NITROSAMINES IN PHARMACEUTICAL ACTIVES

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THE PRESENTER

- Ph.D. Chemist
- Over 30 years' experience as a senior pharmaceutical quality leader
- A Qualified Person since 1995
- Worked on the nitrosamine issue with a number of manufacturers through much of 2019 and all of 2020.

DISCLAIMER

The views and opinions expressed in this presentation are my own. They do not necessarily represent the opinions of NSF or any other organisation.

This presentation makes no claim regarding the regulatory acceptability of any of the actions discussed, or the implications for consumer health and product efficacy.

IN 2018 THERE WERE HEADLINES LIKE THESE


The New York Times | https://nyti.ms/2Loc1vl

Blood Pressure Medicine Is Recalled

By Sheila Kaplan

July 15, 2018


The Washington Post

Democracy Dies in Darkness

FDA identifies contamination source in blood pressure medicines used by millions

By Carolyn Y. Johnson

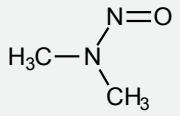
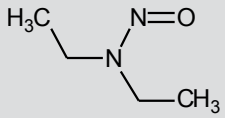
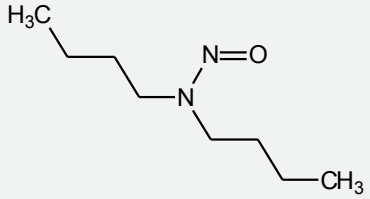
Jan. 25, 2019 at 4:25 p.m. GMT+1

How did this happen?

BACKGROUND

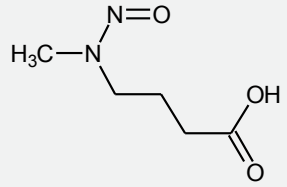
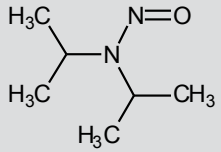
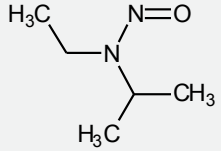
- June 2018 – Notification to FDA of discovery of nitrosamines in Sartans at the Zheijiang Huahai Pharmaceutical Co.
- Rest of 2018 and 2019 – Other manufacturers of Sartans also found to be at risk.
- February 2019 – EMA assessment report EMA/217823/2019
- January to April 2019 – Publication of test methods for nitrosamines from FDA, LOD as low as 5 ppb.
- September 2019 – Reports of nitrosamines in Ranitidine (trade name Zantac) products. Also reports of nitrosamines in Metformin.
- September 2019 – EMA instruction to MAHs to evaluate all medicines, with target date of March 2020. Due to Covid-19, this was rescheduled to October.

WHAT ARE NITROSAMINES? THE MOST COMMON TYPES

Structure	Name	Maximum Daily Intake
	NDMA N-nitrosodimethylamine	96ng
	NDEA N-nitrosodiethylamine	26.5ng
	NDBA N-Nitrosodibutylamine	26.5ng

All are considered genotoxic and carcinogenic agents in animals and are classified as probably carcinogenic to humans (Class 2A carcinogen) by the International Agency for Research on Cancer (IARC, WHO).

OTHER NITROSAMINES

Structure	Name	Maximum Daily Intake
	NMBA 4-(methylnitrosamino)-butyric acid, also called BMSA	96ng
	NDIPA N-nitrosodiisopropylamine, also called DIPNA	26.5ng
	NEIPA N-nitrosoethylisopropylamine, also called EIPNA	26.5ng

These 6 nitrosamines are sometimes referred to as “The Cohort of Concern”

