

Where N-Nitrosamine Assessments for Drug Products meet Extractable / Leachable Qualifications for Pharmaceutical Primary Packaging

31 March 2022



Intro – the issue with N-Nitrosamines

Since July 2018: recalls for

Valsartan
Other “Sartan” Drugs
Ploglitazone
Ranitidine
Metformin
Rifampicin
Rifapentine
Varenicline
Bumetanide
Sumatriptan
Deferasirox

N-nitrosamine contamination

**N-nitroso- chemicals
belong to cohort of
concern (ICH M7):**

**High potency mutagenic
carcinogens!**

**Monitor concentrations as
defined in current
Regulatory Guidelines
(ppt levels)!**

N-nitrosamine formation

During **Synthesis** drug
Substance
(Sartans; NaNO_2 used to quench Azides)

Degradation of the API
(Ranitidine)

Packaging
(Nitrocellulose laminated blister)

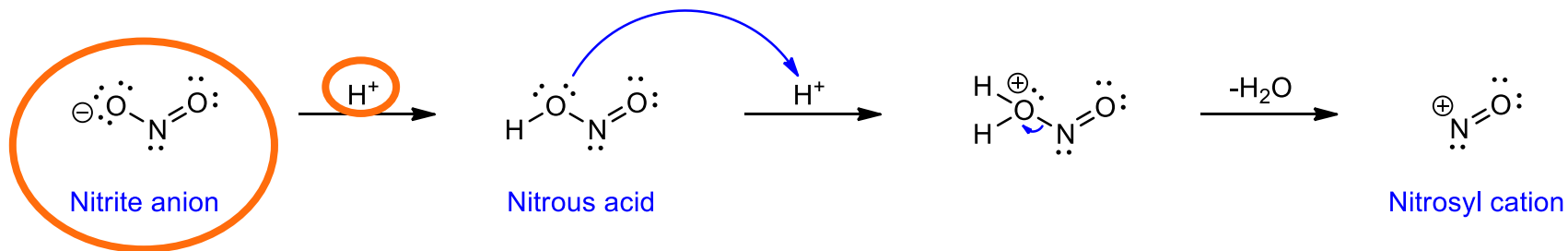
MORE SCRUTINY & CONSEQUENCES FOR:

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

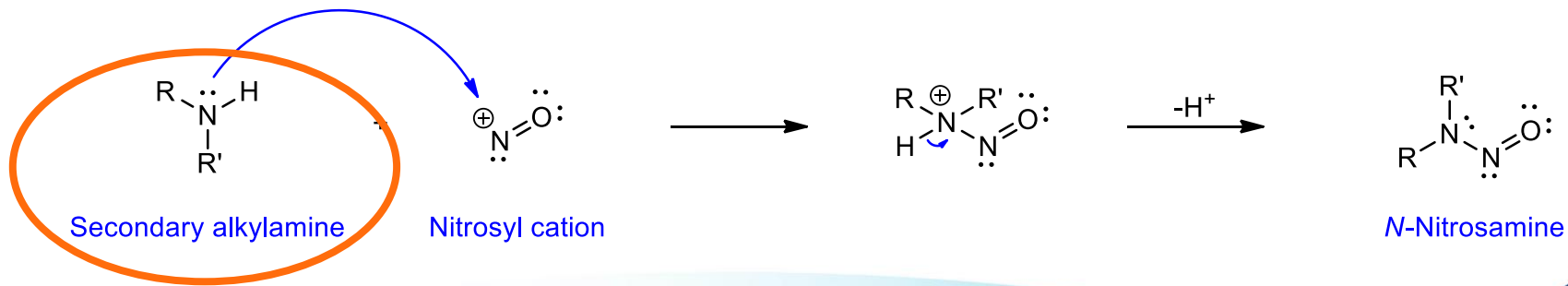
This presentation: N-nitrosamines in relation to E&L assessments

Formation of N-Nitrosamines

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



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



Amine Sources

- 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)
- Additives

Nitrosating Agents

NaNO_2

HNO_2

NO

ClNO

BrNO

N_2O_3

N_2O_4

Organic Nitrites

Side reactions in nitration reactions

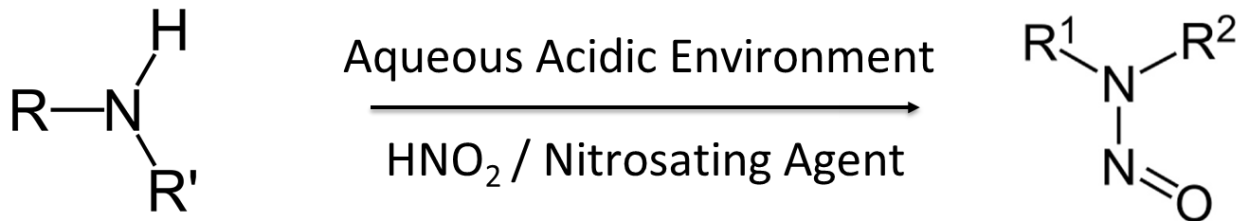
Hydroxylamine under oxidative conditions

Chloramines

Ozone

Other...

