PDA Training Course Extractables & Leachables

01 Jun 2022

Where N-Nitrosamine assessments for drug products meet E&L qualifications for pharmaceutical primary packaging

Ward D’Autry

Introduction

The issue with N-Nitrosamines

The issue with N-Nitrosamines

Since July 2018: recalls for	N-nitrosamine contamination	N-nitrosamine formation
Valsartan *Other "Sartan"Drugs* Ploglitazone Ranitinide Metformin Rifampicin Rifapentine Varenicline Bumetanide Sumatriptan Deferasirox	**Extremely carcinogenic** **Cohort of concern!!** **Monitor concentrations as defined in Regulatory Guidances (ppt levels)!!**	During **Synthesis** drug Substance (Sartans; $NaNO_2$ used to quench Azides) **Degradation** of the API (Ranitidine) **Packaging** (Nitrocellulose laminated blister)

The issue with N-Nitrosamines

MORE BACKGROUND & CONSEQUENCES FOR:

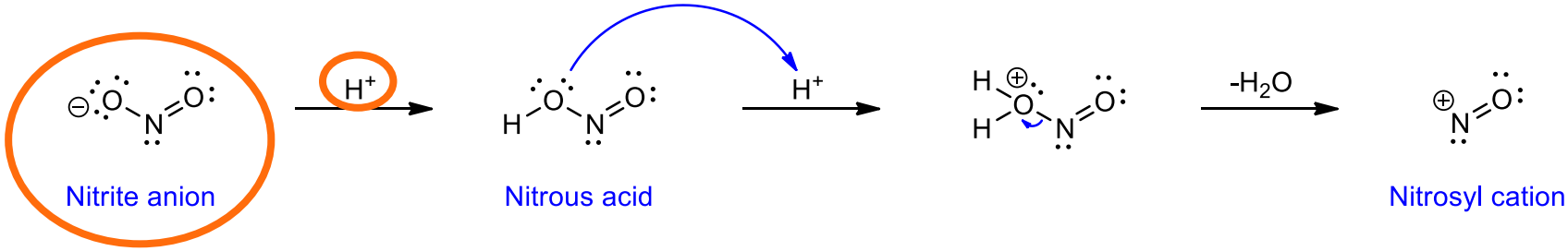
- *The Mutagenic Impurity **Risk assessment***
- *The need for N-Nitrosamine monitoring in drug substances and drug products*
- *The analytical methods: method development & validation considerations*

This presentation: N-nitrosamines in relation to E&L assessments

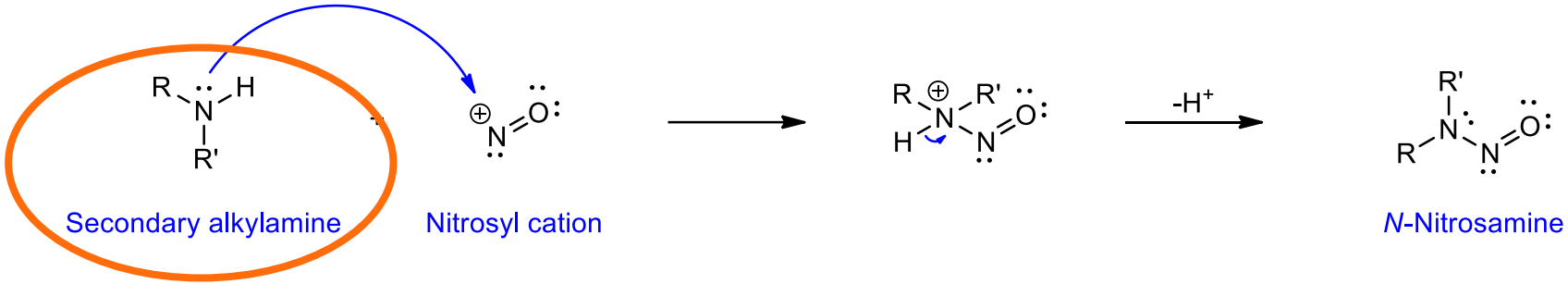
Formation of N-Nitrosamines

The formation of N-Nitrosamines

The actual nitrosation reagent is the nitrosyl cation, NO^+ which is formed *in situ*:



Secondary alkyl or aryl amines yield *N*-nitrosamines:



Potential sources of amines

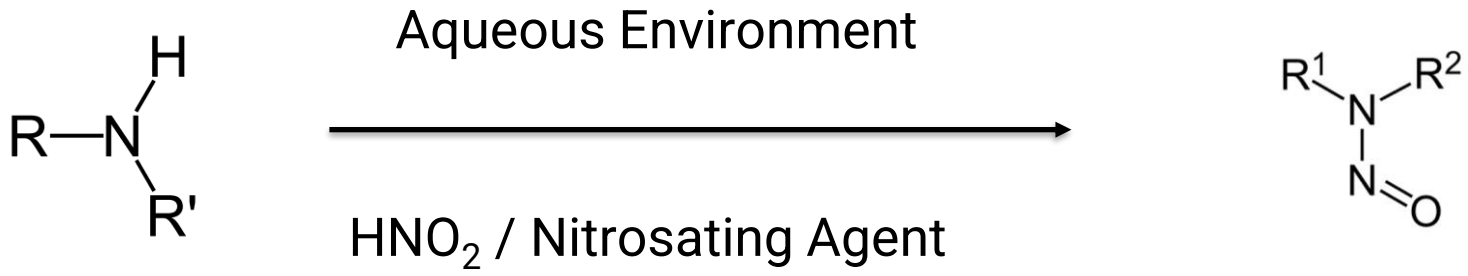
- Secondary Amines
- Tertiary Amines
  - *can easily degrade to secondary amines, e.g.:*
    - *Triethylamine*
    - *Diisopropylethylamine*
    - *N-methylmorpholine*
- Aromatic Amines
- Catalysts
- Solvents
- Impurities

- Dimethylformamide (DMF)
- N-methylpyrrolidinone (NMP)
- Quaternary Ammonium Salts
  - *Tetrabutylammoniumbromide (TBAB)*
- Impurities from monoethylamine

Potential sources of nitrosating agents

$NaNO_2$	Organic Nitrites
HNO_2	Side reactions in nitration reactions
NO	Hydroxylamine under oxidative conditions
ClNO	Chloramines
BrNO	Ozone
N_2O_3	Other…
N_2O_4	

Risk of formation



Low [HNO_2 /nitrosating compound] **Low** [Secondary Amines]	**High** [HNO_2 /nitrosating compound] **Low** [Secondary Amines]	**High** [HNO_2 /nitrosating compound] **High** [Secondary Amines]