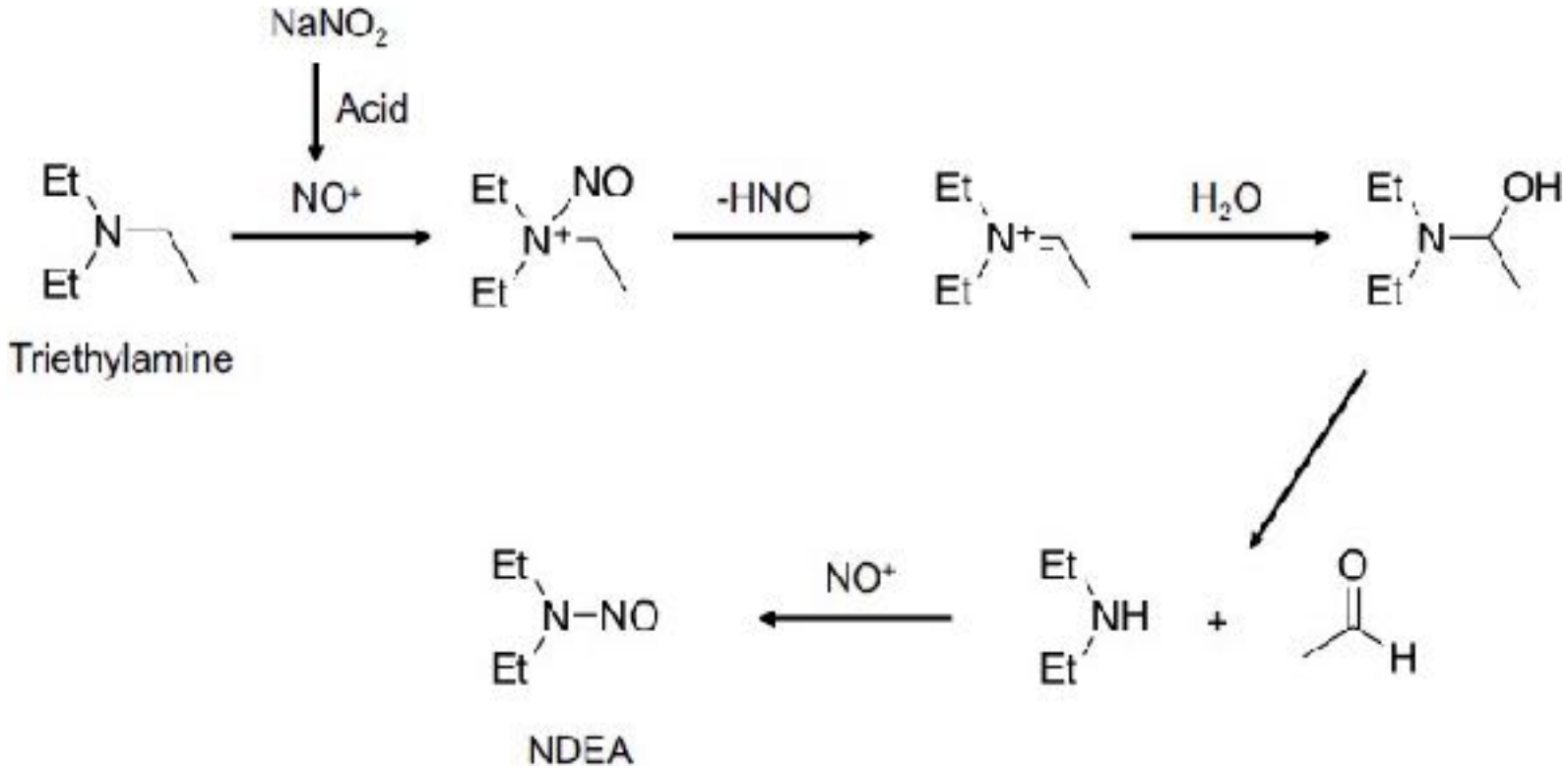
HOW ARE NITROSAMINES FORMED

In general, nitrosamines are formed in a reaction between secondary amines and nitrite ions under acid conditions. For example NDMA is formed from dimethylamine.

HOW NITROSAMINES ARE FORMED

EMA has said in document EMA/ 217823/2019 that it is possible to form NDEA from Triethylamine as shown here.

