



Genotoxic Impurities

Manufacturer perspective

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outline

- Origin
- Fate
- Control

Impurities - origin

- Impurities are present in Drug Product / Drug Substance / Additives
 - API Production processes
 - Intermediates
 - Starting Materials
 - Solvents
 - Degradation
- Nature and levels of impurities depends on type of process

Impurities - Genotoxic

- GTI – causes heritable genetic change
 - Threshold / non-threshold
 - Mutagens
 - Chromosomal effecting agents
- Structural features associated with mutagenicity
 - Nitro / nitroso / Azo / Aziridines / hydrazines
 - Epoxides
 - Alkylating agents

Why impurities are neglected?

- Early Phase
 - Large number of NCE candidates
 - Speed to clinic
 - Often discovery synthesis is scaled up
- Late Phase / commercial
 - Cost Vs quality
 - 99% 1 X
 - 99.5% 2 X
 - 99.9 3 X
 - Too many sites / several technology transfers
 - Multiple processes / sites for supply chain security
 - Commercial sources for key raw materials

Detection

- How low is low – closer to zero but not zero
- Avoidance is always desirable but
 - Multi step synthesis
 - Complex chemistry
 - Low yields
- Not feasible to eliminate
 - Mesylate salts
 - Oxalate salts

Analytical concerns

- Sample preparation
 - % or ppm or ppb
- Sensitivity / selectivity
 - LOQ / LOD
- Availability of toxic impurities
- Preparation and qualification
- Increased sensitivity
 - Low robustness
 - Technology transfer problems
- Sanctity of limit tests
 - Visual
 - instrumental

Genotoxic agents – day to day life

- Sources of Genotoxic substances
 - Generated within the cell
 - Pollution
 - Ionizing radiation
 - Contaminants in water and air
 - From food and food supplements
 - Natural supplements
 - Medicines
- Average intake of 1.5 g of Genotoxic material per day

Control

- Multi functional effort required
 - Process Chemistry
 - Synthetic route development and optimization
 - Analytical
 - Qualification of impurities
 - Robust analytical methods
 - Toxicology
 - Safety assessment
 - Risk management
 - False negatives
 - Regulatory
 - TCC – Threshold of Toxicological concern
 - ASARP – As Low As Reasonably Possible

Concerns

- Total exposure or ppm
- It can be done or it should be done?
- Potential *vs* known Genotoxic impurities
- Absolute *vs* relative risk
- Risk *vs* benefits



Thank you

TTC

- Threshold of Toxicology Concern – 1.5 mg per day
- Virtually safe dose - 10^{-6} life time risk of cancer
- TD_{50} – Incidence of Tumour 1 in 10^6 incidences
- Concentration Limit = TTC in micro g per day / dose in g per day