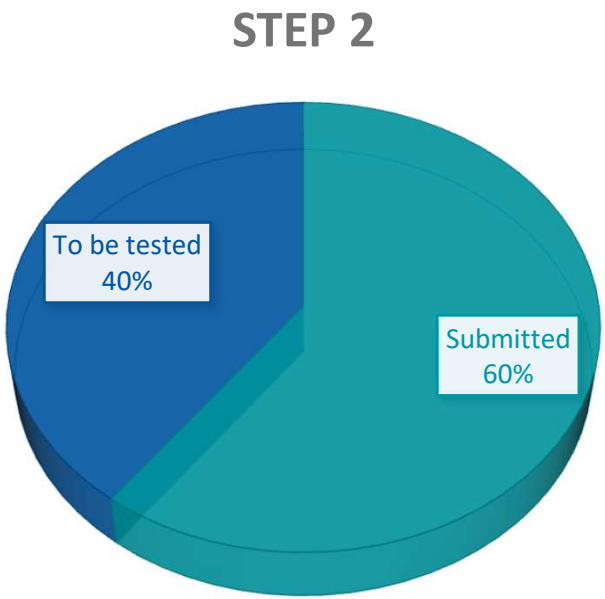
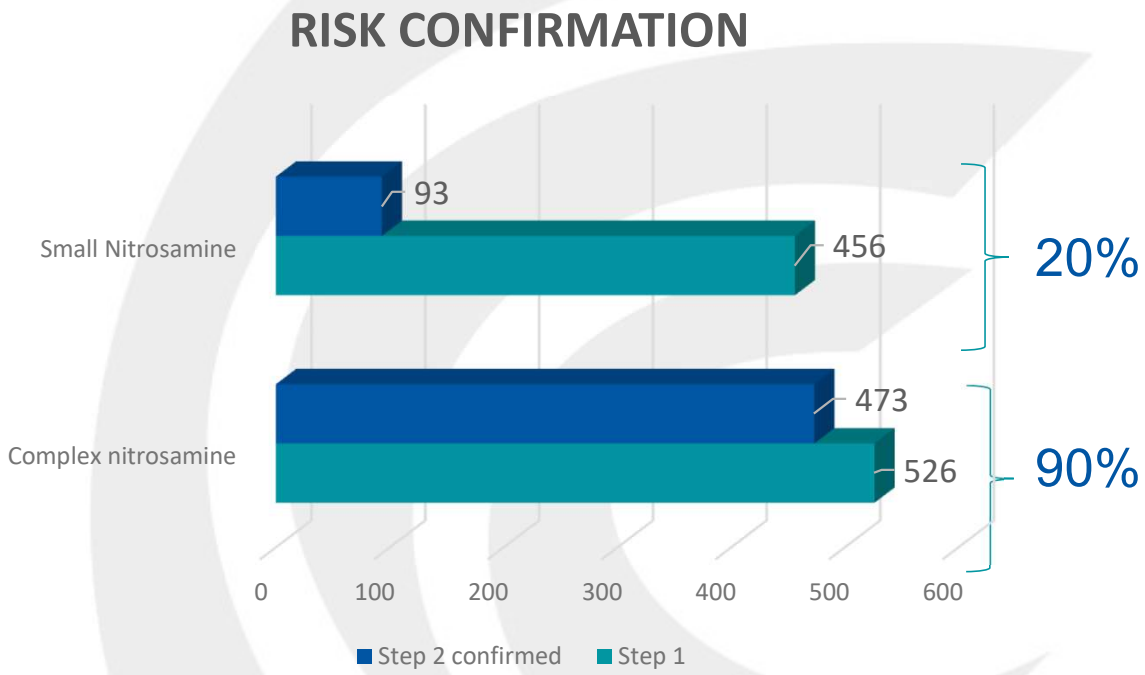
NIOG meeting

30 November 2022

Nitrosamine assessment and Variations impact





10 companies participating in the survey for a total of 1825 products in step 1

Nitrosamine assessment and Variations impact

Reported reasons for test delays

- Lack of capacity (equipment and human resources)
- Still investigating all risk factors that may potentially lead to nitrosamine formation
- Analytical method challenges, e.g. availability and stability of the nitrosamine specific standards
- Scheduling interrupted by ad-hoc HA requests for testing
- Re-evaluation of risk assessments
- New ad-hoc request and strict timeline to deal with

Market Impact

- Maintenance of supply of products with complex nitrosamines (Nitrosamines Drug Substance Related Impurities).
- Complex nitrosamines (NDSRIs) are present in a large fraction of drug products, both brand and generic*:
  - 40% of the APIs listed in GSRS (Global Substance registration system) database
  - 25% of WHO list of essential medicines
  - 35% of US top 200 drugs with respect to sales volumes
- Appreciate the idea to set interim limit of 178 ng/day but it will not help in most cases
- Consider practical pathways to deal with nitrosamines in vulnerable products, one approach could be adoption of the M7 TTC limit on an interim basis for data-poor nitrosamines

* Joerg Schlingemann et al. The Landscape of Potential small and Drug Substance related Nitrosamines in Pharmaceuticals - in press

Regulatory Impact

- Ongoing procedures
  - Evolving requirements - Retroactive requests for active procedures to immediately comply while the product is commercial with a different due date
  - Procedures in stop-clock

- New submissions
  - Rescheduling and delaying new submissions