In my experience this is a very low risk during sartan manufacture.

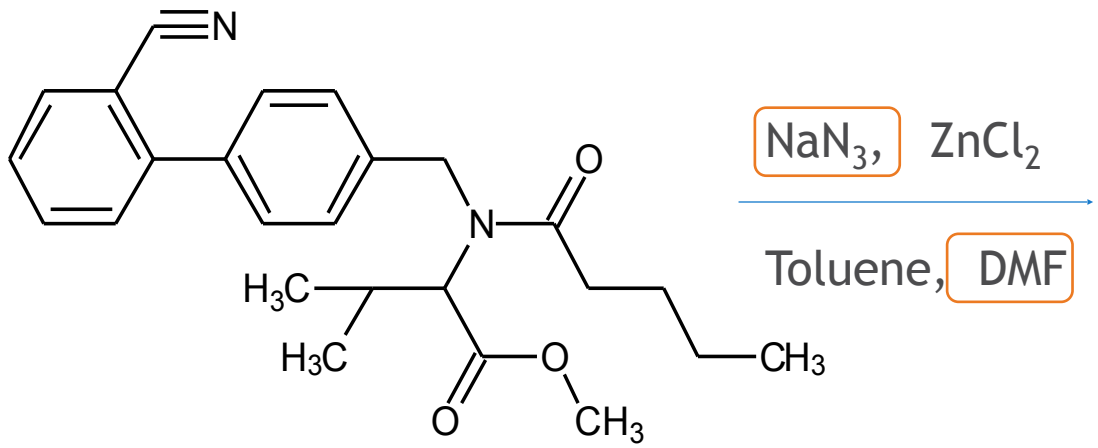


WHAT ARE SARTANS

- Sartans belong to a class of medicines called Angiotensin Receptor Blockers (ARBs).
- They are an effective medication against hypertension.
- Generally well tolerated in the body, with relatively few adverse effects.
- All are characterised by the presence of a tetrazole ring.

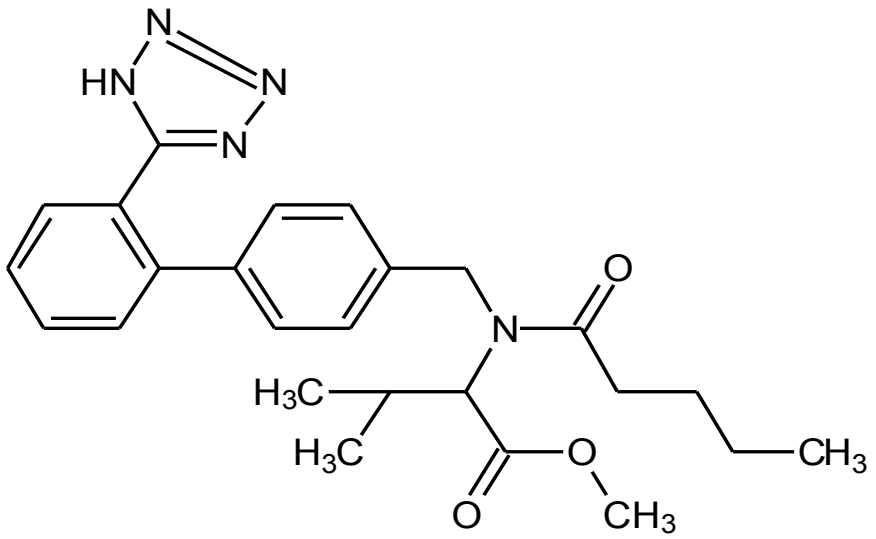
VALSARTAN

Where are the amines?
Where is the nitrite?



