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The Southern California Pharmaceutical Discussion Group (SCPDG)

Nitrosamines Risk Assessment

Panelists:

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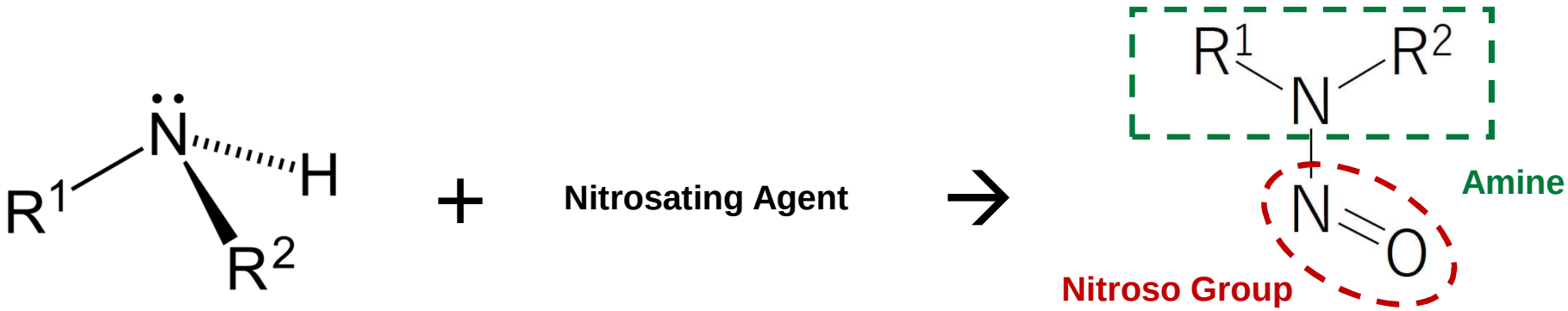
March 20, 2023
Costa Mesa, CA

Agenda


Introduction
What are nitrosamines?
How it all started?
Current situation
Path forward
API & Excipients
Risk Assessment
Drug Products
Risk Assessment Workflow
Analytical
Targets, Limits, and Test Methods
Panel Discussion
Questions & Answers

What are Nitrosamines?

- Organic compounds containing a nitroso group bound to an amine
  - ▶ Reaction triggered by an acidic environment
- They exists in low levels in water and foods including meat, vegetables and dairy products
- **Risks**: Cancer if exposed to higher than acceptable levels for longer period

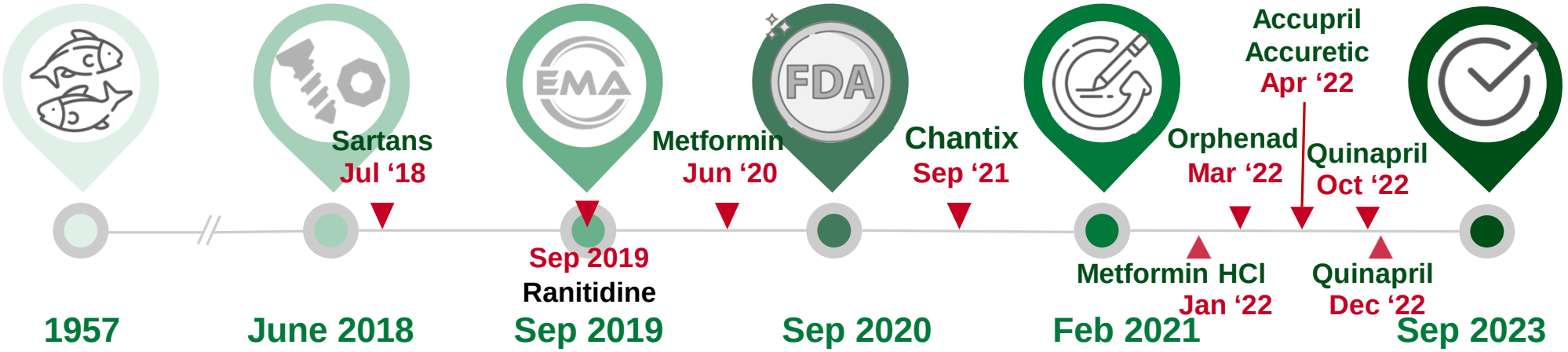


Secondary or Tertiary Amine

How it all started?

Why now?

Availability of modern analytical testing tools making it possible to determine impurities (ppb).



1957

Norway's farm animals fed fish (herring) developed liver cancer.

- $NaNO_2$ was used in as a preservative of fish meal.
- The meal contained 100ppm dimethyl nitrosamine.

June 2018

FDA learned about unacceptable levels of NDMA in Valsarten of ZHP Co.

- 2012: ZPH found unidentified peak in in residual solvent chromatograph of Valsartan's API
- 2017: FDA inspection of ZHP indicated equipment rusting and accumulation of black metallic particles in their product
- 2018: ZHP disclosed presence of an unidentified impurity in Valsartan after receiving customer complaint

Sep 2019

EMA guidance published

Sep 2020

FDA published initial risk assessment for API and DP manufacturers.

Feb 2021

FDA released a revision to specify the timeframe for completion of nitrosamine mitigation activities

- Risk assessment to be completed by Mar 31, 2021

FDA listed excipient supplier qualification as a mitigation strategy

Sep 2023

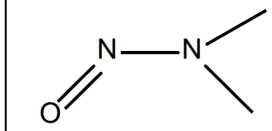
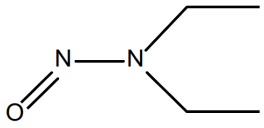
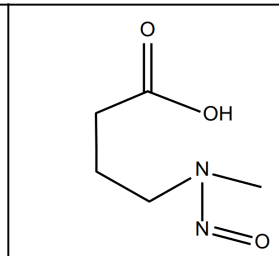
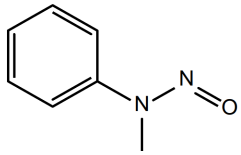
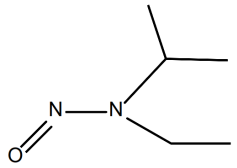
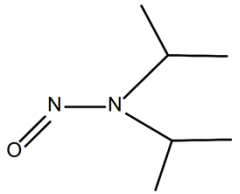
Deadline to complete confirmatory testing of DPs and submission of any necessary changes in drug application.

Nitrosamines in Drug Products

WHO's International Agency for Research on Cancer (IARC) classifies agents based on their carcinogenicity level

- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans

Acceptable Intake* limit (ng/day) of Nitrosamines

					
N-Nitrosodimethylamine	N-Nitrosodiethylamine	N-nitroso-N-methyl-4-aminobutanoic acid	N-nitrosomethylphenylamine	N-nitrosoisopropylethyl amine	N-nitrosodiisopropylamine
NDMA	NDEA	NMBA	NMPA	NIPEA	NDIPA
96	26.5	96	26.5	26.5	26.5

Group 2A **Group 1**

*Acceptable Intake is a daily exposure to a Nitrosamine that approximates a 1:100,000 cancer risk after 70 years of exposure.