Formation of N-Nitrosamines



Low [HNO₂ /nitrosating compound]
Low [Secondary Amines]

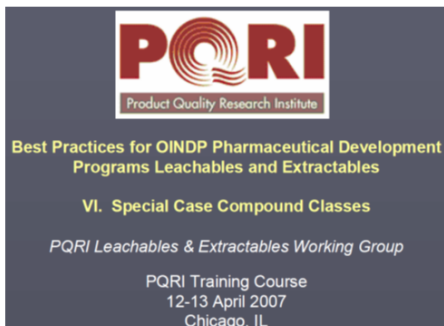
High [HNO₂ /nitrosating compound]
Low [Secondary Amines]

High [HNO₂ /nitrosating compound]
High [Secondary Amines]

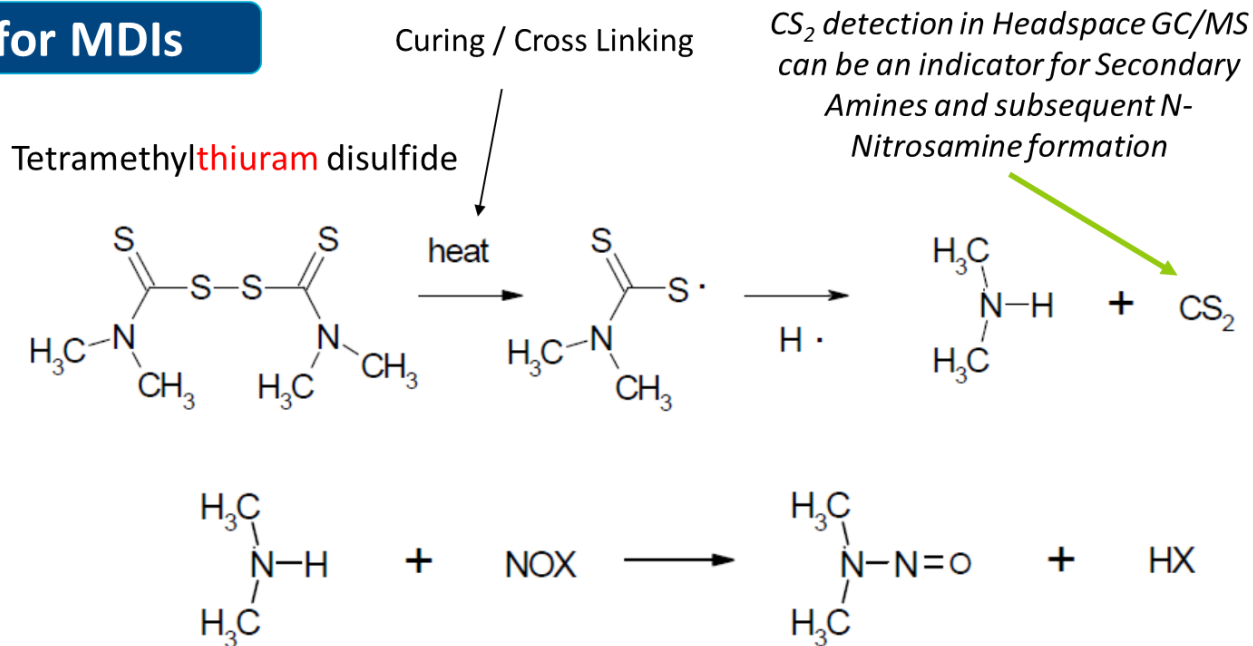
Increasing risk of N-Nitrosamine Formation

Historical cases of N-Nitrosamines related to packaging

Rubber gaskets for MDIs



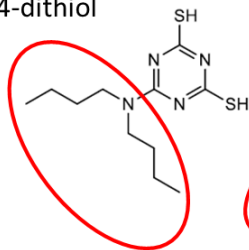
Based on work done by Dan Norwood & James O. Mullis



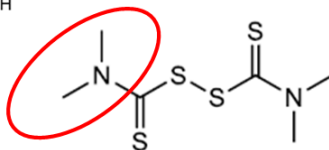
Historical cases of N-Nitrosamines related to packaging

Rubber gaskets for MDIs – Overview of old and new vulcanizers / accelerators

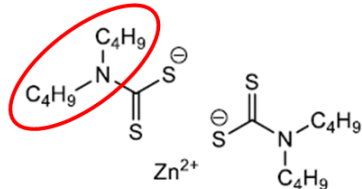
6-(**dibutylamino**)-1,3,5-triazine-2,4-dithiol



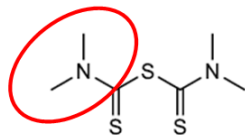
Tetramethyl**thiuram** disulfide



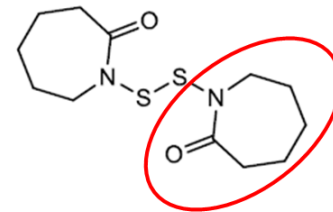
Zinc bis(dibutyl**dithiocarbamate**)



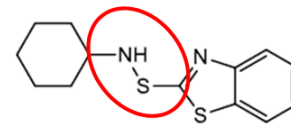
Tetramethyl**thiuram** monosulfide



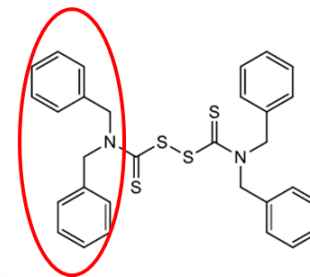
N,N'-Caprolactam disulfide



N-cyclohexyl-2-benzothiazole sulfenamide



N,N,N',N'-Tetrabenzyl**thiuram** disulfide



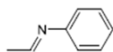
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Rubber gaskets for MDIs – Overview of old and new vulcanizers / accelerators

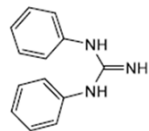
Hexamethylene tetramine (HMT)



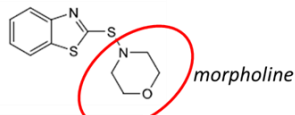
Ethylidene aniline (EA)