Increasing risk of N-Nitrosamine Formation

Historical Cases

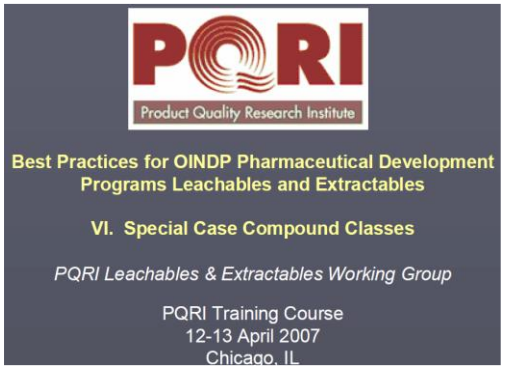
Pharma primary packaging as source of N-Nitrosamines

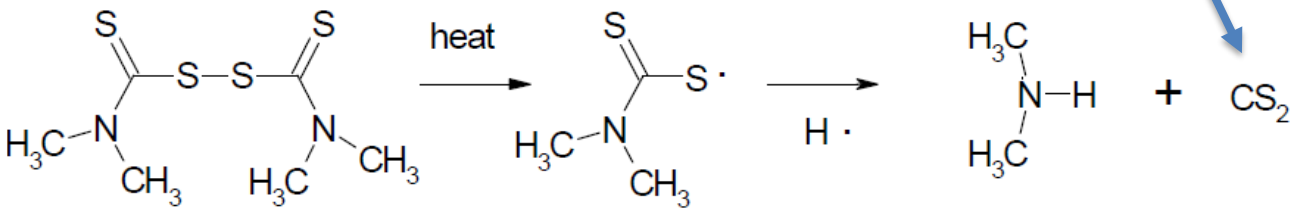
Rubber gaskets for MDIs

CS_2 detection in Headspace GC/MS can be an indicator for Secondary Amines and subsequent N-Nitrosamine formation

Curing / Cross Linking

Tetramethylthiuram disulfide





Based on work done by Dan Norwood & James O. Mullis

Rubber gaskets for MDIs

PQRI
Product Quality Research Institute

Best Practices for OINDP Pharmaceutical Development Programs Leachables and Extractables

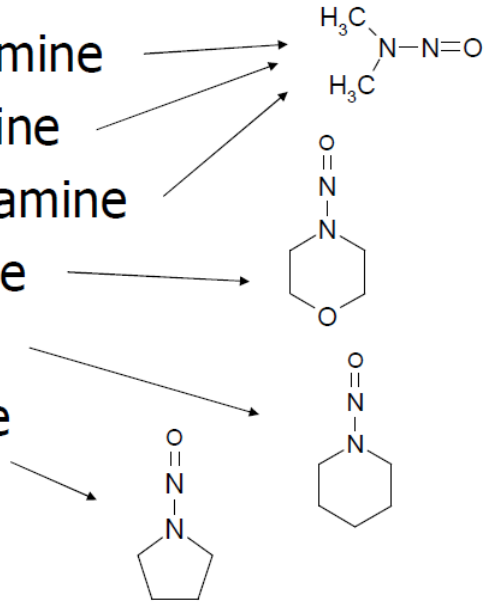
VI. Special Case Compound Classes

PQRI Leachables & Extractables Working Group

PQRI Training Course
12-13 April 2007
Chicago, IL

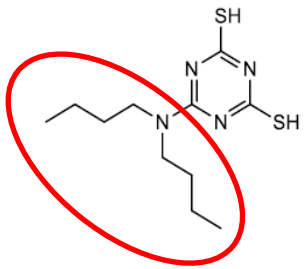
Target N-nitrosamines

- N-nitrosodimethylamine
- N-nitrosodiethylamine
- N-nitrosodi-n-butylamine
- N-nitrosomorpholine
- N-nitrosopiperidine
- N-nitrosopyrrolidine

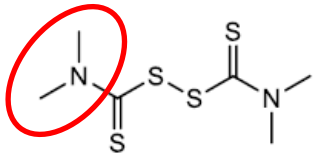


Overview of old & new vulcanizers (1)

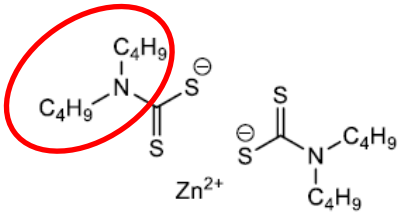
6-(dibutylamino)-1,3,5-triazine-2,4-dithiol



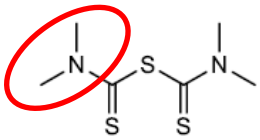
Tetramethylthiuram disulfide



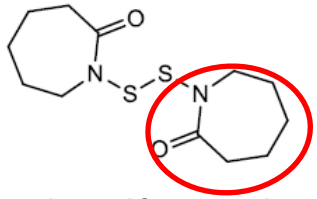
Zinc bis(dibutyldithiocarbamate)



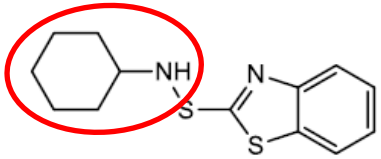
Tetramethylthiuram monosulfide



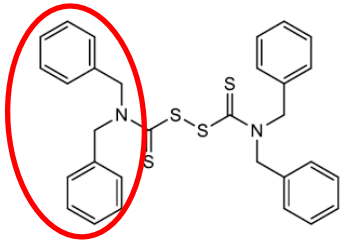
N,N'-Caprolactam disulfide



N-cyclohexyl-2-benzothiazole sulfenamide



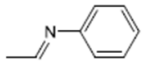
N,N,N',N'-Tetrabenzylthiuram disulfide



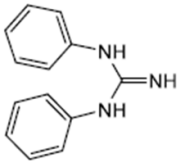
Overview of old & new vulcanizers (2)

Hexamethylene tetramine (HMT)

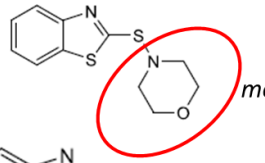
Ethylidene aniline (EA)



Diphenyl guanidine (DPG)

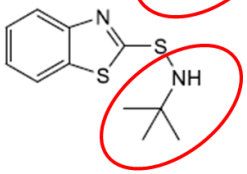


N-Oxydiethylbenzthiazylsulfenamide (NOBS)

