# ICH M7 Principles - Impurity Identification and Control

***Session 3: Prevention Part 1***

R.Ogilvie, for EFPIA

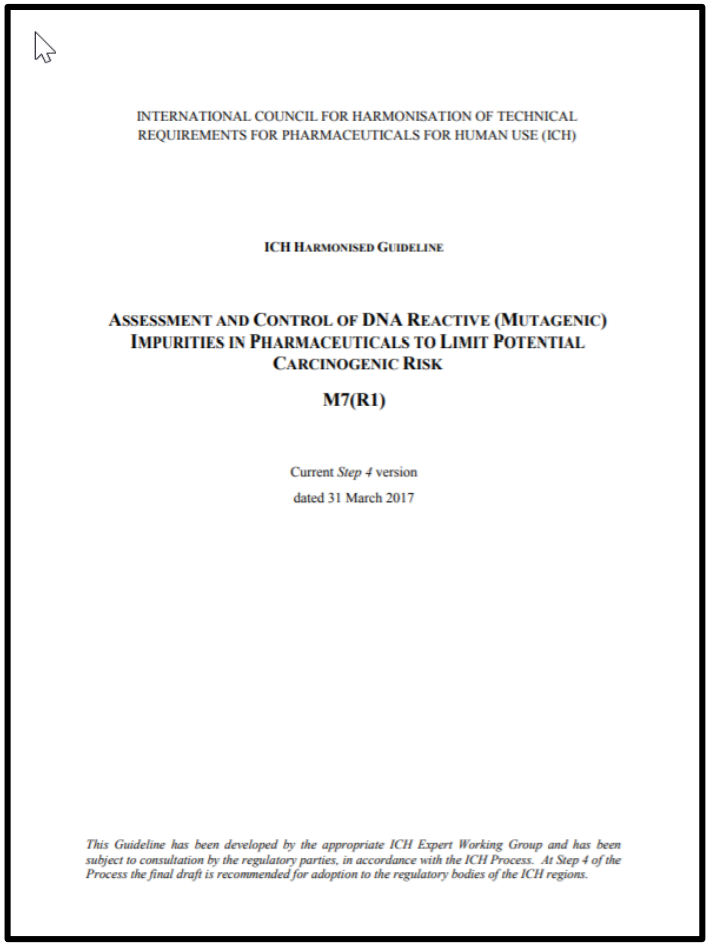
EMA Sartans with N-nitrosamine impurities
Lessons Learnt Exercise - Interested Parties Meeting
Amsterdam, 04. November 2019

# ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

**Framework for a science based control of mutagenic impurities**

- ***N*-Nitrosamines explicitly in scope as part of 'cohort of concern'**
- **Multidisciplinary Guideline**
  - Application of scientific principles from multiple disciplines incl. e.g., Process Chemistry, Analytical Chemistry, Toxicology
- **Globally accepted framework for the assessment and control of mutagenic impurities**
  - Risk-based quality management (ICH Q9)

Mutagenic Impurities: ICH M7 (R1) https://ich.org
https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7(R1)