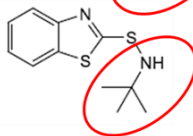
Diphenyl guanidine (DPG)



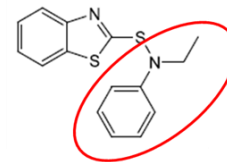
N-Oxydiethylbenzthiazylsulfenamide (NOBS)



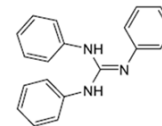
N-t-butylbenzthiazylsulfenamide (NS)



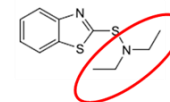
Ethyl phenyl thiocarbamate



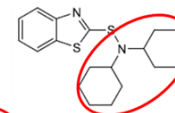
Triphenyl guanidine (TPG)



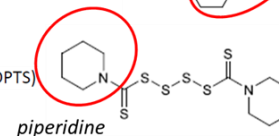
Diethyl (di)thiocarbamate



N,N'-Dicyclohexylbenzthiazylsulfenamide (DZ)



Dipentamethylene thiuram tetrasulfide (DPTS)



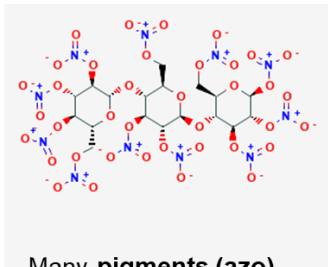
Rubber gaskets for MDIs – Overview of old and new vulcanizers / accelerators

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

Historical cases of N-Nitrosamines related to packaging

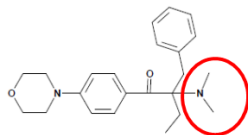
Nitrocellulose blister foil

Nitrosating compound:
Nitrocellulose

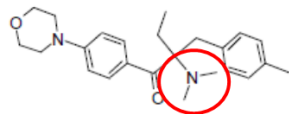


Many **pigments (azo)** used in printing inks contain nitrogen in their chemical structure. some **may contain secondary and tertiary amine functional groups on the skeletal exterior.**

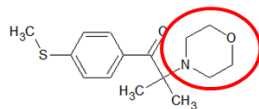
UV-Curing Agents
Irgacure 369



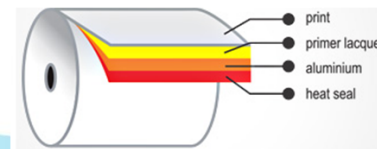
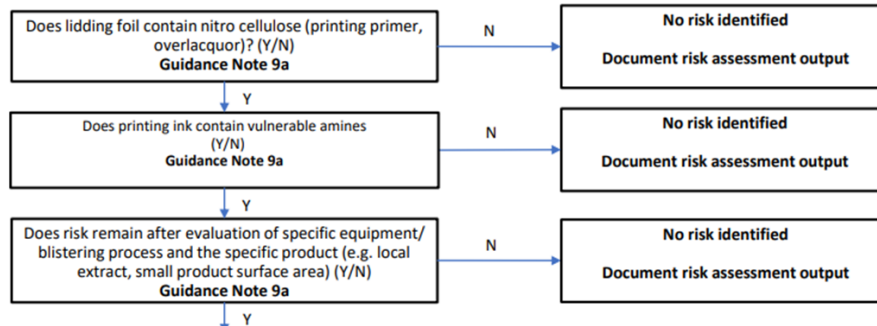
Irgacure 379



Irgacure 907



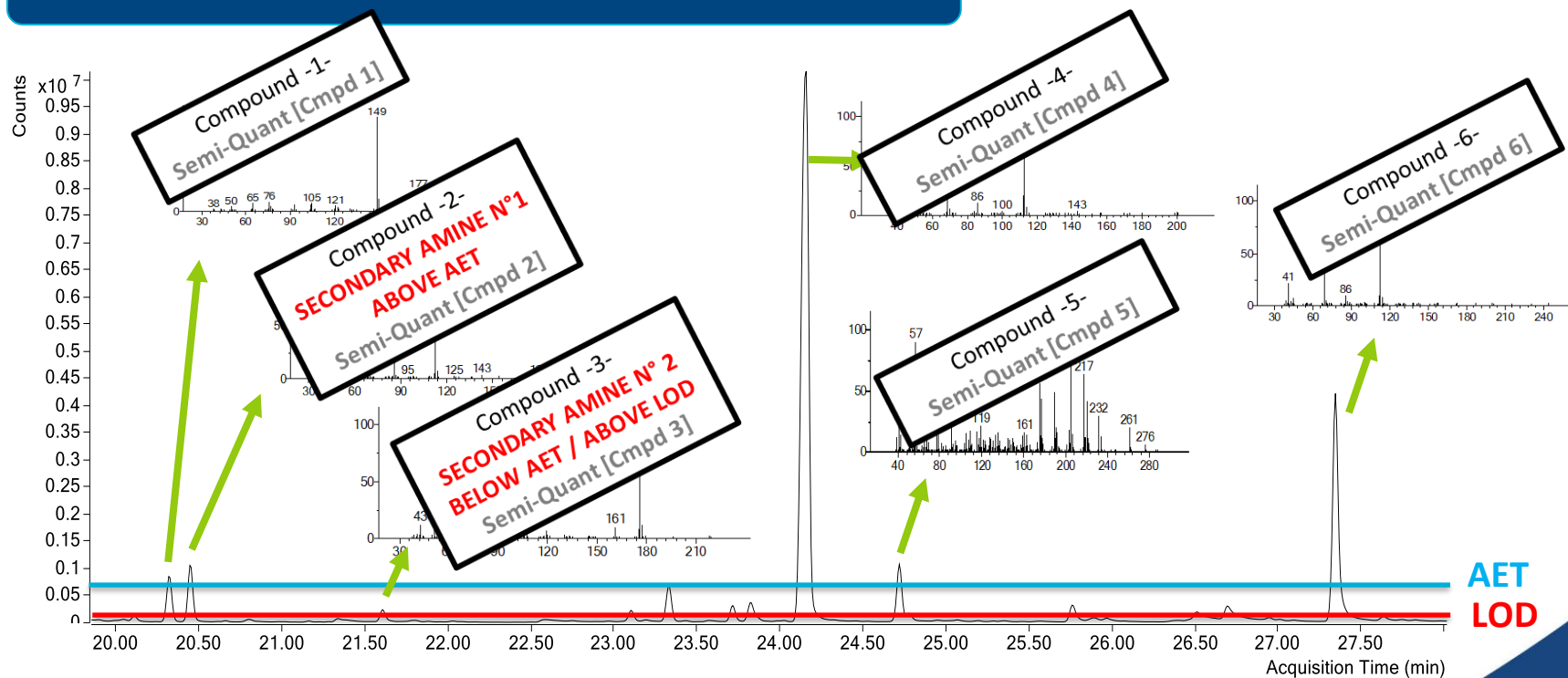
3. Risk Assessment for Nitrocellulose Packaging Materials