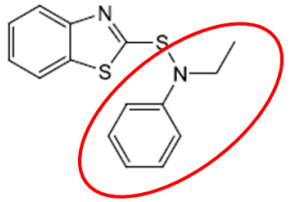


morpholine

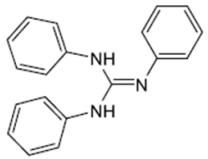
N-t-butylbenzthiazylsulfenamide (NS)



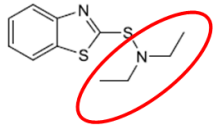
Ethyl phenyl thiocarbamate



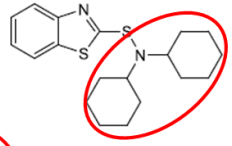
Triphenyl guanidine (TPG)



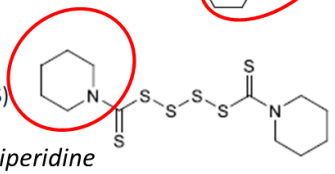
Diethyl (di)thiocarbamate



N,N'-Dicyclohexylbenzthiazylsulfenamide (DZ)



Dipentamethylene thiuram tetrasulfide (DPTS)



piperidine

Overview of old & new vulcanizers (3)

Rubber accelerators: A lot of Tertiary Amines which easily degrade to secondary amines during the rubber curing!!

Blister foil (1)

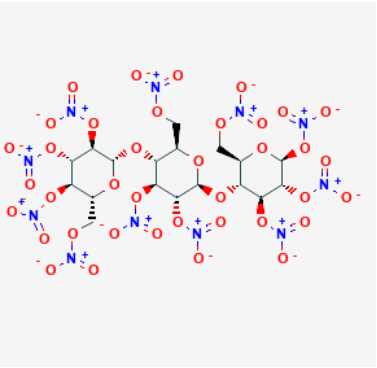
Nitrocellulose multilayer blister foil

Nitrosamine contamination has been observed in a finished product stored in blister.

It was hypothesized that the lidding foil containing **nitrocellulose printing primer** may react with **amines in printing ink** to generate nitrosamines, which would be transferred to the product under certain packaging process conditions.

Blister foil (2)

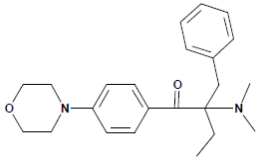
Nitrosating compound: Nitrocellulose



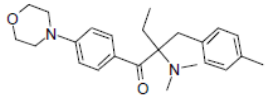
Many **pigments (azo)** used in printing inks contain nitrogen in their chemical structure. some **may contain secondary and tertiary amine functional groups on the skeletal exterior.**

UV-Curing Agents

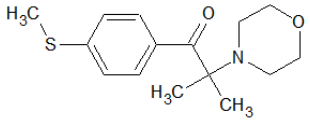
Irgacure 369



Irgacure 379

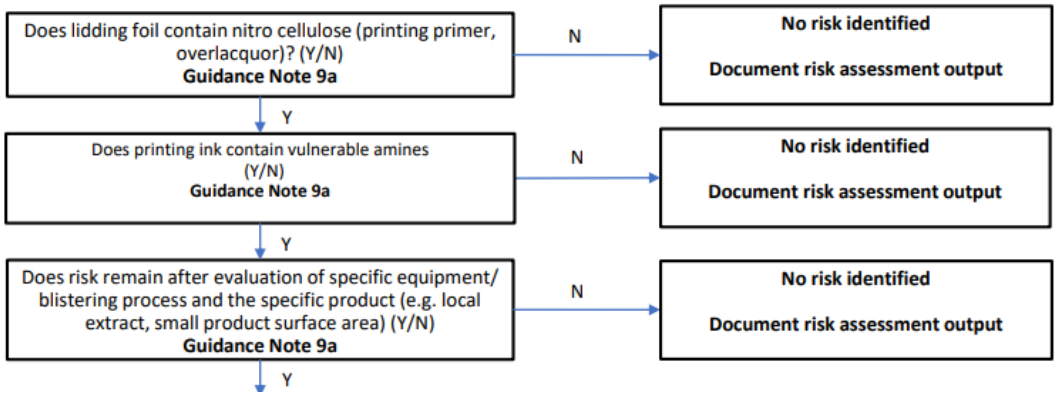


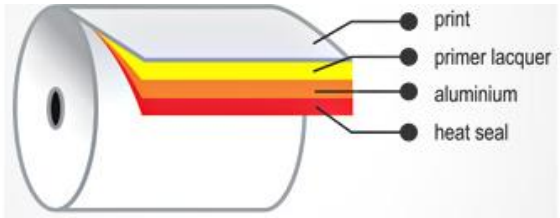
Irgacure 907



3. Risk Assessment for Nitrocellulose Packaging Materials

efpia





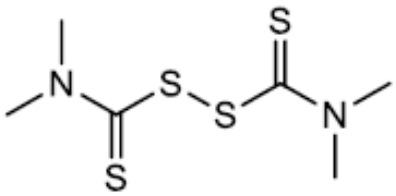
Nitrile rubber gloves

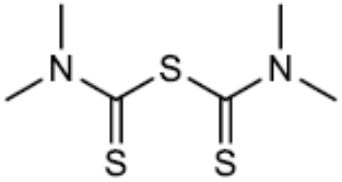
PAPER • OPEN ACCESS

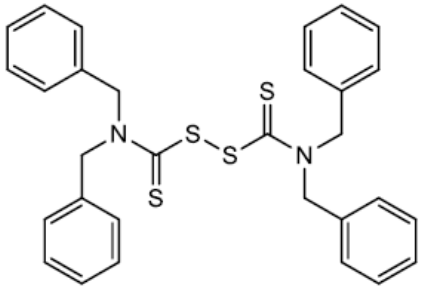
Migration of N-nitrosamines from rubber gloves for handling food - Effect of extraction media

To cite this article: O Pinprayoon and W Mae 2019 *IOP Conf. Ser.: Mater. Sci. Eng.* **548** 012022

Origin: accelerators for cross linking (thiurams)