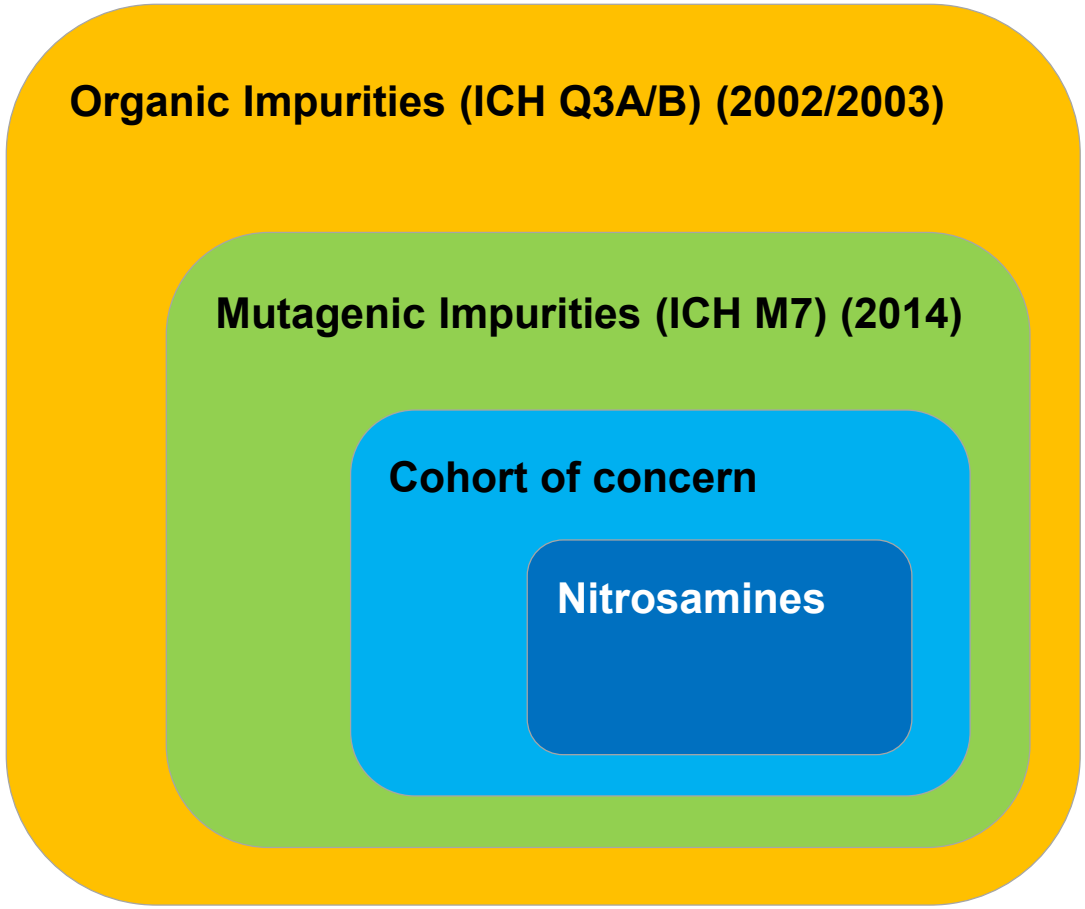
Current *Step 4* version

dated 31 March 2017

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the ICH regions.*

# Global Regulatory Framework for Impurities:
## *N*-Nitrosamines are a subset of the cohort of concern and are within the scope of ICH M7

- ICH M7 principles are in place to be applied, and are appropriate to be applied, to the 'cohort of concern' impurities.
- Potent 'cohort of concern' impurities need to be controlled to lower levels than general M7 threshold of toxicological concern



# ICH M7 provides a science and risk based approach to mutagenic impurity control

## Impurity Identification

**Process-related Impurities**
- Actual Impurities
- Potential Impurities
  - Predicted byproducts

**Degradation Products**
- In Drug Substance
- In Drug Products

**Expert evaluation and analytical data**

## Impurity classification

- **Known mutagenic carcinogens (PDE)**
- **Known mutagens, unknown carcinogenic potential (TTC)**
- **Alerting structures (TTC)**
- Impurities free of predicted mutagenicity (not needing low level controls)

**Expert review of toxicology data and predictive software**

## Impurity control to assure suitable safety

- **Control through Process Design**
- **Control through in process or intermediate testing**
- **Control through analytical testing of API**

**Process design, control strategy and testing**

# ICH M7 (+ other ICH expectations) applies to Development, and Medicine Supply to Patients post approval

- **ICH M7: Mutagenic impurity management expectations.** Including evaluation of changes to manufacturing for impact on the quality of drug substance and drug product.

  **Process and controls assessed at approval and through subsequent change.**

- **Other ICH Impurity Guidances**
  - Q3A and B - Impurity management expectations for non-mutagenic impurities
  - Q3C – residual solvents; Q3D elemental impurities