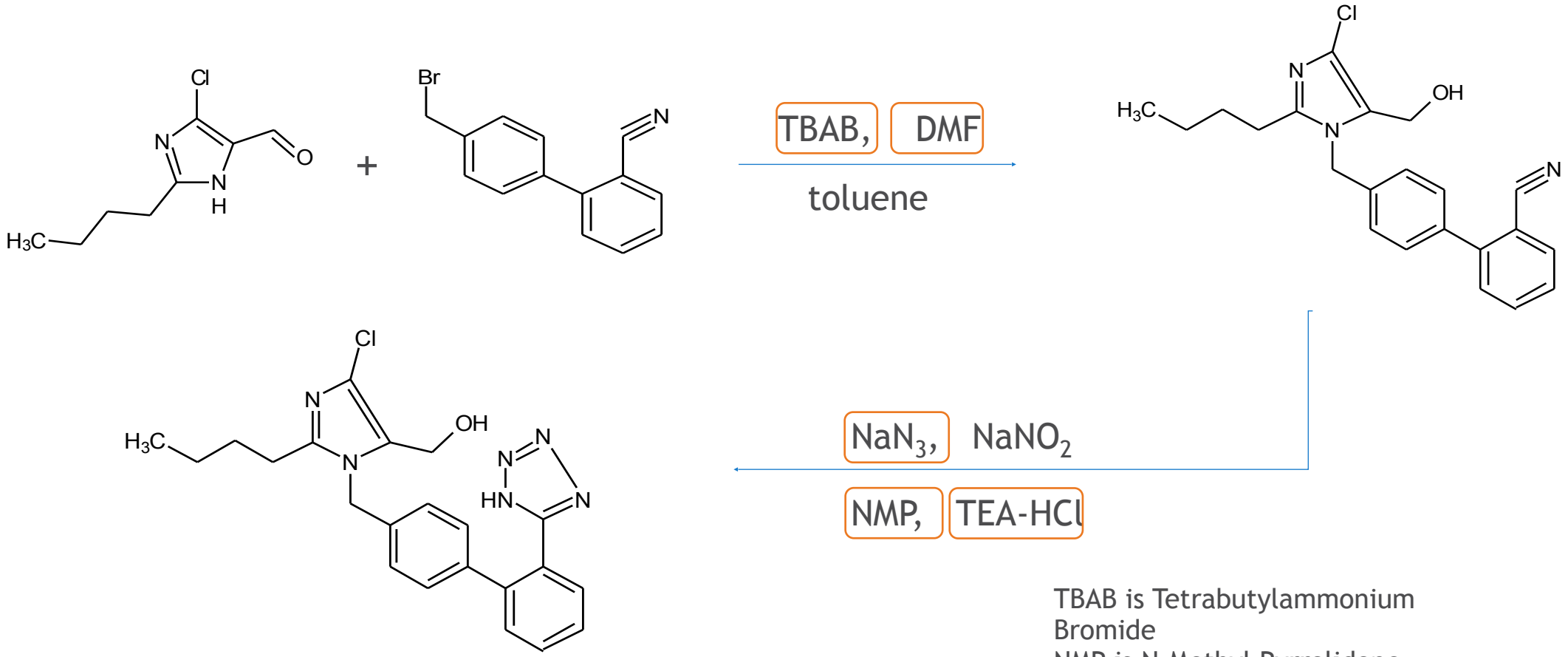
NaN_3, $ZnCl_2$

Toluene, DMF



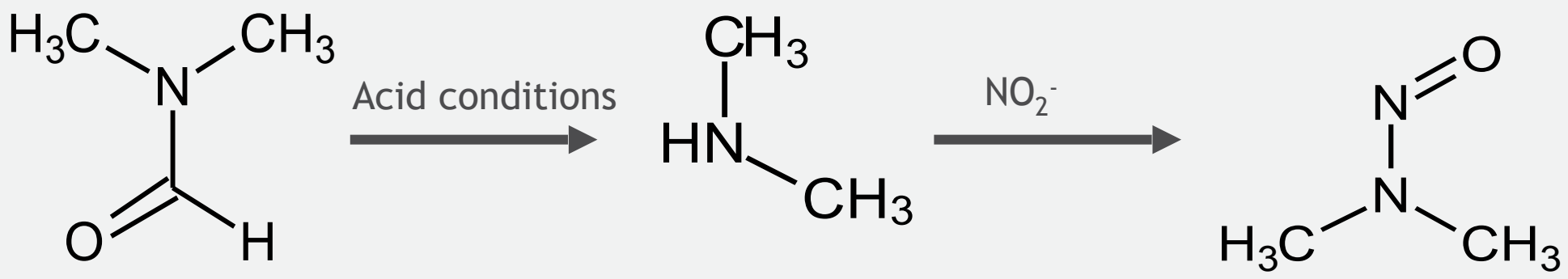
The reaction is quenched with sodium nitrite to remove excess sodium azide