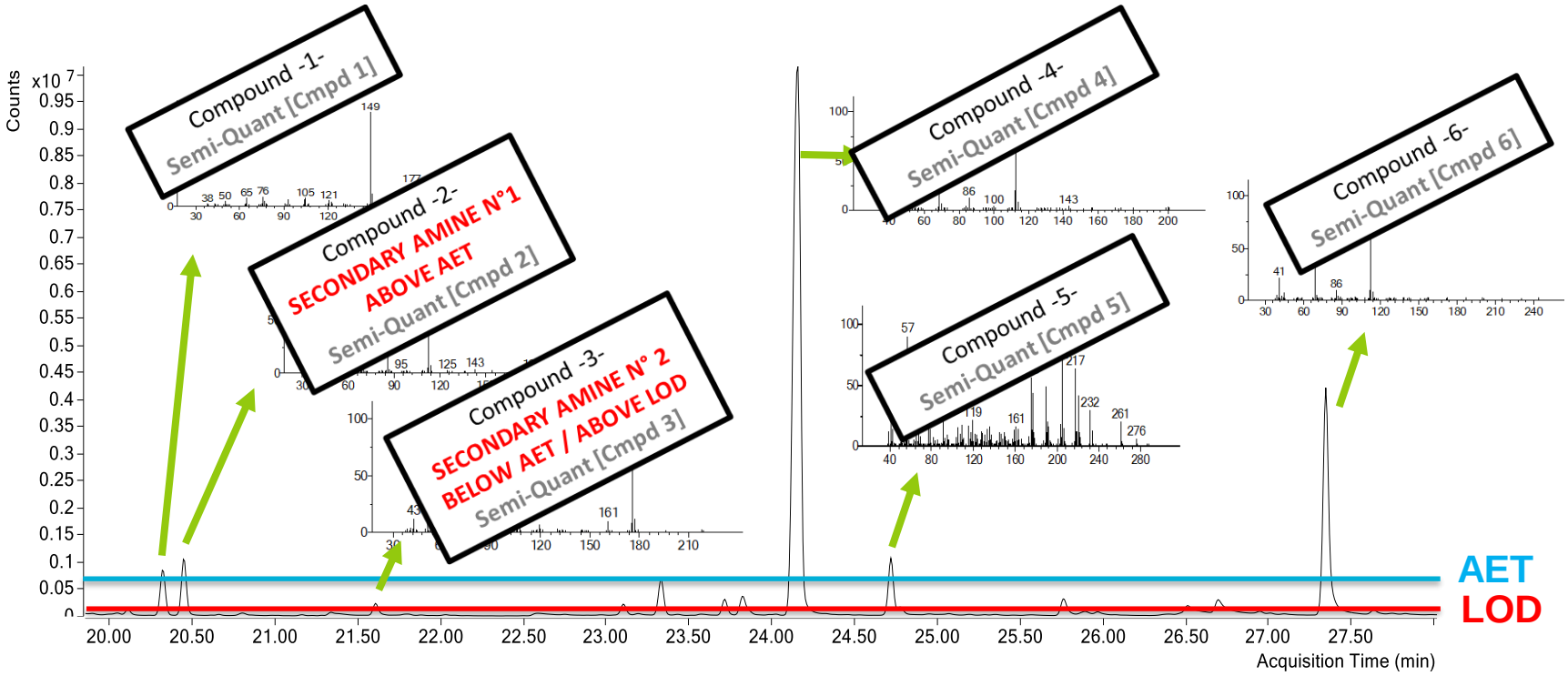
Open questions

- What about **other materials**?
- **Not all have the same risk** for presence of secondary amines
  - **Risk assessment**: check the known composition of the material to see if any compounds are present that could lead to generating secondary amines
- **How can the risk of presence** of N-Nitrosamines in packaging components **be assessed**?
- Do **all components** and materials **need to be assessed**?
- **Can we be selective** in what should be evaluated?

E&L screening

Can it contribute to N-Nitrosamine detection?

Chromatographic screening process



Chromatographic screening process

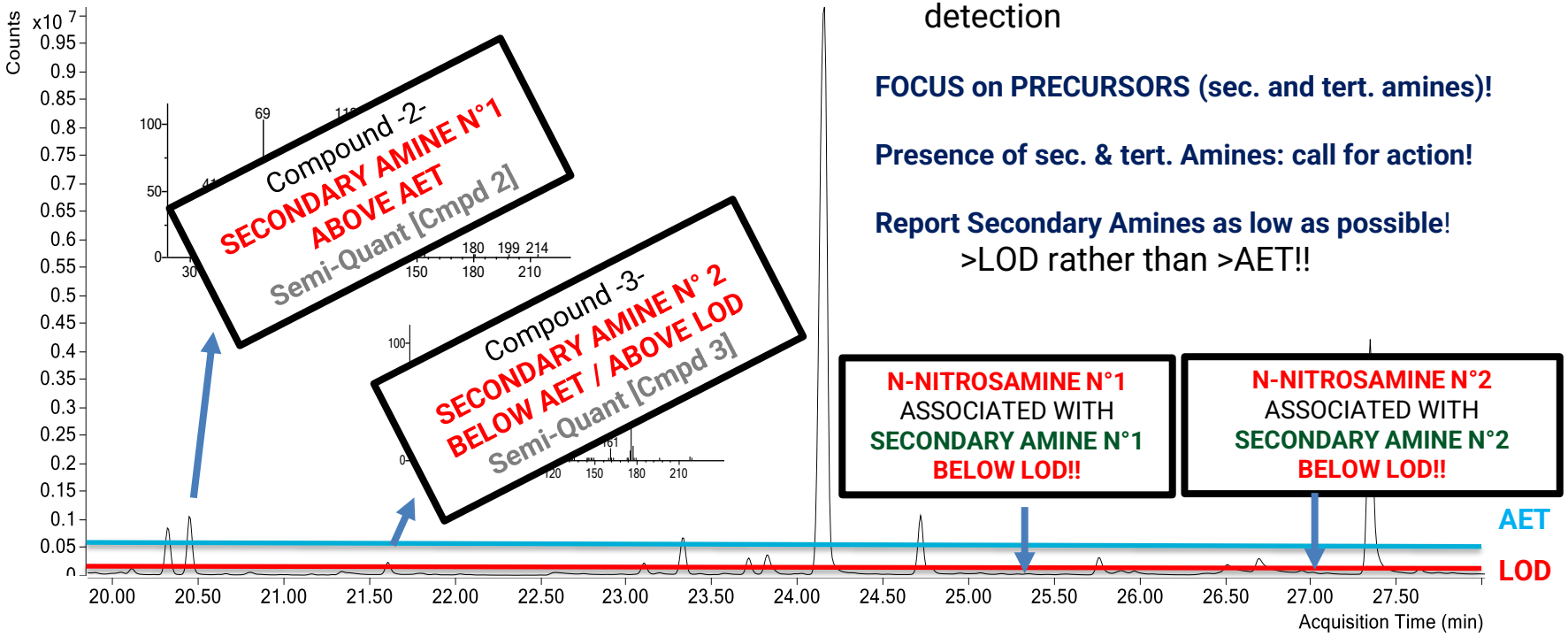
LOD for GC/MS: 30 µg/L for Standard Screening