Regulatory situation in market

- Agencies including FDA have requested that sponsors evaluate marketed products for the potential presence of nitrosamines.
- Evaluations must be conducted for APIs and finished drug products to determine the risk of nitrosamine formation/presence.

Risk Assessments Considerations

- Are there any nitrites, nitrosating agents, primary, secondary and tertiary amines present that could interact?
- Consider intrinsic and extrinsic sources
- Risk = the sum of evaluations for API, DP (including excipients), manufacturing process, packaging materials and storage.
- Authorities are expecting the risk evaluation to be “Yes” or “No” including a rationale for the decision.
- Testing is not expected unless a potential risk has been determined

If potential risk is determined

- Immediately inform the agency and take appropriate action to minimize patient exposure
- Ensure a control strategy for confirming the presence of nitrosamines

Nitrosamines Impurities: What is Next ?

- It is ultimate responsibility of a manufacturers to understand the processes and prevent unacceptable impurities.
- Manufacturers are responsible for developing suitable test methods

Is source of nitrosamine impurities known?

- It is a developing science
  - ▶ The first and only US-FDA guidance published in Sep. 2020 (updated on Feb. 2021)
- **“**Known” - “Knowns”
- “Known” - “Unknowns”
- “Unknown” - “Unknowns

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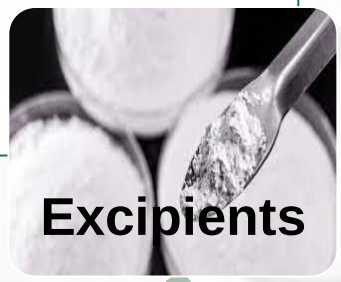
API and Excipient Risk Assessments Each Represent 1 Piece of the Nitrosamine Puzzle

- Manufacturing process
- Impurities



- Manufacturing process
- Impurities

- Manufacturing process
- **Interaction between components of the formulation**
- Stability
- Packaging

Confirmatory testing

Communication between the Suppliers and Drug Product Manufacturers is Key

- Ingredient origin
- Are nitrosating agents used, likely, known?
- Have nitrites, nitrates, nitrosamines been analyzed?
- Nitrites and nitrates in manufacturing water?
- Amines, amides, ammonium salt
- Solvents
- Shared equipment

- IPEC Federation template (previously IPEC Europe template)
- Many excipients contain low-levels of nitrites
  - ▶An excipient supplier may or may not have analytical data

version 1
Feb 2023

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Nitrosamine Drug Product Risk Assessment General Workflow

Nitrosamine Impurities and Contaminants

- Formulation components (drug substance, excipients)
- Primary packaging components
- Manufacturing facilities

Nitrosamine Formation in Drug Product

Secondary or tertiary amines ✚ Nitrosating agent (nitrite) ✚ Microenvironment pH ≤ 5

If all conditions are met, reaction conditions are favorable for nitrosamine formation. Perform kinetic simulation estimate nitrosamine content at the end of DP shelf-life and compare with acceptable limits.

Nitrosamine Formation in Primary Container

Secondary or tertiary amines ✚ Nitrosating agent (nitrite)

If all conditions are met, reaction conditions are favorable for nitrosamine formation. Estimate nitrosamine content generated during manufacturing and at the end of DP shelf-life and compare with acceptable limits.

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Sources of Nitrosamine Impurities and Contaminants

Drug substance (DS)

- Refer to DS risk assessment of nitrosamine contaminants and formation during DS manufacturing

Manufacturing facilities

- Gilead outsources most clinical and commercial drug product manufacturing
- Rely on Gilead designed questionnaires to determine risk of contamination from other products
  - Water quality (type/grade, nitrite content, specified nitrosamine/nitrite concentrations)
  - Equipment cleaning (solvents/cleaning agents, water quality)
  - Analytical (methods capable of detecting nitrites and/or nitrosamines)
  - Use of recovered/recycled solvents, catalysts, reagents

Excipients & primary packaging components

- Little information on nitrosamine impurities is available from vendors and literature
- For excipients, evaluate based on excipient structure
  - In progress: send IPEC questionnaire to all excipient vendors
- For packaging components, identify if there are amines and/or nitrosating agents that could react

Processing water*

- Little information on purified water
- Determine amount of water used during manufacturing process and assume 100% transfer of NDMA to formulation

*Water is assumed to have 0.1 ug/L N-nitrosodimethylamine (NDMA) based on WHO limit for potable water

NDMA: N-nitrosodimethylamine

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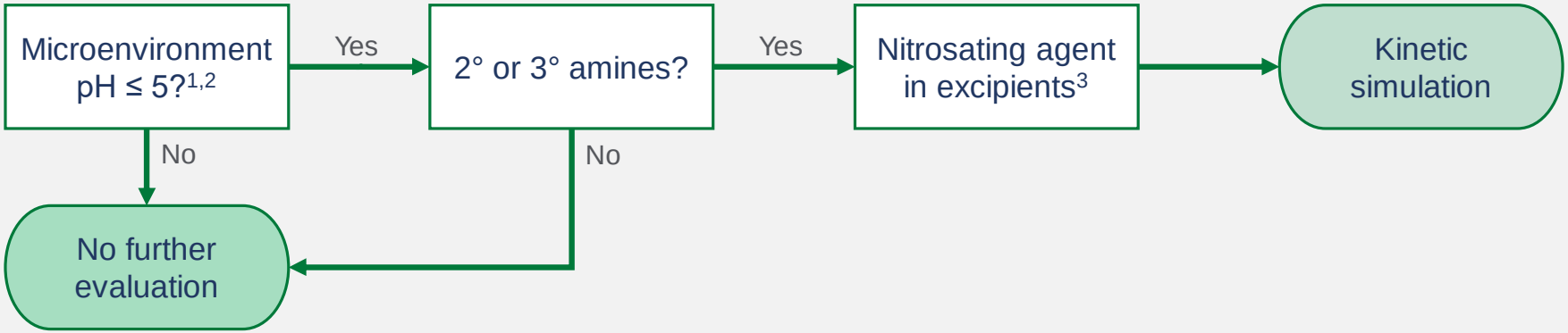
Evaluation of Nitrosamine Formation During Long-Term Storage

Are the reaction conditions present in the formulation?



1) pH 5 cut-off is based on published solution-state data. New data suggests that reaction in the solid-state is less dependent on pH. Impurities such as chloride and aldehydes may catalyze the reaction above pH 5. Regulatory agencies are requesting testing for many products above pH 5. Aldehyde: https://doi.org/10/1016/j.xphs.2022.10.033.

2) Microenvironment pH in the solid-state is measured using the slurry pH method. Although an industry standard, does not seem to be accepted by regulatory agencies.

3) All excipients are assumed to contain low levels of nitrites. Nitrite content in excipients is measured via ion chromatography.