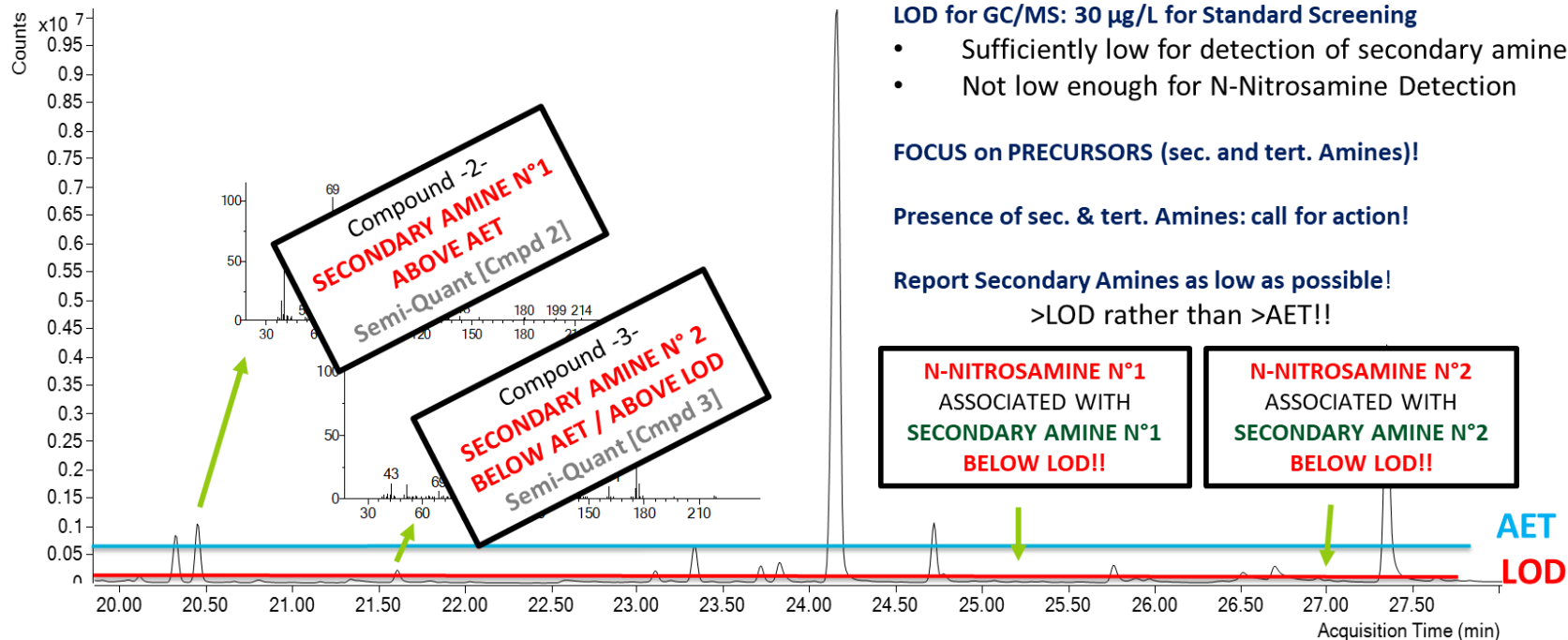
OPEN QUESTIONS

- 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?