- Sufficiently low for detection of secondary amines
- Not low enough for N-Nitrosamine detection

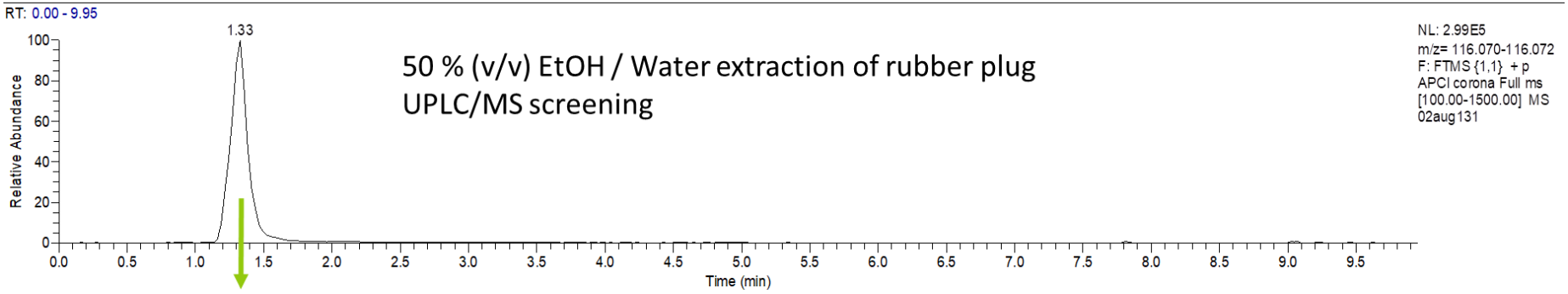
FOCUS on PRECURSORS (sec. and tert. amines)!

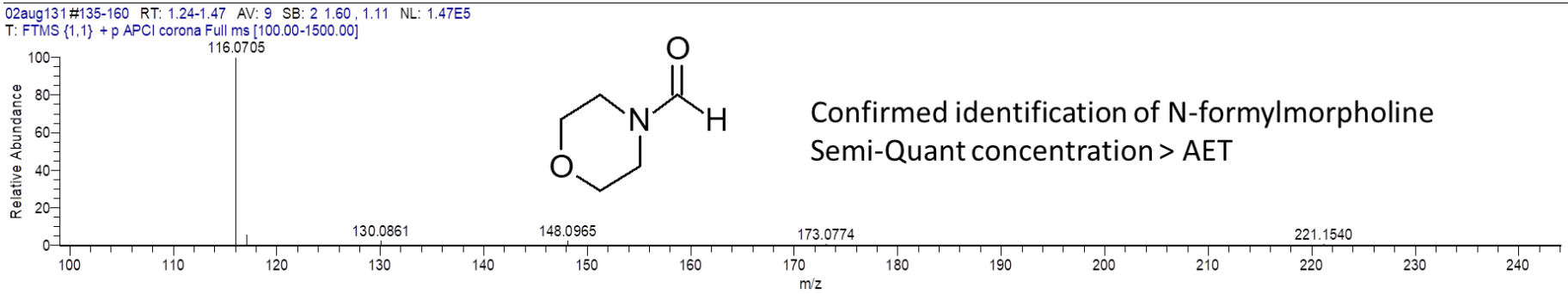
Presence of sec. & tert. Amines: call for action!

Report Secondary Amines as low as possible!
>LOD rather than >AET!!

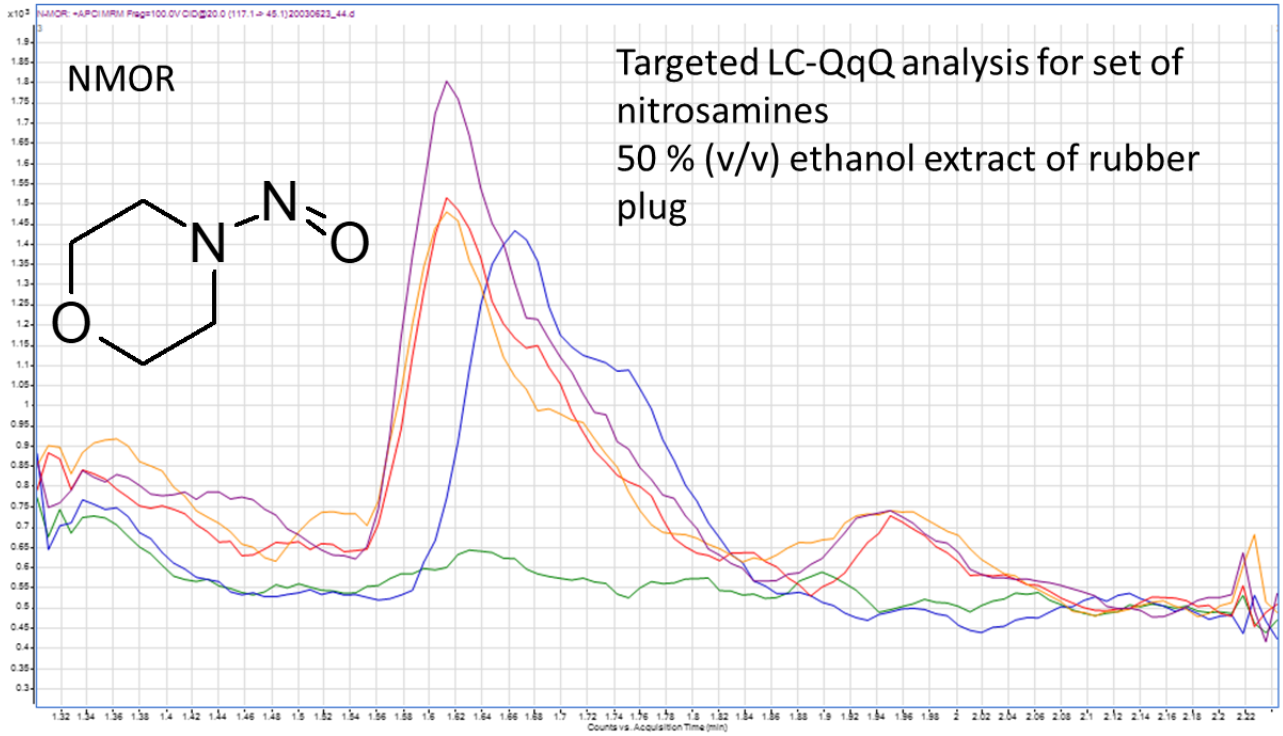


Case study 1: rubber plug (2020)