Nitrosamine Drug Product Risk Assessment General Workflow

Nitrosamine Impurities and Contaminants

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Nitrosamine Formation in Primary Container

Packaging Configuration	Risk	Response
Bottles	None	None
Glass vials with stoppers[1]	None	None
Blisters[2]	Nitrocellulose foil lidding	Switched to nitrocellulose free lidding
Devices	Case-by-case basis	None

1) https://doi.org.10.1208/s12249-022-02491-7

2) Risk of nitrosamine depositing on tablets when packaged in pre-printed nitrocellulose lacquered foil lidding. Print ink is known to contain amine impurities. Formation of NMDA and NDEA will only occur during the high heat blistering process and will not continue to grow on storage.

NDMA: N-nitrosodimethylamine, NDEA: N-nitrosodiethylamine

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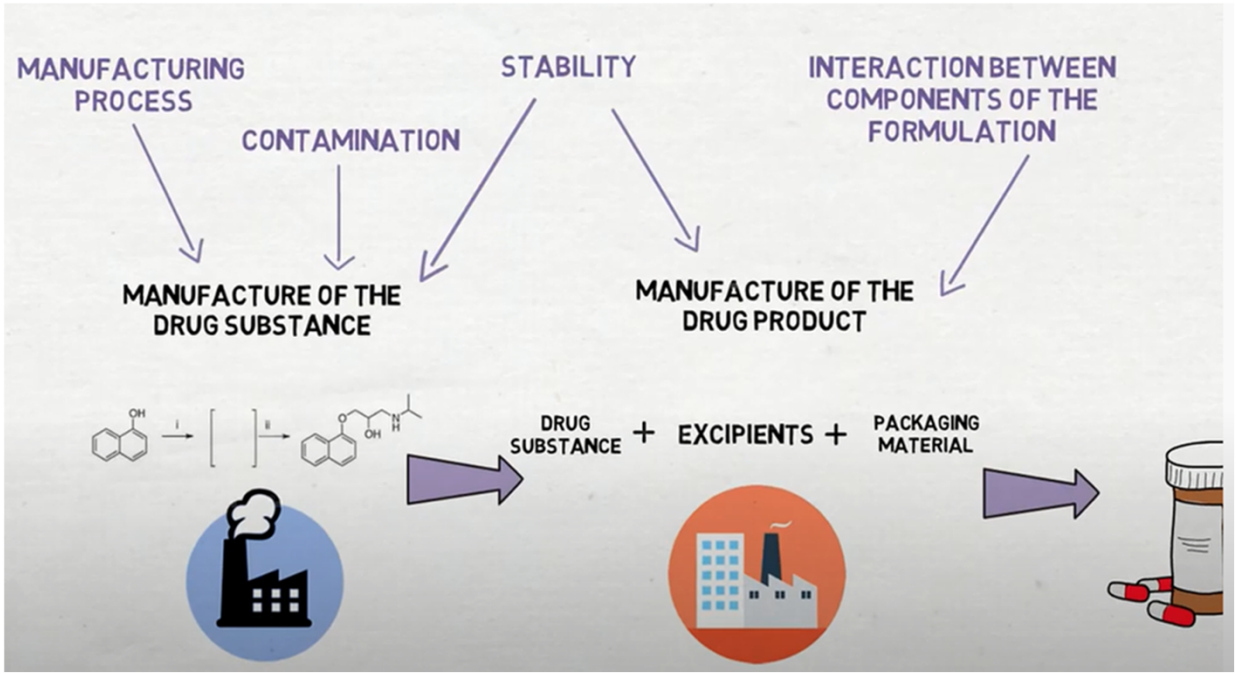
Process

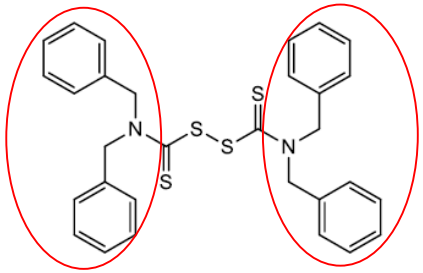
Step 1
Risk evaluation

Step 2
Confirmatory testing

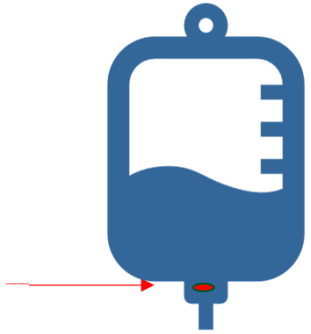
Step 3
Changes to the marketing authorisation

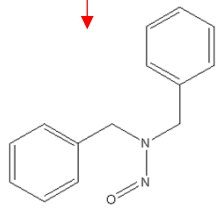
A few months later....
Risk evaluation in progress - Large Volume parenteral





N,N,N',N'-Tetrabenzylthiuram disulfi





N-Nitrosodibenzylamine

Case Study 1

STEP 1 - Analytical Testing - Elastomeric part

SOP 0272 nitrosamine screening

Target compound	CAS number
N-nitrosodimethylamine (NDMA)	62-75-9
N-nitrosodiethylamine (NDEA)	55-18-5
N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)	61445-55-4
N-Nitrosodiisopropylamine (DIPNA)	601-77-4
N-Nitrosoethylisopropylamine (EIPNA)	16339-04-1
N-Nitrosodibutylamine (NDBA)	924-16-3
N-Nitrosomorpholine (NMOR)	59-89-2
N-Nitrosodiphenylamine (NNDPhA)	86-30-6
N-Nitrosopiperidine (NPIP)	100-75-4
N-Nitrosodipropylamine	621-64-7
N-Nitrosopyrrolidine (NPYR)	930-55-2
N-Nitrosoethylmethylamine	10595-95-6
N-Methylnitrosopiperazine (MeNP)	16339-07-4
N-Nitrosomethylphenylamine (NMPA)	614-00-6
N-Nitrosodibenzylamine	5336-53-8

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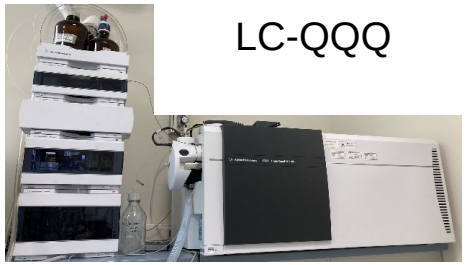

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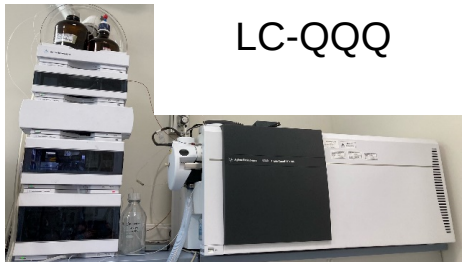
Extracts – worst case and DP simulating solvents