CHROMATOGRAPHIC SCREENING PROCESS



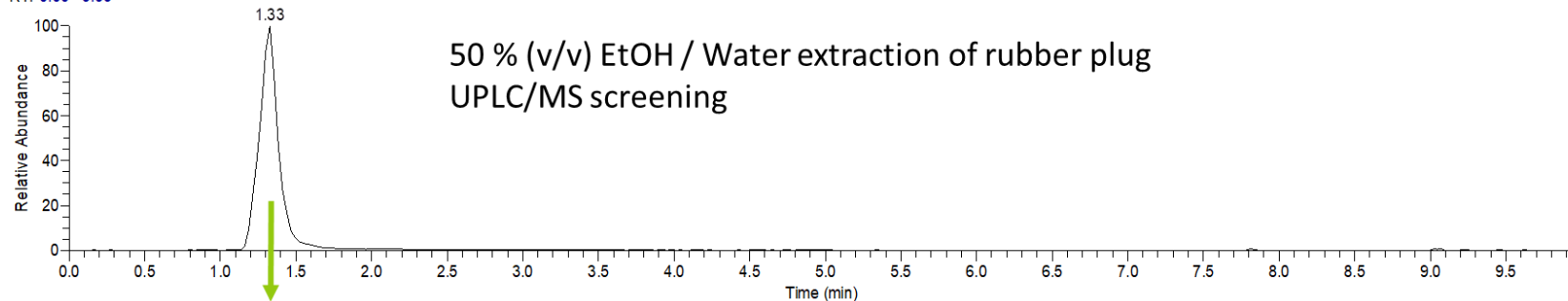
CHROMATOGRAPHIC SCREENING PROCESS



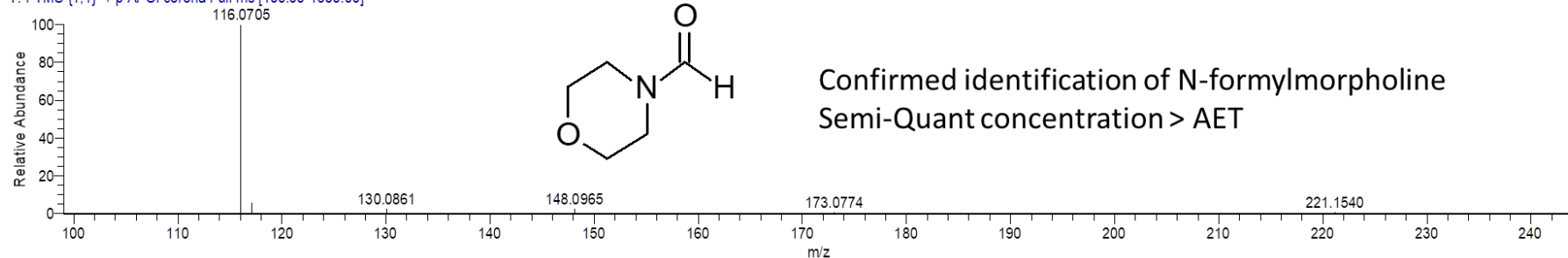
Role of E&L screening for N-Nitrosamine detection

CASE STUDY 1: RUBBER PLUG (2020)

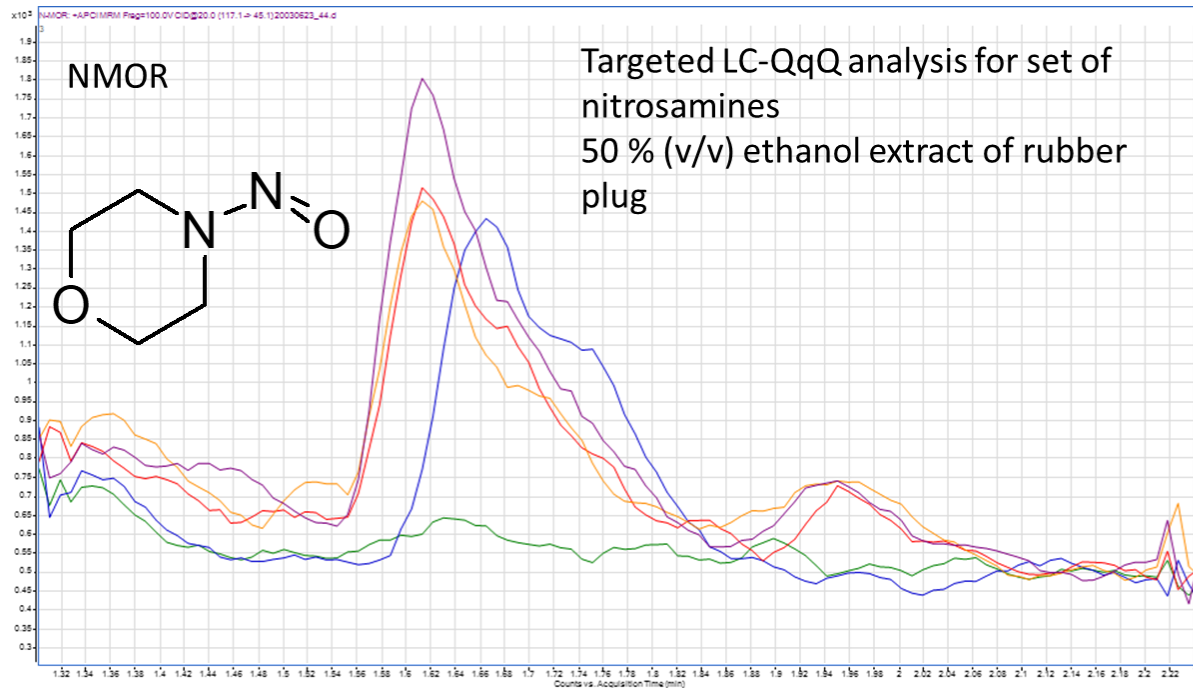
RT: 0.00 - 9.95



02aug131#135-160 RT: 1.24-1.47 AV: 9 SB: 2 1.60, 1.11 NL: 1.47E5
T: FTMS {1,1} + p APCI corona Full ms [100.00-1500.00]



CASE STUDY 1 (cont): RUBBER PLUG (2020)