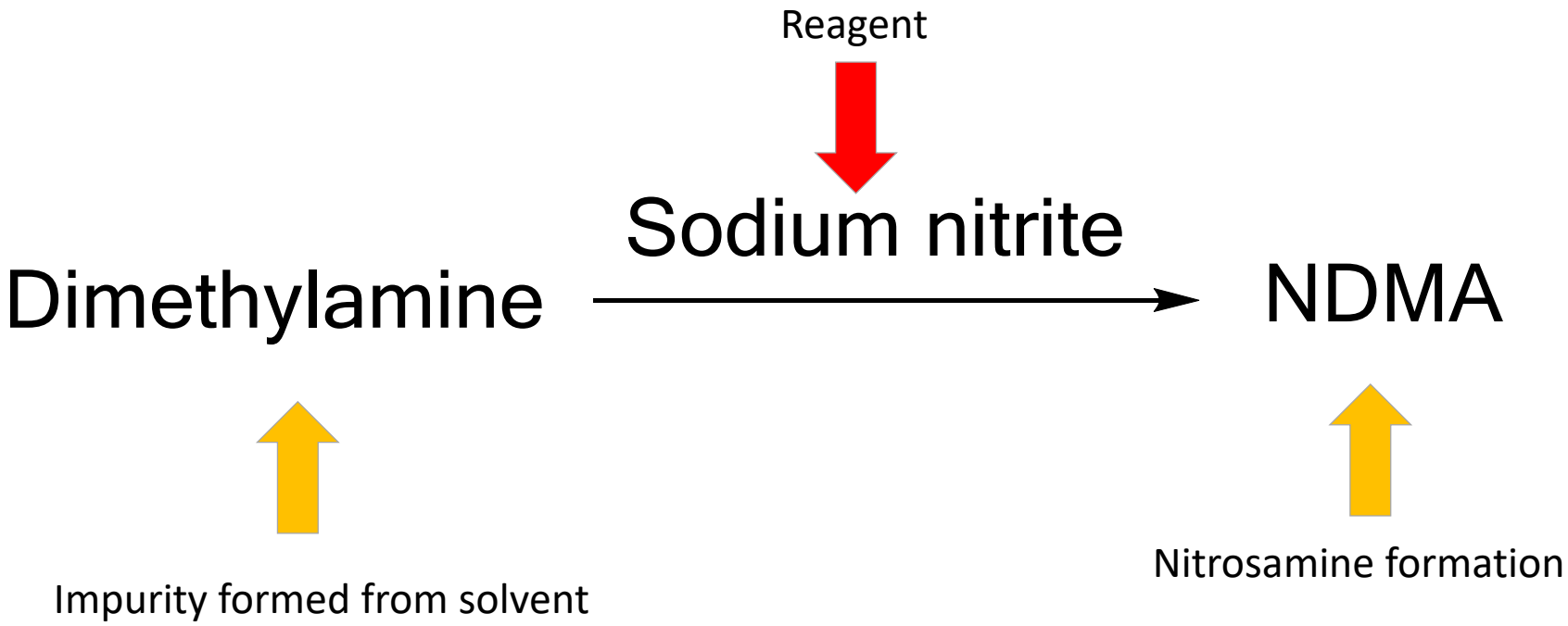
- **ICH Q9:** Quality risk management
  - Evaluation of risks to quality based on scientific knowledge, to protect the patient
  - The Quality risk management process expected to be commensurate with the risk.

- **ICH Q7 – GMP**
  - Good Manufacturing Practices

- **ICH Q10: Quality system -** Science-based and risk-based approaches throughout lifecycle of product and its manufacture

## Sartans learnings provide new understanding of root causes

- M7 risk assessment using this knowledge could identify the potential for nitrosamine formation in API manufacturing




**ICH M7 expectations + Learnings support one another**

# Science-based approaches for mutagenic impurity risk assessment and management remain foundational

- **ICH M7 guideline provides the internationally-harmonised framework for identification, classification and control of mutagenic impurities**
- Control of mutagenic impurities can be achieved by e.g.,
  - Controls on ingoing materials
  - In-process and intermediate testing during manufacture
  - Release testing of APIs
  - GMP-controls incl. prevention of cross-contamination

- **Impurity prediction and identification is based on expert knowledge and understanding of chemistry (impurity formation and removal)**
  - N-nitrosamines formation during production of certain sartans can be predicted once the risk factors are identified as present
    - Standard nitrite treatment after sartan ring formation can nitrosate a vulnerable amine (hydrolytic impurity in reaction solvent)
  - This risk is now fully appreciated by industry and regulators