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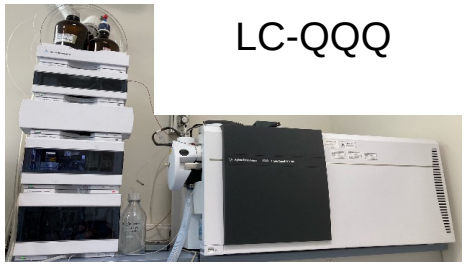
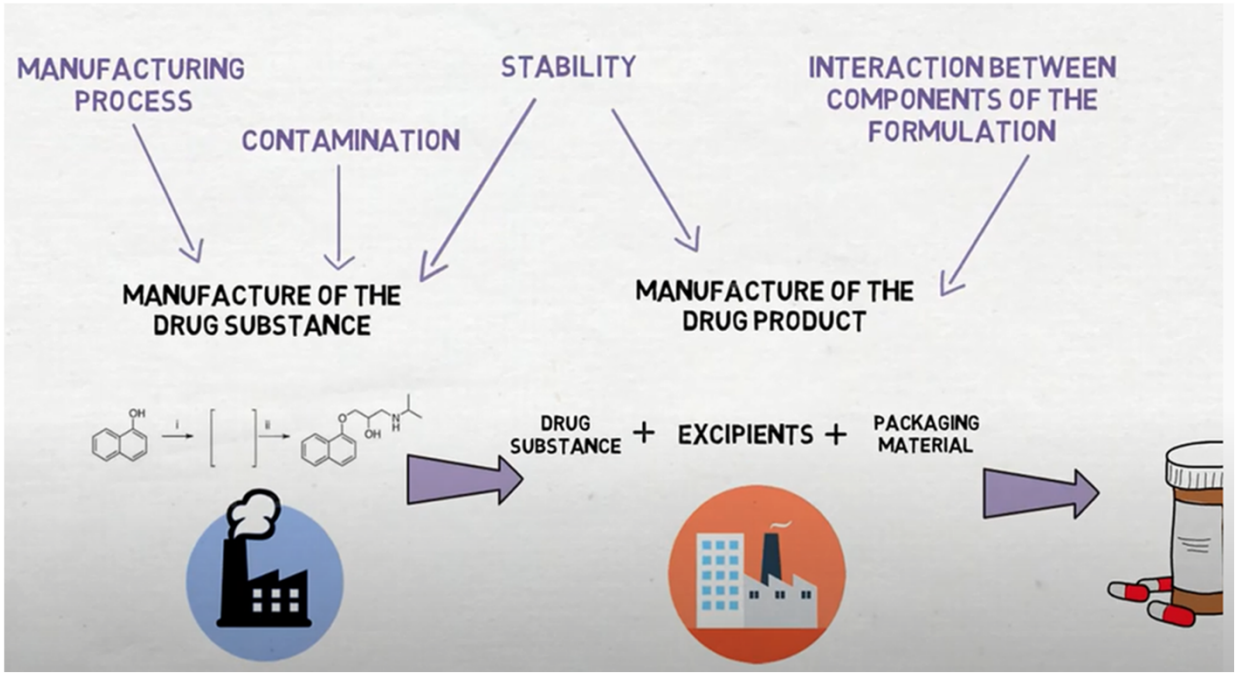
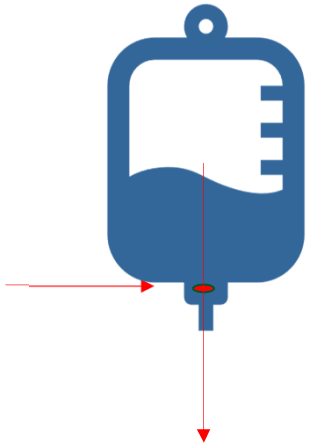
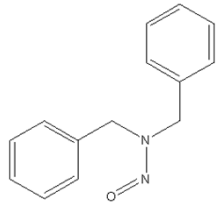


Detected above the sponsor limit - 4 ng/part
in worst case solvent &
high organic content simulation solution

Risk evaluation - Large Volume parenteral







N-Nitrosodibenzylamine

STEP 2 confirmatory testing in **Drug Product**

Analytical Testing – Targets and limits

1 nitrosamine at risk – Acceptable intake (AI)

Target compound*	CAS number	EMA Limit*	Other nitrosamines
N-nitrosodimethylamine (NDMA)	62-75-9	96.0 ng/day	Default Class specific TTC of 18 ng/day
N-nitrosodiethylamine (NDEA)	55-18-5	26.5 ng/day	ICH(M7) approach for **lifetime daily exposure**
N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)	61445-55-4	96.0 ng/day	
N-Nitrosodiisopropylamine (DIPNA)	601-77-4	26.5 ng/day	
N-Nitrosoethylisopropylamine (EIPNA)	16339-04-1	26.5 ng/day	
N-Nitrosodibutylamine (NDBA)	924-16-3	26.5 ng/day	
N-Nitrosomorpholine (NMor)	59-89-2	127 ng/day	
N-Nitrosopiperidine (NPip)	100-75-4	1300 ng/day	
N-Nitrosodipropylamine (NDPrA)	621-64-7	26.5 ng/day	
N-Methylnitrosopiperazine (MeNP)	16339-07-4	26.5 ng/day	
N-Nitrosomethylphenylamine (NMPA)	614-00-6	34.3 ng/day	
*EMA/409815/2020 rev. 11 (29 Jul 2022)			

N-nitrosodibenzylamine
18 ng/day x 3 L/day = 6 ng/L

NDEA
26.5 ng/day x 0.5 L/day = 53 ng/L

NDEA
26.5 ng/day x 0.001 L/day = 26 500 ng/L

Confirmatory Analytical Testing

- Validated methods
- Target nitrosamines
- LOQ based on Acceptable intake limits
- Matrix (DP, API, intermediates,..)

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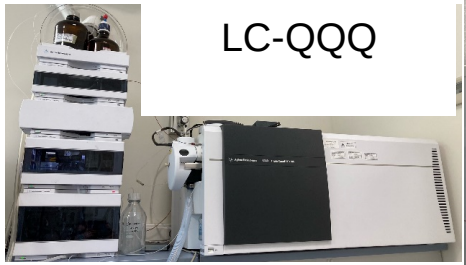
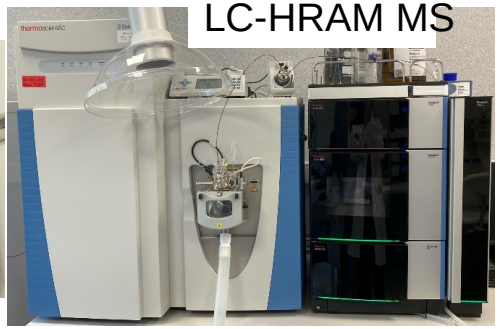
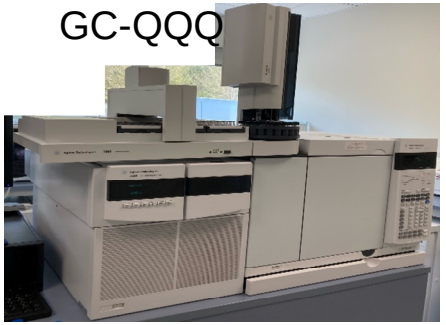