Case study 1: rubber plug (2020)



Blank extract

Sample 1

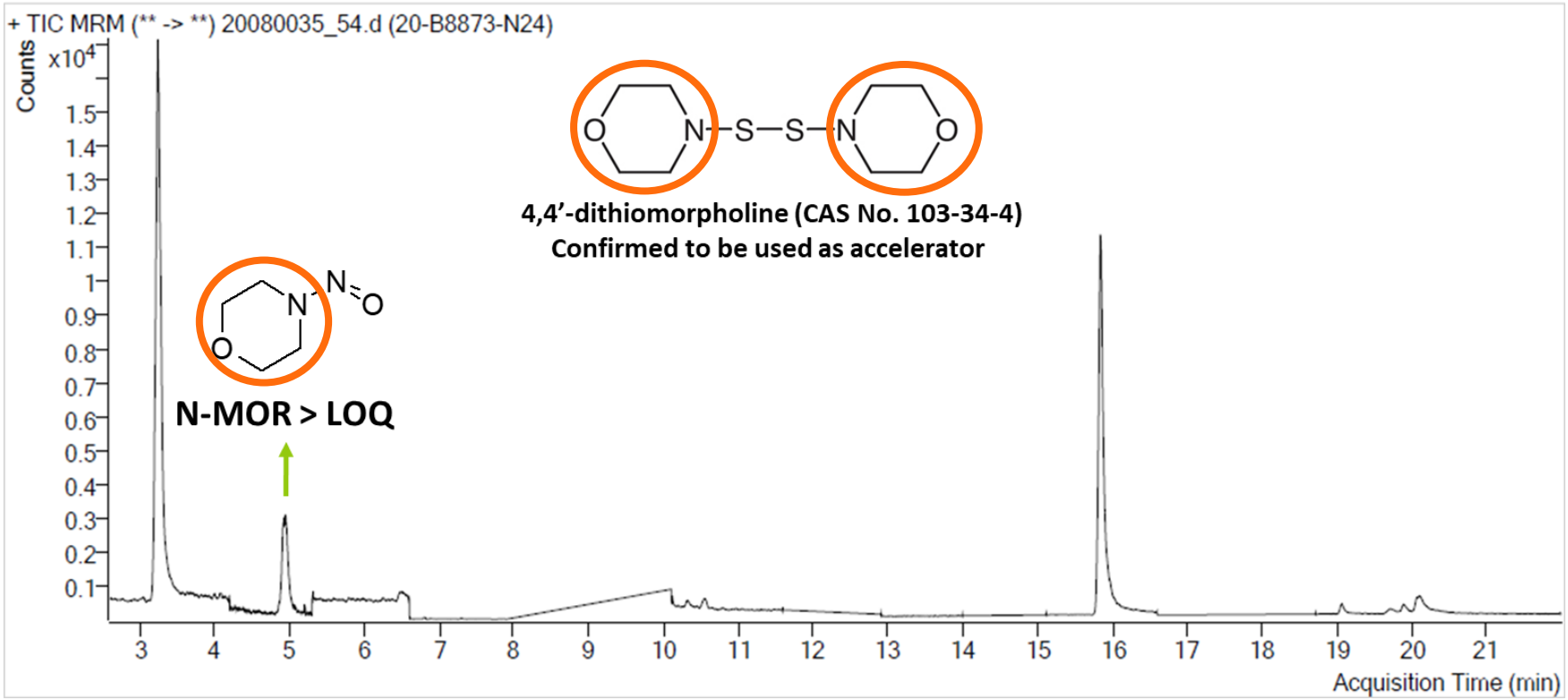
Sample 2

Sample 3

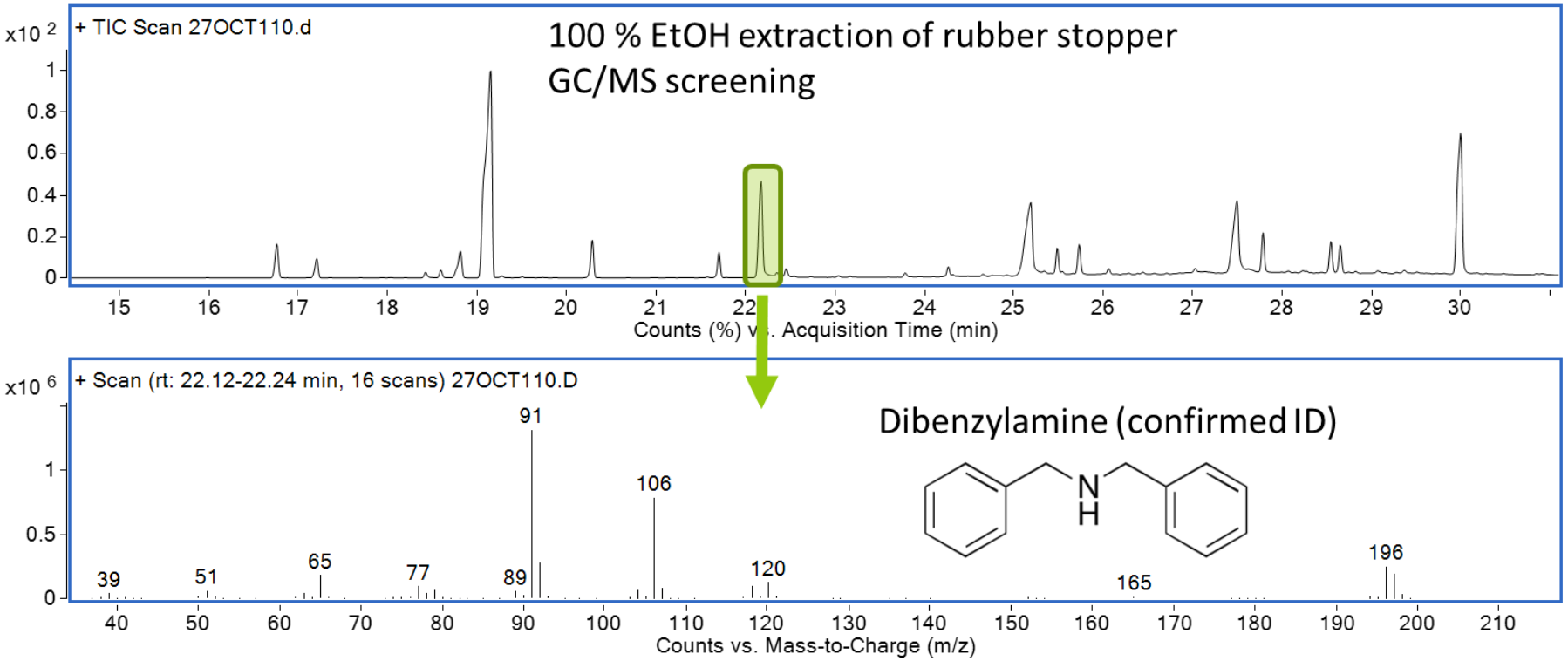
Sample 4

N-nitrosomorpholine > LOQ

Case study 2: rubber stopper (2020)