Blank extract

Sample 1

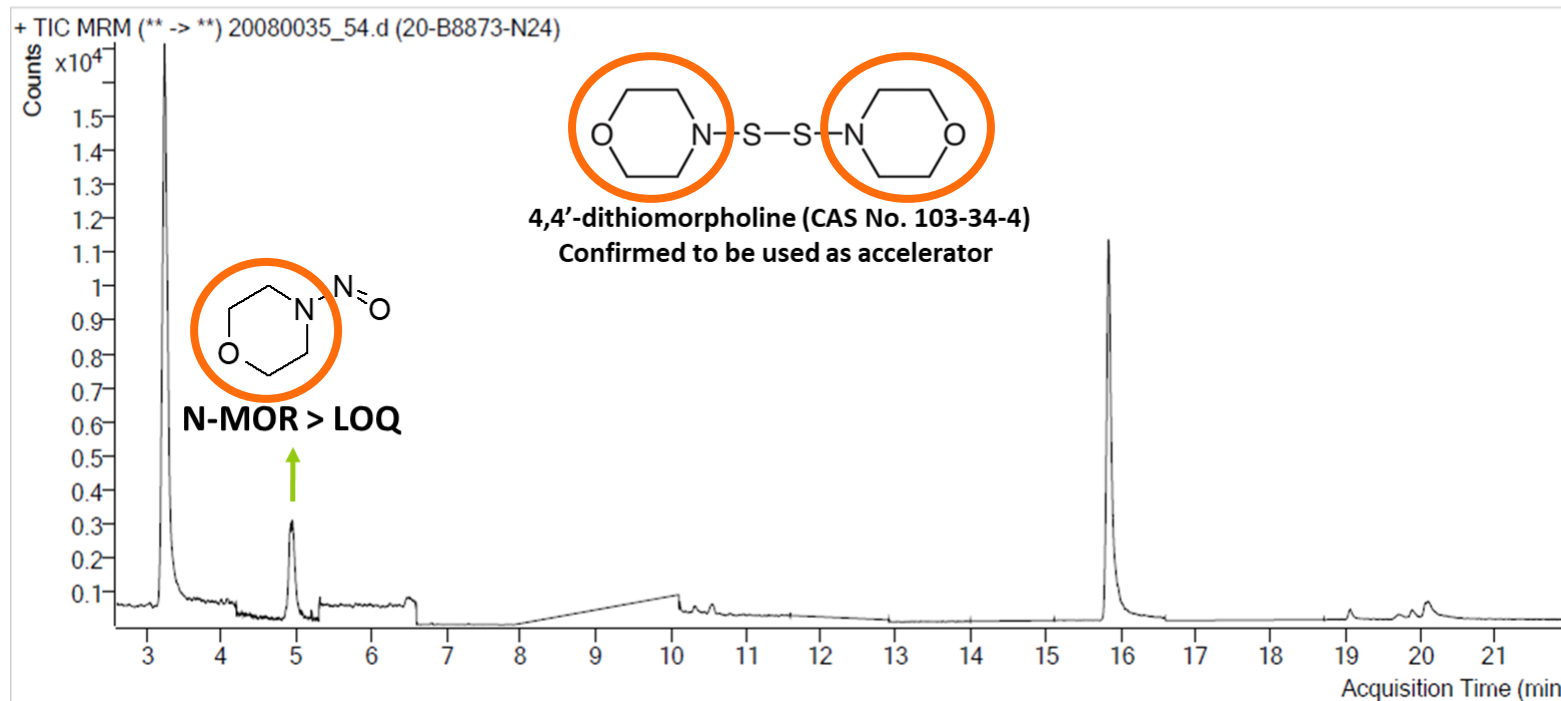
Sample 2

Sample 3

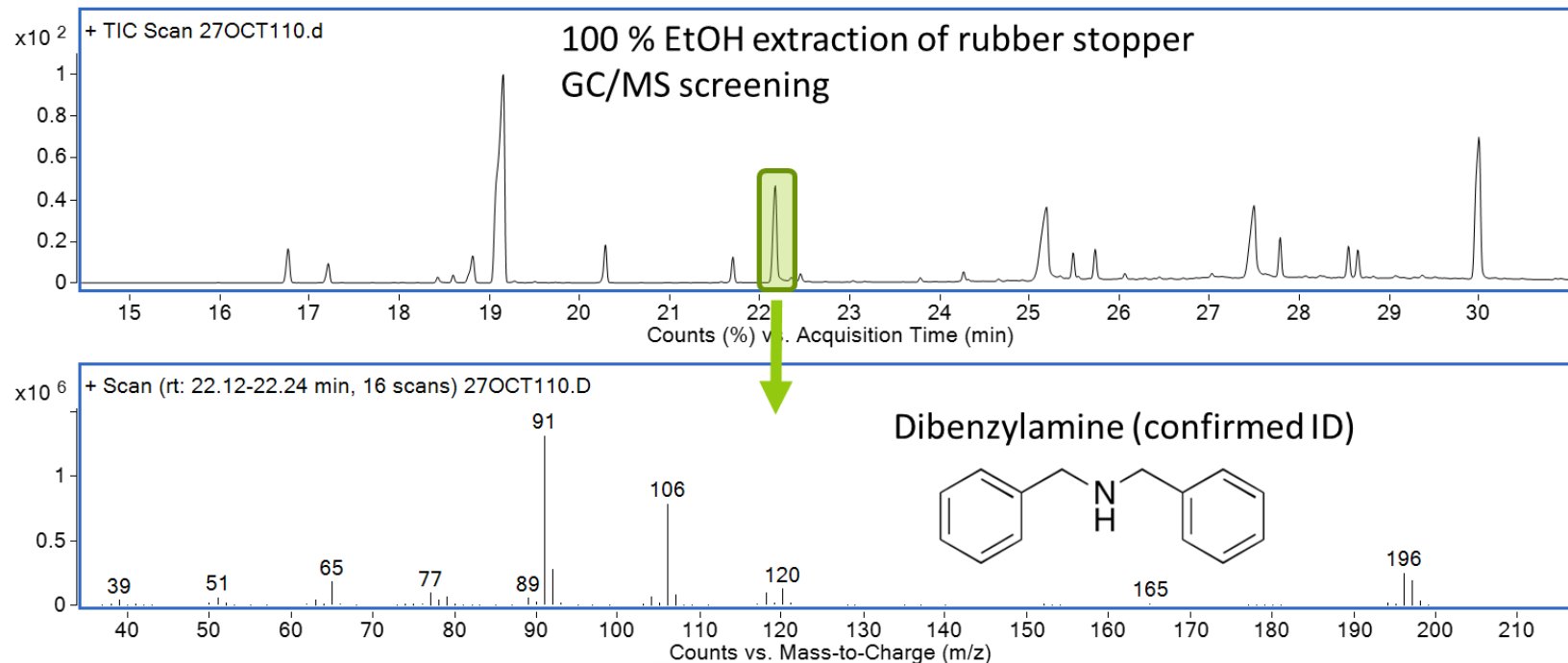
Sample 4

N-nitrosomorpholine > LOQ

CASE STUDY 2: RUBBER STOPPER (2020)

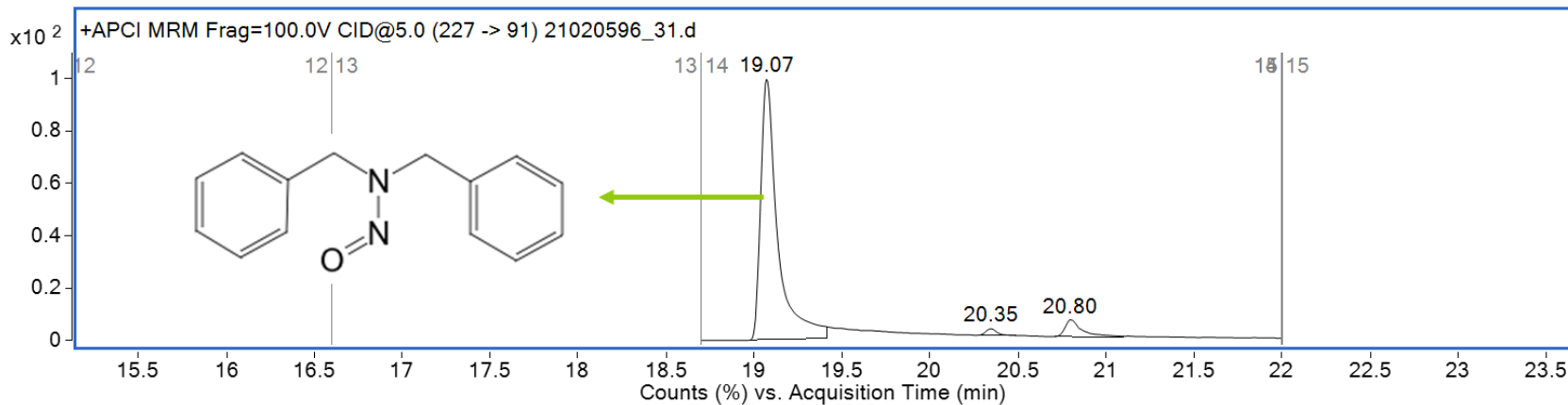


CASE STUDY 3: RUBBER STOPPER (2021)



CASE STUDY 3 (cont): RUBBER STOPPER (2021)