LC-HRAM MS



HS GC-MS

GC-QQQ



GC-HRAM MS

Guidance in EMA and FDA documents

Confirmatory Analytical Testing - Challenges

- AI limits - LOQ analytical procedure

  Maximum daily dose 3L/day – limit 18 ng/day

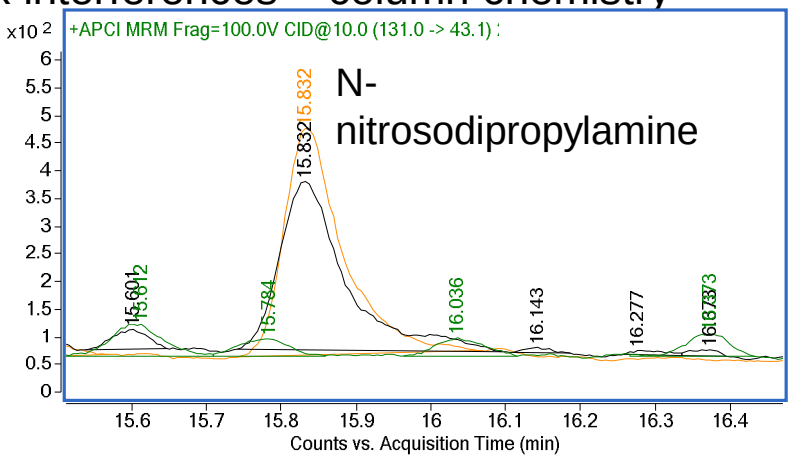
- If quantitative testing is performed as a routine control, the LoQ should be ≤ of the acceptable limit based on the relevant acceptable intake (AI) for the respective nitrosamine impurity; — 6 ng/L
- If quantitative testing is performed to justify skip testing, the LoQ of the analytical procedure employed should be ≤ 30% of the acceptable limit based on the AI;
- If quantitative testing is performed to justify omission of specification, the LoQ of the analytical method employed should be ≤ 10% of the acceptable limit based on the AI; — 0.6 ng/L
- Exceptions are anticipated for medicinal products used at high daily doses (AI may be below technical feasibility of the method), or in case more than one nitrosamine is anticipated or identified in a given medicinal product.

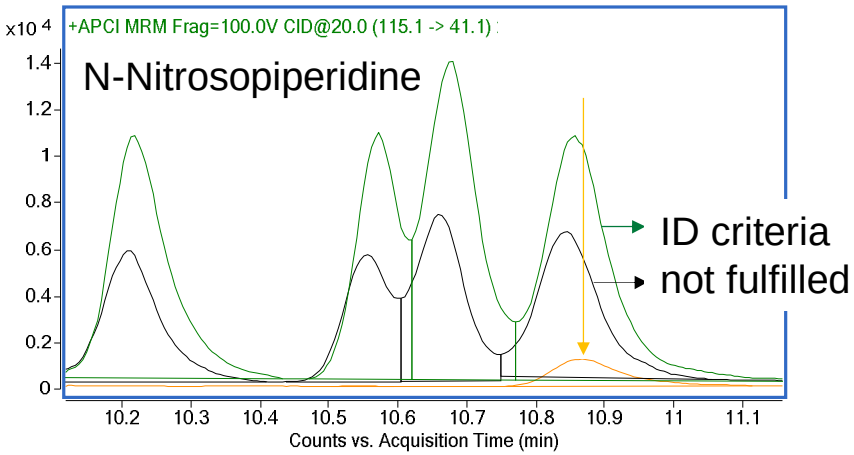
EMA /409815/2020 rev.1 29 January 2021

Confirmatory Analytical Testing - Challenges

- Selectivity/Specificity
  - matrix interferences ~ column chemistry

Standard in solvent
Spiked sample
Sample





Analytical Testing - Challenges

- False positives

Gloves

Filter

Analytical Testing - Challenges

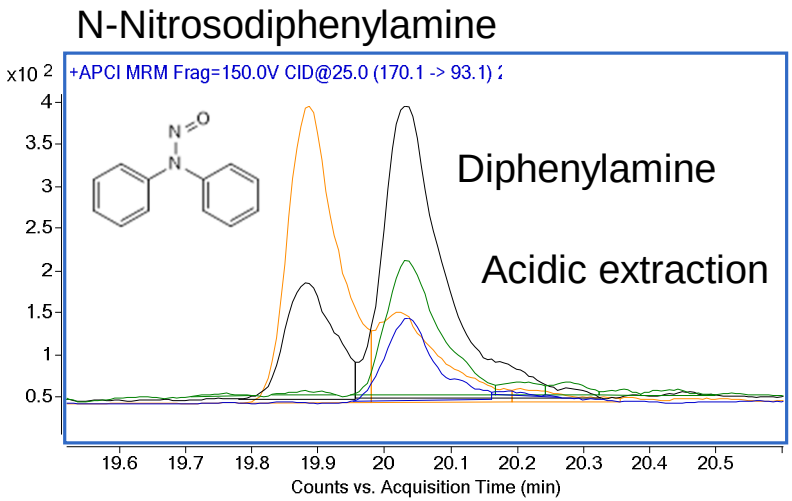
- False positives

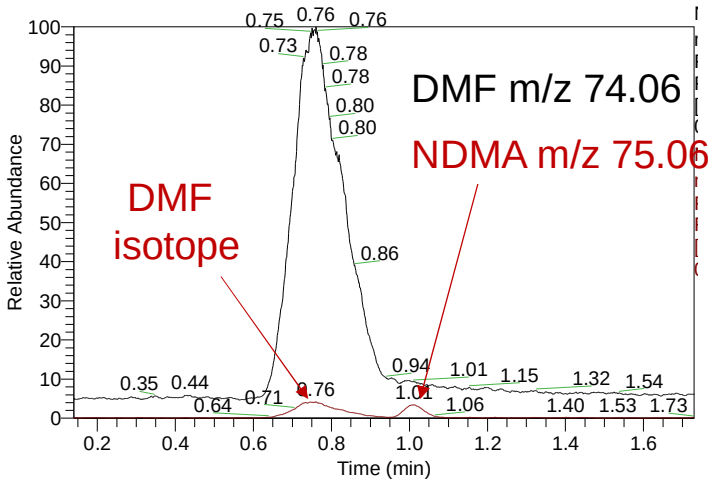
Chromatographic resolution!