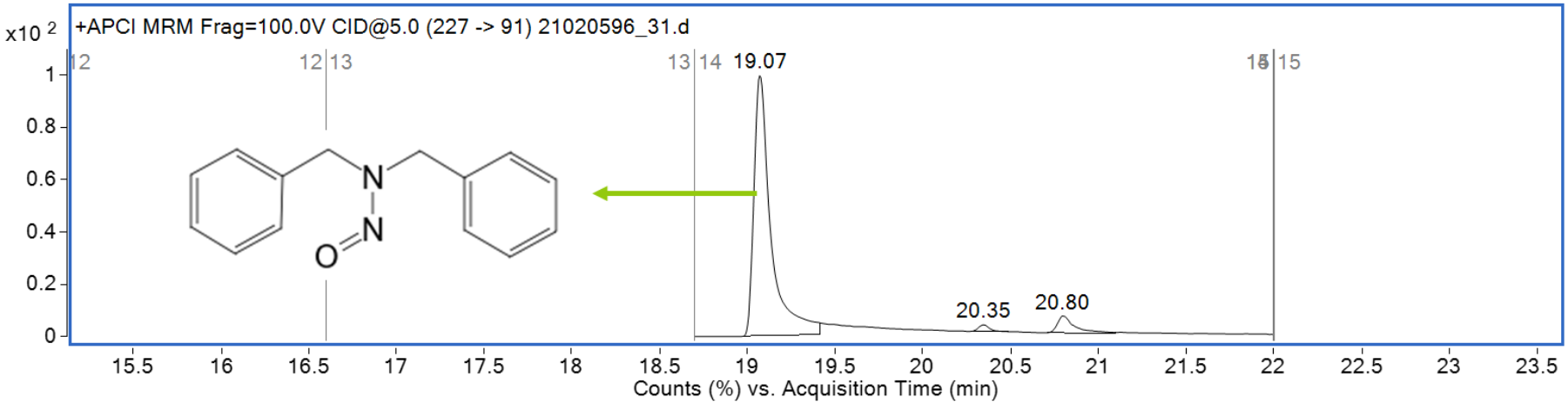


Case study 3: rubber stopper (2021)



Case study 3: rubber stopper (2021)

Targeted LC-QqQ analysis for set of nitrosamines - 50 % (v/v) ethanol extract of same rubber stopper



Impact on E&L studies?

Potential consequences on E&L study design

Extractables study

Presence of amines in materials / components: TRIGGER for ACTION

Be sure you can **identify all relevant secondary and tertiary amines** in materials research (DATABASE!)

Report Secondary & Tertiary Amines above the LOD, rather than above the AET!

When secondary Amines are present: Further **investigate the material for N-Nitrosamine presence** with targeted, sensitive analytical method

Two options:

- **Specific N-nitrosamine quantification** related to the observed secondary amines
- **Broader detection** of a list of N-Nitrosamine compounds

Leachables study (1)

Scenario 1: no amines detected > LOD in extractables study

no immediate concern of N-nitrosamine presence from a packaging perspective

no direct consequence for the **leachable study**

(which does not mean N-nitrosamines can't be present in the drug product)

Leachables study (2)

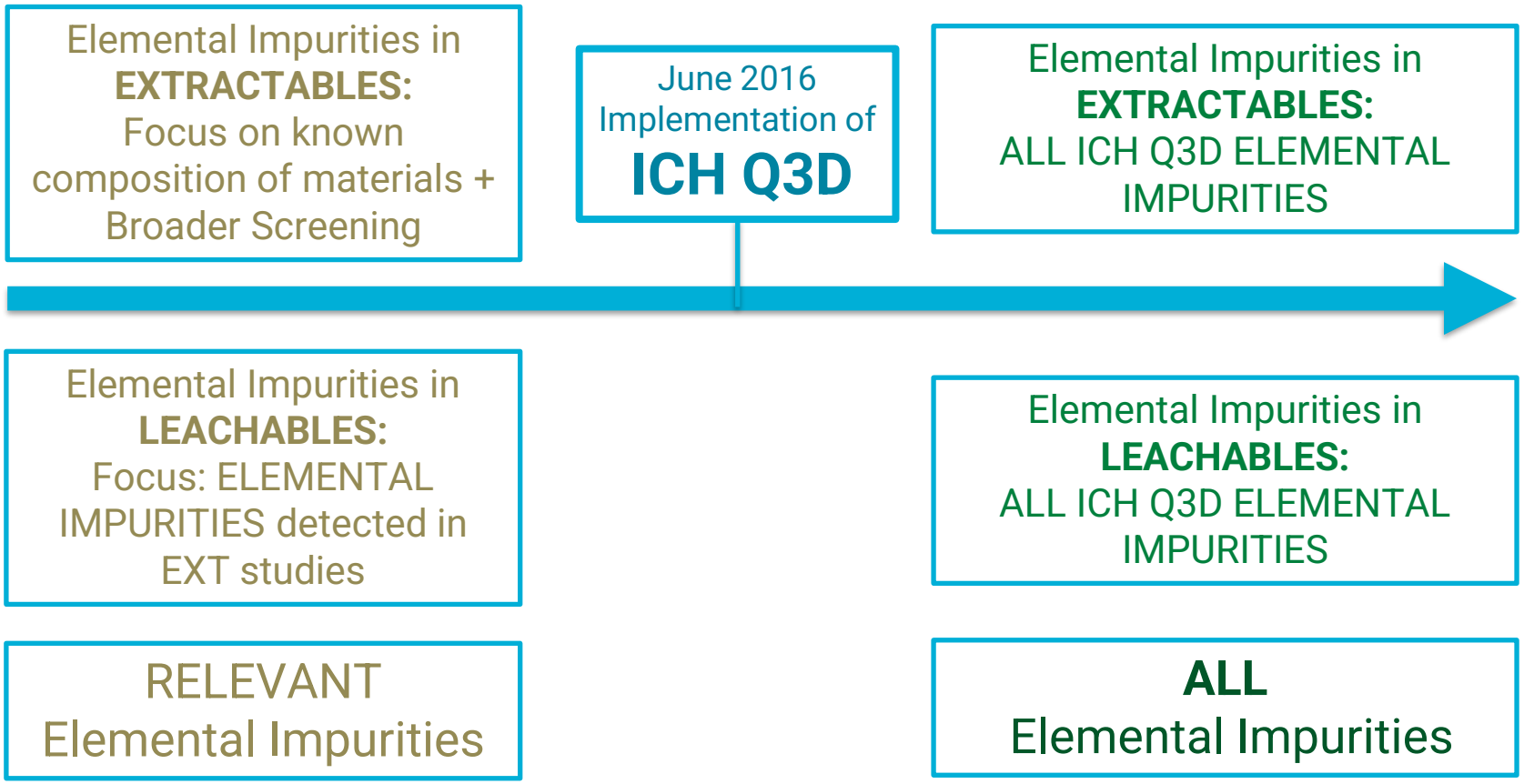
Scenario 2: N-Nitrosamines are directly detected in a material extract