LOSARTAN



TBAB is Tetrabutylammonium Bromide
NMP is N-Methyl Pyrrolidone
TEA is Triethylamine

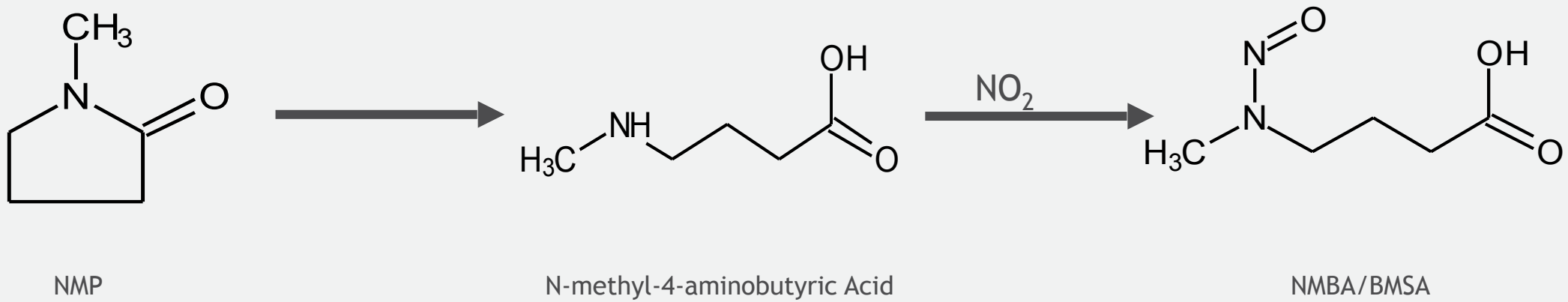
THE ROLE OF DMF IN NITROSAMINE FORMATION



DMF | Dimethylamine | NDMA

DMF readily breaks down to diethylamine and formic acid The dimethylamine can then react with nitrite to form NDMA.

THE ROLE OF NMP IN NITROSAMINE FORMATION



NMP

N-methyl-4-aminobutyric Acid

NMBA/BMSA

NMP is a cyclic amide which readily opens to form a secondary amine. This can then react with nitrite ions to form BMSA (NMBA).