Standard in solvent

Spiked sample

Sample Diphenylamine Standard in solvent



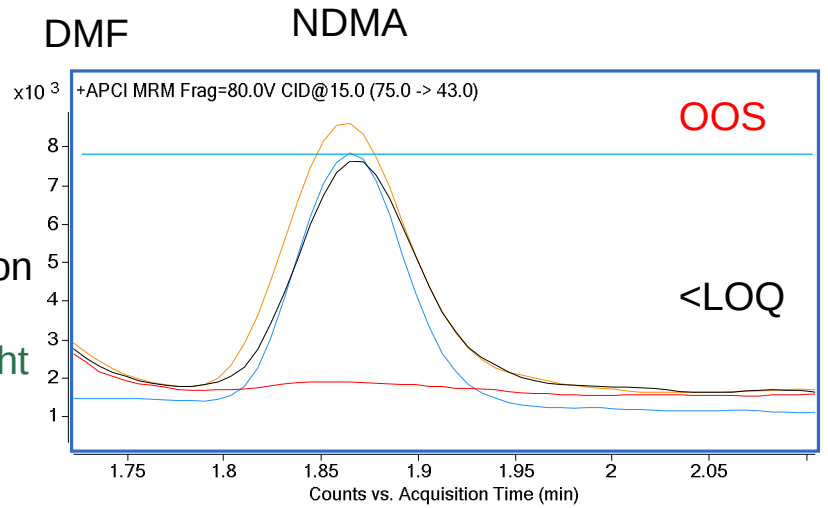


Analytical Testing - Challenges

- False negatives ~ stability/light sensitivity

Sample freshly prepared
Sample over the weekend on the bench - light protection
NDMA Standard at Specification limit
Sample over the weekend on the bench – direct sunlight

DMF from the tablet matrix
NDMA-d_6 as internal standard



Conclusion

- Regulatory spotlight on nitrosamines
- 3 step process

Do not forget:
Packaging!

Validated analytical methods
Challenging, e.g. limits

BASF
We create chemistry

GILEAD
Creating Possible

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A Sotera Health company

The Southern California Pharmaceutical Discussion Group (SCPDG)

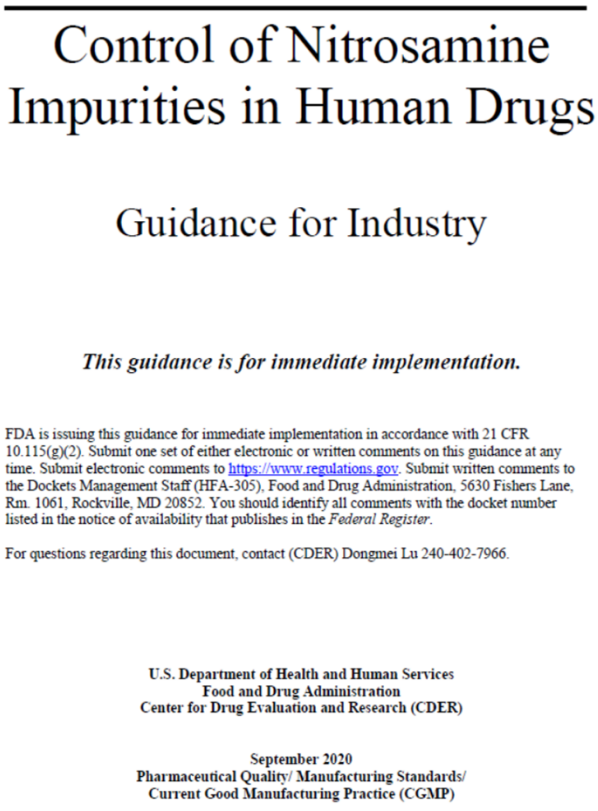
THANK YOU!

Questions & Answers!

FDA Guideline issued 2020

- Similar to EMA position but there are differences.

- More definitive instruction on management of some risks:
  - No mention of Biologics.
  - Report only if a risk.
  - Minimum default lower limit, based on NDEA i.e. 26 ng/day.
  - Specific risks associated with some solvents called out – including fresh solvents.
  - Specific requirements in terms of recycling
  - Replacing nitrites with other quenching agents for azide decomposition processes.
  - ….



Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact (CDER) Dongmei Lu 240-402-7966.

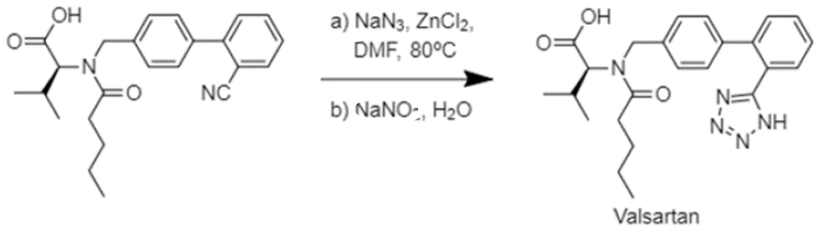
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2020
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

Now Revision 1 available (February 2021)

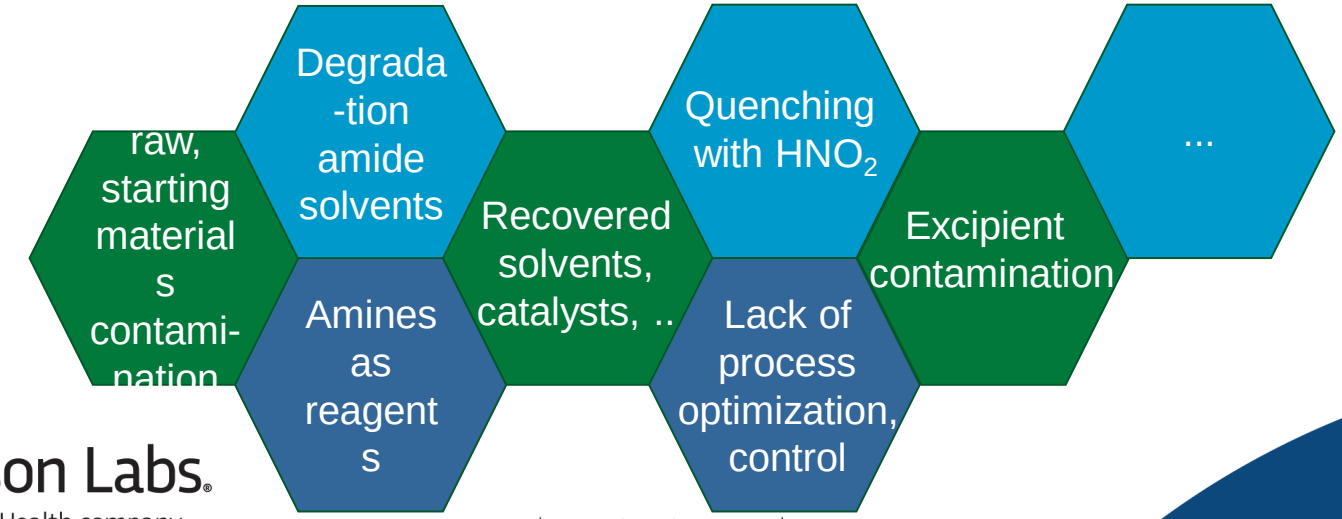
Nitrosamines - What has been learnt?