- Consider **change of material of construction**?
- No material change: **monitor the N-Nitrosamine** in the drug product leachables study

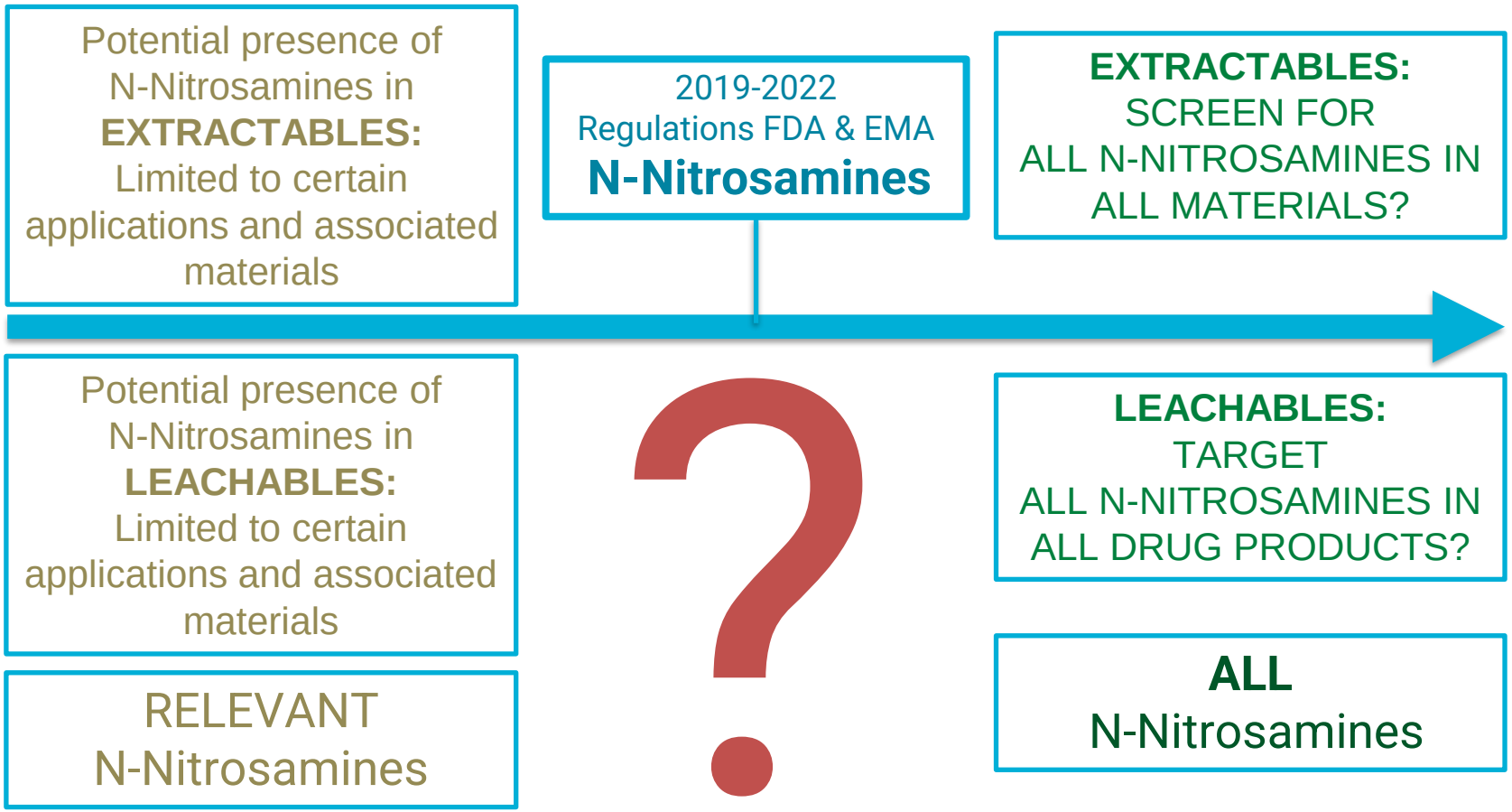
Scenario 3: Amines detected > LOD but no N-Nitrosamines

- **Can N-nitrosamines be formed in the Drug Product** (during stability) from "secondary Amine" Leachables from the materials?
  - **Little is known** about the "in-situ" formation of N-Nitrosamines in the drug product
  - **Perform a Nitrosamine risk assessment – if not yet done**:
    - Are there any **nitrosating agents** present in the **drug product**?
    - Is the **reaction environment** favorable to form N-Nitrosamines?
- Consider:
  - **To include the amine as a target compound** for follow-up in leachables study
  - To monitor the **associated N-Nitrosamine** in leachables study

Parallel with ICH Q3D implementation?



Parallel with ICH Q3D implementation?



Conclusion

Conclusion

- There is a **general concern** about the presence **of N-Nitrosamines in Drug Products**
- One of the **potential sources** of N-Nitrosamines is the **packaging** of the drug product
- **Historical Cases** showed N-Nitrosamine contamination of the Drug Product from the Packaging
- **Do we know everything** about the packaging already?
    - Assessment of production and composition of packaging materials
- For **Extractable Studies**: focus on **precursors of N-Nitrosamine** formation above LOD
    - Secondary Amines
    - Tertiary Amines
- Potentially **monitor secondary/tertiary amines** during **Leachable** studies
- Include associated **N-Nitrosamine monitoring** at low levels in **Leachable** studies?
- **What will the future bring**? General monitoring of N-Nitrosamines in Leachable Studies?
- Time will tell…

wdautry@nelsonlabs.com