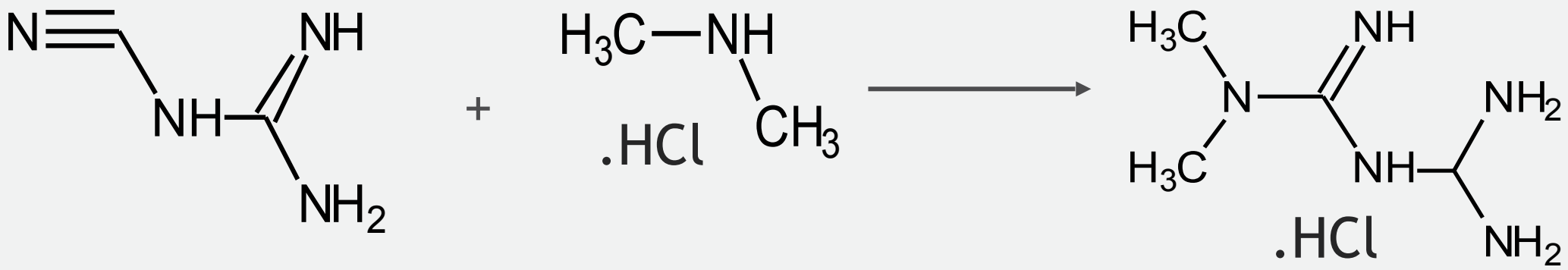
SOME OF THE ACTIONS TAKEN

- Improved phase separation after quenching in the Valsartan reaction.
- Improvements to reagent specifications
  - e.g. Maximum nitrite level in Sodium Azide reduced from 1.0% to 0.1%
- Increased washes of the organic layer. NDMA is relatively soluble in water.
- Increased controls on use of recovered solvent.
- Improved analytical techniques capable of detecting down to 3ppb for NDMA and 1ppb for NDEA and NMBA.
- Currently capable of producing sartans with non-detectable nitrosamine levels.

METFORMIN

- A commonly used generic medicine in the treatment of Type 2 Diabetes.
- Has been manufactured in a “one-pot” synthesis since 1922.
- The method of synthesis has been modified over the years since then, but remains essentially the same.

SYNTHESIS OF METFORMIN



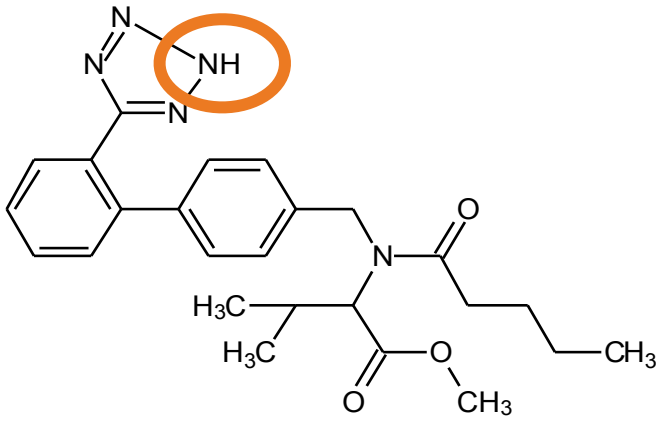
Dicyanodiamide

Diethylamine Hydrochloride

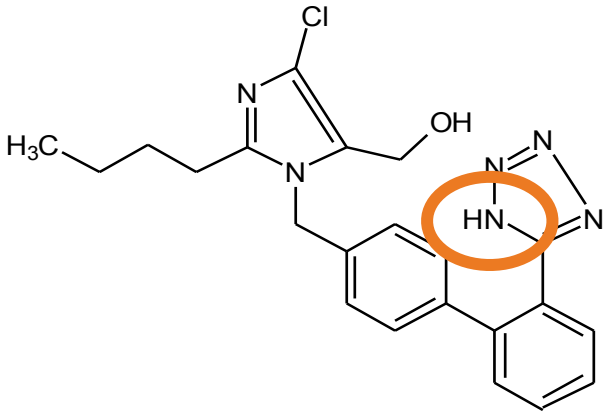
Metformin Hydrochloride

Because the diethylamine and the hydrogen chloride are already present, the nitrosamines are thought to come from impurities in the reagents. This would explain the variable nitrosamine test results for API from different manufacturers using similar processes.

ANOTHER CONCERN IS N-NITROSO DERIVATIVES OF THE API



Valsartan



Losartan

The possibility of such derivatives should be considered during product development.
If present, toxicity studies would be required to establish valid limits.

SOME RECENT DEVELOPMENTS

- The deadline for risk assessment completion has been extended by EMA until March 2021.
- In June 2020, EMA issued a “Lessons Learned” document. It is recommended reading.
- In July 2020, the EMA requirement to carry out a risk assessment was applied to biological medicines, with a deadline of July 2021.
- In September 2020, FDA issued a guidance document: Control of Nitrosamine Impurities in Human Drugs. That also requires risk analysis and corrective actions.

AND THE STORY CONTINUES…

THANK YOU.