- Initial concerns related to synthesis



+ NDMA

- Also related to…



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Questions

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Targets and limits – EMA guidance

1 nitrosamine at risk – Acceptable intake (AI)

Target compound*	CAS number	EMA Limit*	Other nitrosamines
N-nitrosodimethylamine (NDMA)	62-75-9	96.0 ng/day	Default Class specific TTC of 18 ng/day
N-nitrosodiethylamine (NDEA)	55-18-5	26.5 ng/day	ICH(M7) approach for **lifetime daily exposure**
N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)	61445-55-4	96.0 ng/day	
N-Nitrosodiisopropylamine (DIPNA)	601-77-4	26.5 ng/day	
N-Nitrosoethylisopropylamine (EIPNA)	16339-04-1	26.5 ng/day	
N-Nitrosodibutylamine (NDBA)	924-16-3	26.5 ng/day	
N-Nitrosomorpholine (NMor)	59-89-2	127 ng/day	
N-Nitrosopiperidine (NPip)	100-75-4	1300 ng/day	
N-Nitrosodipropylamine (NDPrA)	621-64-7	26.5 ng/day	
N-Methylnitrosopiperazine (MeNP)	16339-07-4	26.5 ng/day	
N-Nitrosomethylphenylamine (NMPA)	614-00-6	34.3 ng/day	
*EMA/409815/2020 rev. 11 (29 Jul 2022)			

What is the correct limit? Case Study NMPA

- Different limits proposed by different agencies

FDA

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

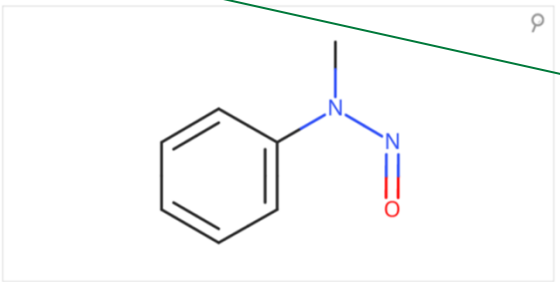
Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Summary

Species	Lhasa TD_{50} (mg/kg/day)	Gold TD_{50} (mg/kg/day)	Result	Sex	Tumour sites	Notes
Rat	0.106	0.142	POSITIVE	Female	Oesophagus	
			POSITIVE	Male	Oesophagus	
			POSITIVE	Not specified	Oesophagus	

Chemical structure

CAS Number: 614-00-6
Chemistry unique identifier: 614-00-6
Chemical name: N-Nitroso-N-methylaniline
Synonym(s): Methylphenylnitrosamine; N-Methyl-N-nitrosoaniline; N-Methyl-N-nitrosobenzenamine; N-Nitrosomethylphenylamine; Phenylmethylnitrosamine
Molecular weight: 136.15
Molecular formula: C7H8N2O
SMILES: N(N(C=1C=CC=CC=1)C)=O
InChI: InChI=1/C7H8N2O/c1-9(8-10)7-5-3-2-4-6-7/h2-6H,1H3



EMA

N-Nitrosomethylphenylamine (NMPA)	614-00-6	34.3 ng/day
*EMA/409815/2020 rev. 11 (29 Jul 2022)		

26.5, 34.3 or 106 ng?

Analytical Testing – Targets and limits

> 1 nitrosamine at risk

Published limit		No published limit
EMA	Limit total quantity	Default class specific TTC of 18 ng/day per nitrosamines OR ICH M7 (R1) approach – lifetime daily exposure – duly justified -> Option 1 or 2
Option 1	TDI ≤ lowest AI	
Option 2	Total risk ≤ 1:100 000	
Exceptions ICH S9, mutagenic/clastogenic API		
FDA	Limit Total quantity;	ICH M7 (R1) approach Contact FDA for acceptability of proposed limit.
MDD < 880 mg/day	0.030 ppm (≤26.5 ng/day)	
MDD > 880 mg/day	26.5 ng/day	

Step 1
Risk evaluation

Step 2
Confirmatory testing

Step 3
Changes to the marketing authorisation

Often forgotten root cause

PACKAGING

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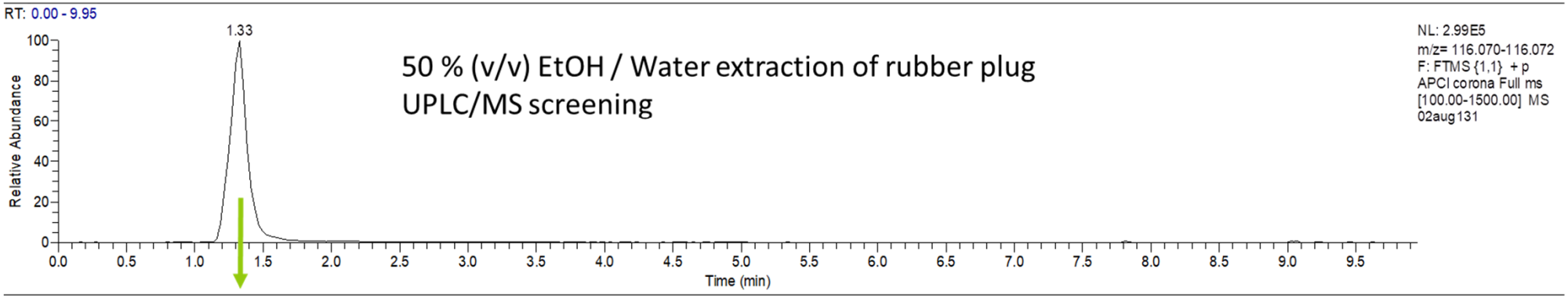
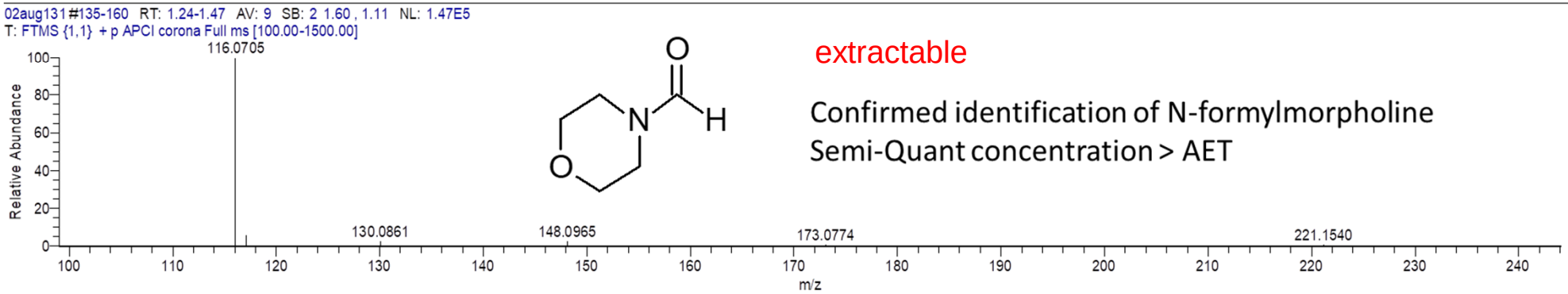
Role of E&L screening for N-Nitrosamine detection

CASE STUDY 1: RUBBER PLUG (2020)