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



Potential consequences for extractables study design

Presence of secondary (& tertiary) 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

If no amines were 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)

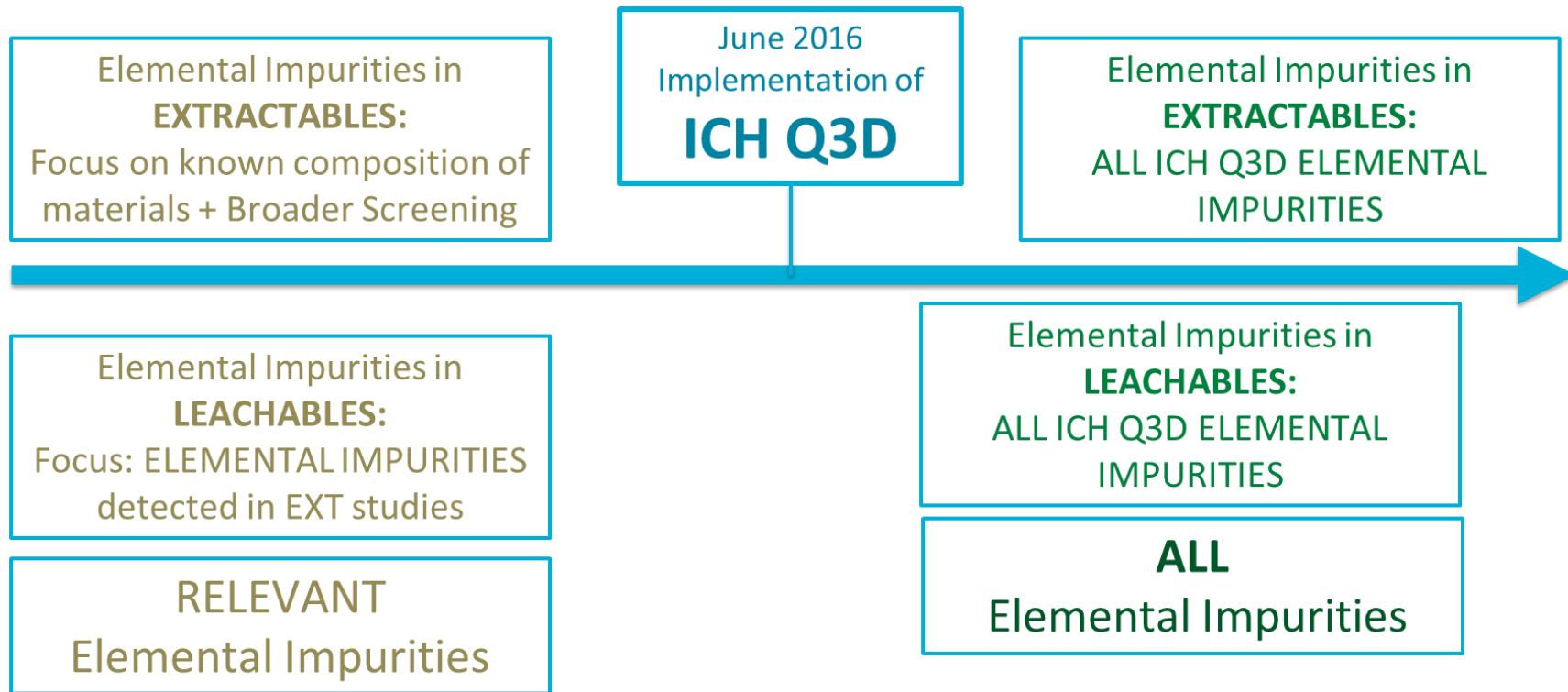
When N-Nitrosamines should be monitored in a leachables study?

