
6. What is the level of due diligence required to support the N-nitrosamine risk assessment for a biologic medicinal product.

Discussion Notes:

Thermo-Fischer is very involved in N-NO risk assessments. They would like to understand what Biopharma custome need in the way of methods for N-nitrosamines

The table discussed the following points for pure biologics:

- Biological active substances are manufactured and formulated into and stored in Water for Injection (WFI) which has been derisked for nitrosating agents.
- Most manufacturing steps for biological active substances (and products) are suboptimal for nitrosation reactions (time, temperature, pH, nitrosating agent concentration)
- Liquid biological medicinal products are stored under low temperature conditions that would reduce the likelihood of nitrosation which is temperature dependent.
- Low mass, small molecule impurities are inherently cleared in the manufacturing process by standard unit operations such as bind/elute and size exclusion chromatography, and ultrafiltration/diafiltration that all purge low molecular mass impurities.
- Biological active substances have multiple primary amines that can act as N-nitrosating agent scavengers
- Biological active substances are too large for cellular metabolism/activation via cytochrome P450 dependent enzymes to generate a potent mutagenic species (diazonium species) from any nitrosamine formed from the active substance,

For conjugated biomolecules where the conjugate is a small molecule – look at the synthetic route stating at the GMP starting material (no further back) and risk assess there. If a potential risk is identified, use Teasdale's purge factors to determine any risk.

EFPIA has published a white paper on N-nitrosamine risk for biologics which is linked here: https://www.efpia.eu/media/413726/efpia-ifpma-nitrosamines-global-position-paper.pdf

1. If there is no conjugation or synthetic step in the preparation of the drug substance, is there any risk of N-nitrosamines from the drug substance? THere is no risk as no secondary amines or nitrosating gents used in the process
2. For a N-nitrosamine to form, a vulnerable amine and a nitrosating source must be present. For formulations that use excipients that do not contain vulnerable amines but may contain traces of nitrosating agents, is there any risk? – No
3. What efforts must be taken to demonstrate the container closure system (primary packaging/labelling) does not pose a risk to N-nitrosamine formation. -The stopper and plungers potentially may contain N-NO compounds - Rely on vendors for testing – if they don't have testing then send a sample of the polymer to a vendor to test.
4. For a chemically/synthetically (conjugates) modified biologic medicinal drug substance, where should the risk assessment start? – Start with GMP synthesis no further back
5. For biologic medicinal products that have the potential to contain N-nitrosamines, how will this be evaluated. – If risk assessment for potential N-NO compound is positive, implement Teasdale type assessment for level – testing; if high enough test with validated methods
6. What is the level of due diligence required to support the N-nitrosamine risk assessment for a biologic medicinal product. — Risk Assess small mol containing components if risk found do limited tested