50 % (v/v) EtOH / Water extraction of rubber plug
UPLC/MS screening



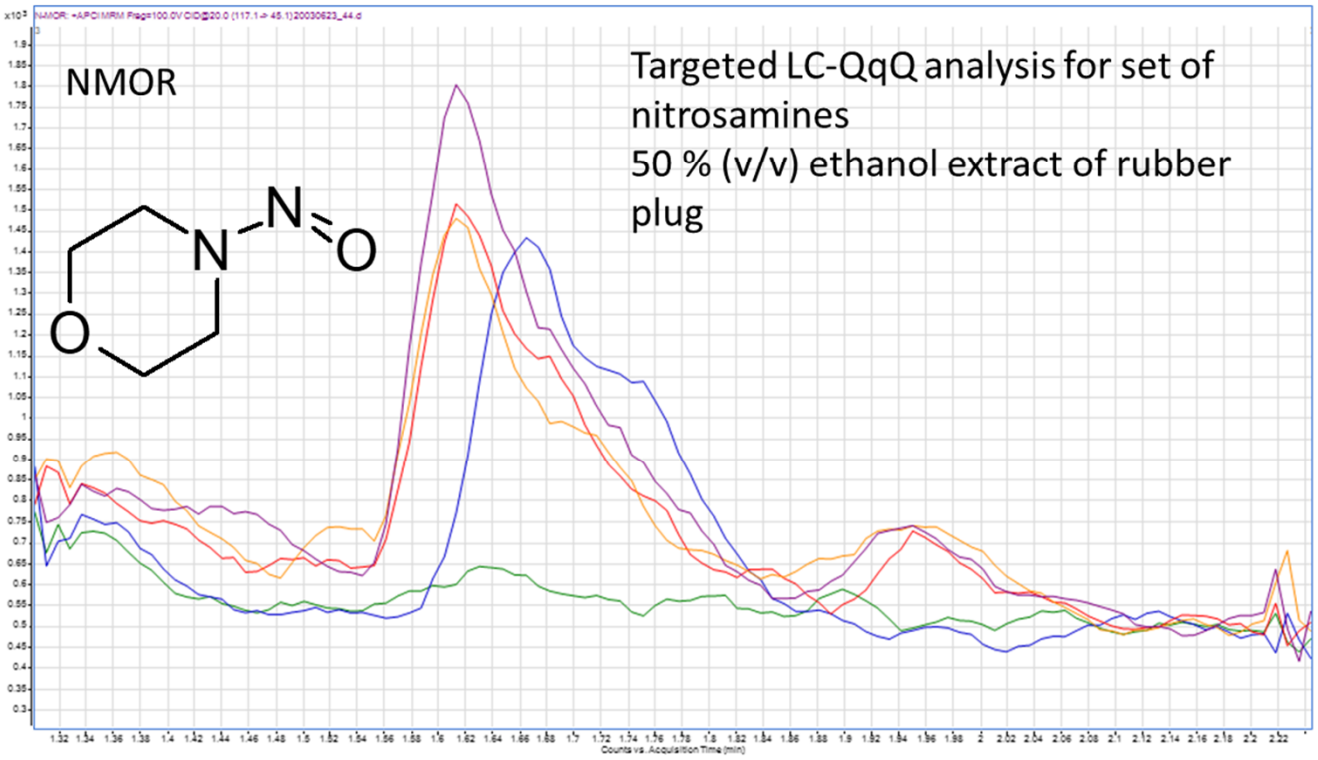
extractable

Confirmed identification of N-formylmorpholine
Semi-Quant concentration > AET

→ Potential precursor for nitrosamines
→ Trigger for action to target nitrosamine with specific method

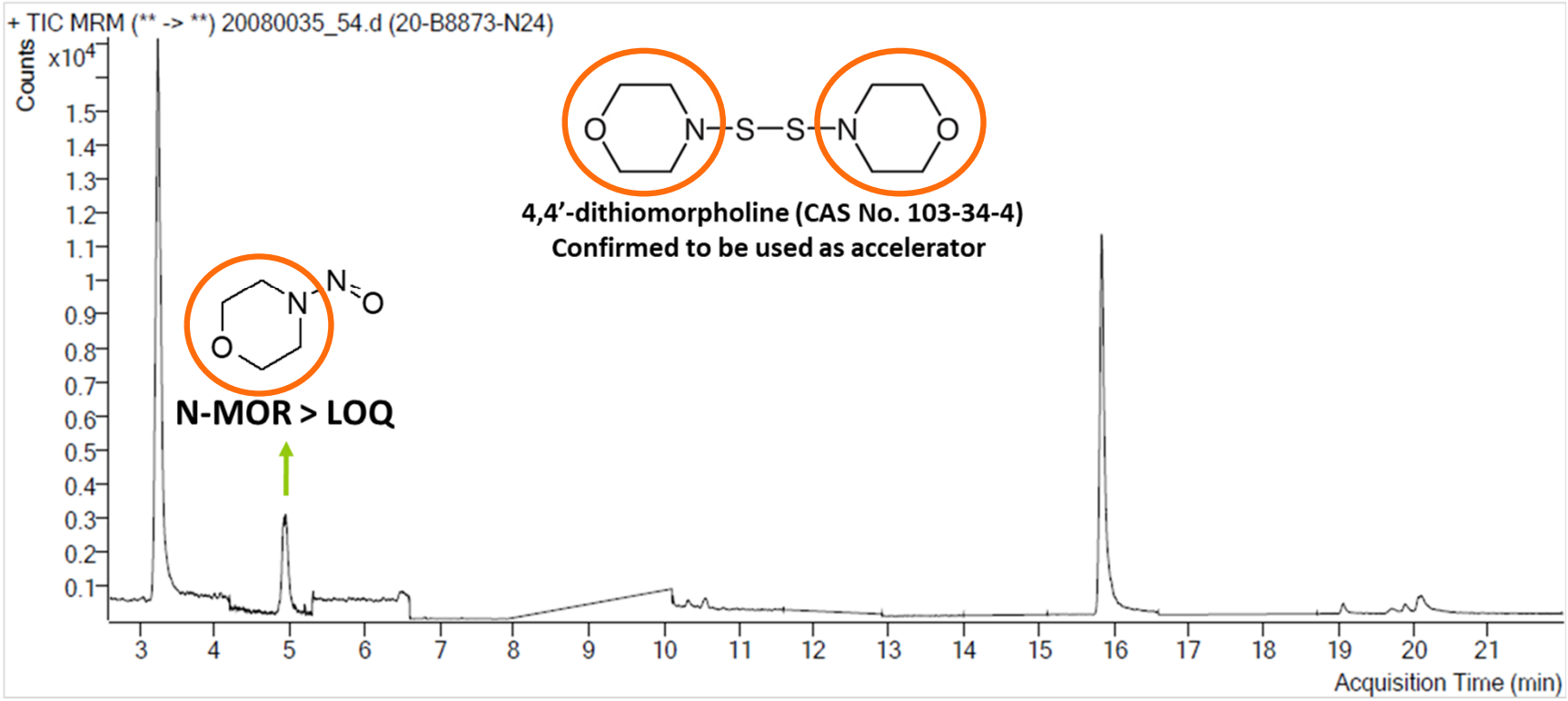
Role of E&L screening for N-Nitrosamine detection

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



Role of E&L screening for N-Nitrosamine detection

CASE STUDY 2: RUBBER STOPPER (2020)



Thank you for your time and attention!

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