- **OBVIOUS:** if 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
- **LESS OBVIOUS:** if secondary (& tertiary) amines are detected in the material, but no N-nitrosamines present in the material
 - **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
 - Are there any **Nitrosating Agents** present **in the drug product**?
 - Is the **reaction environment** favorable to form N-Nitrosamines?

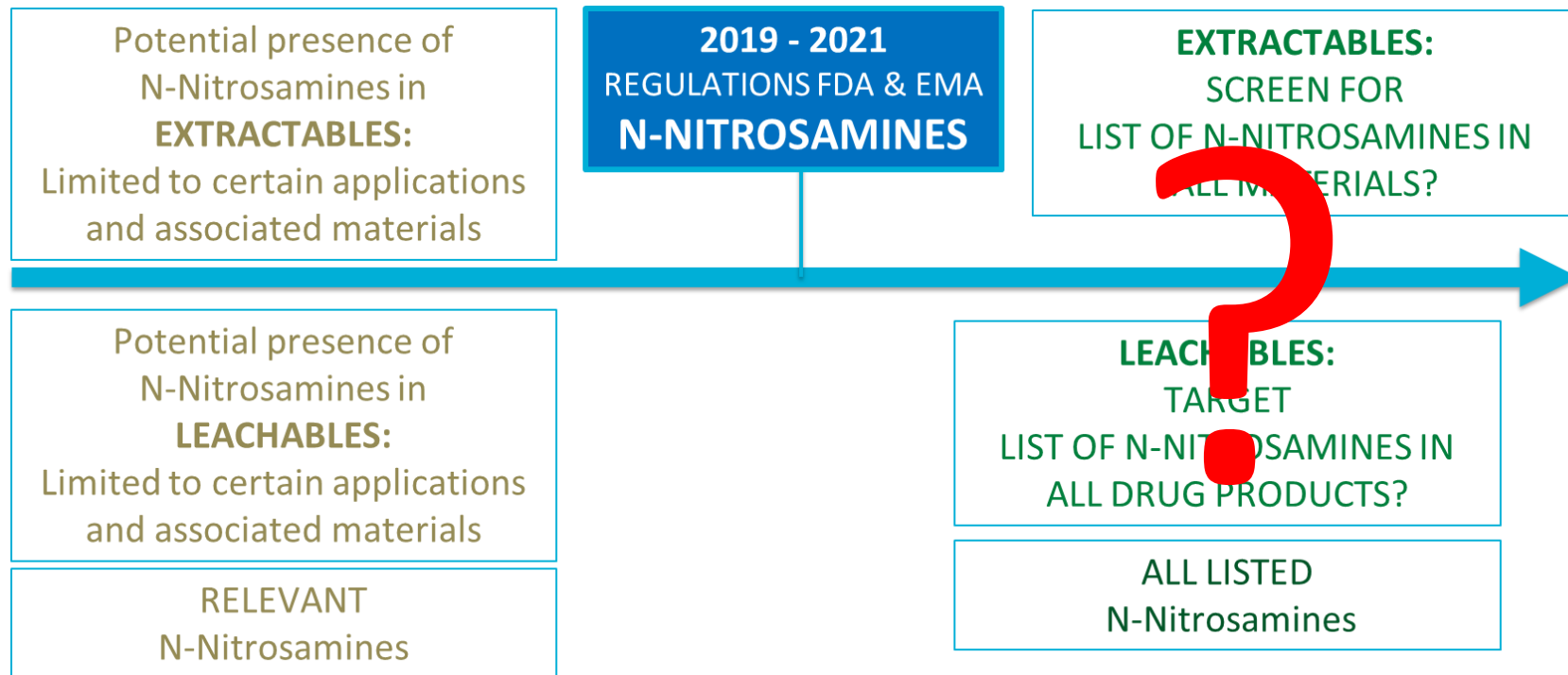
HOWEVER

It cannot be excluded that in future
a broader targeted method for specific – and
regulated N-Nitrosamines
will be included into the Leachable study design

What can we learn from the ICH Q3D implementation on E/L-strategies?



What can we learn from the ICH Q3D implementation on E/L-strategies?



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...



Thank you

Questions?

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