Sartan Case Study

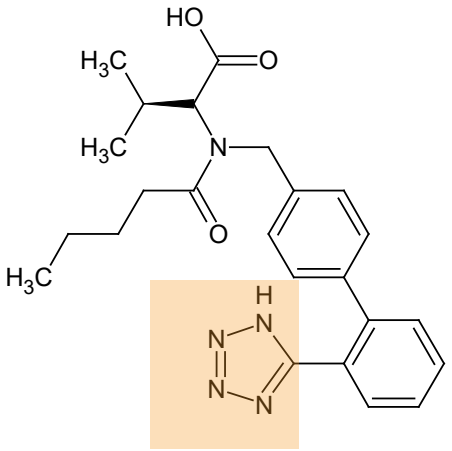
Session 4: Prevention Part II

Andrew Teasdale

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

Valsartan Recall – Key Points

- **Issue arose due to a change in the manufacturing process**
  - The exact change was not initially reported.



- **However it is considered that the issue arose during the manufacture of the tetrazole ring**
  - Usually manufactured using an azide + nitrile
    - e.g. tributyl tin azide + R-CN

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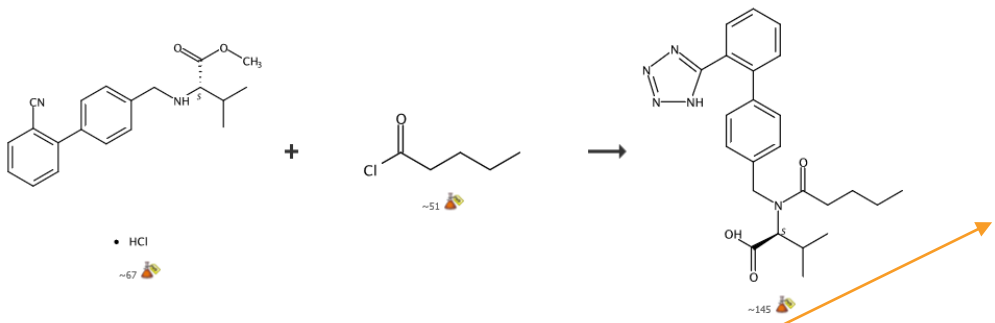
Valsartan Recall – Key Points

- **To generate NDMA requires the presence of Dimethylamine + Nitrite *where do they come from?***
  - *Zhjiang Patent – $NaNO_2$ used in process*



Steps/Stages

1.1 R:Disodium carbonate, S:H_2O, S:PhMe, rt → 20°C; 2 h, 20°C
2.1 R:NaN_3, R:$ZnCl_2$, S:DMF, 13 h, rt → 80°C; 80°C → rt
2.2 R:$NaNO_2$, S:H_2O
3.1 S:AcOEt, rt → 15°C; 8-15 h, 15°C → 10°C

Overview

Steps/Stages

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Notes

1) optimization study, optimized on temperature, 2) Aliquat 128 used (stage 1), optimization study, optimized on solvent, time and temperature, Reactants: 2, Reagents: 4, Solvents: 4, Steps: 3, Stages: 4, Most stages in any one step: 2

References

Improved tetraazole ring formation method in preparation of antihypertensive drug valsartan intermediate
Quick View PATENTPAK
By Zhu, Xiaoren et al
From Faming Zhuanli Shenqing, 104045602, 17 Sep 2014

- ***A third factor is suitable conditions e.g. acid to generate Nitrosyl cation etc***

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Valsartan Recall – Key Points

Preliminary Investigation – Establish the Root Cause

- To generate NDMA: requires the presence of Dimethylamine + Nitrite *where do they come from?*

- DMF from the azide step may contain dimethylamine which carries into the $NaNO_2$ step.
- Disproportionation of DMF to dimethylamine and CO is known to be catalysed by acids and bases so the $ZnCl_2$ may also lead to dimethylamine under the conditions over the 13hours at 80° C.

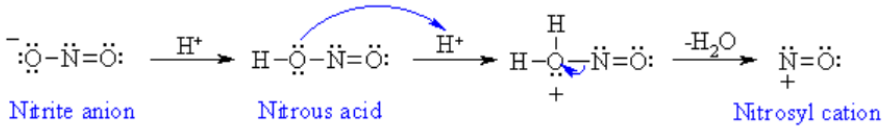
- **Why use $NaNO_2$?**

Chemical reactions [edit]

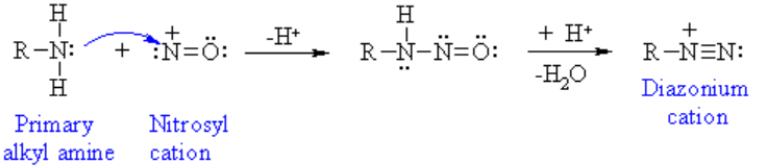
In the laboratory, sodium nitrite can be used to destroy excess sodium azide.[39][40]

$$2\ NaN_3 + 2\ NaNO_2 + 4\ H^+ \rightarrow 3\ N_2 + 2\ NO + 4\ Na^+ + 2\ H_2O$$

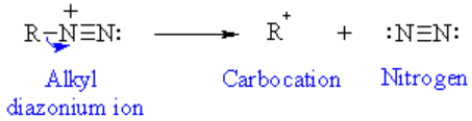
- The actual nitrosation reagent is the nitrosyl cation, NO^+ which is formed *in situ*:



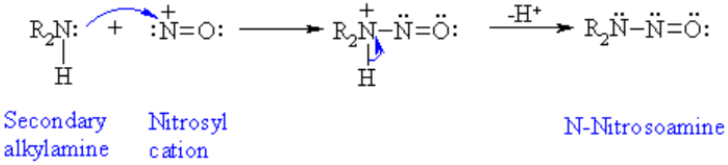
- The nature of the product depends on the nature of the initial amine
- **Primary alkyl or aryl amines** yield diazonium salts (hence the **diazotisation reaction**)



- Alkyl diazonium salts are very unstable and yield carbocation-derived products by loss of the very good leaving group, N_2:



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



Not all processes – even to sartans' are equally at risk

Example Risk assessment

- **The following slides represent another Sartan**
- **Although it contains the same tetrazole ring as Valsartan the synthesis is very different:**
  - DMF not used in tetrazole stage
  - Tetrazole stage multiple stages from API
- **Risk Assessment followed the principles of M7.**
  - Identified compounds of concern (Nitrite, secondary / tertiary amines)
    - Purge calculations
    - Control strategy

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ICH M7 – Mutagenic Impurities
Section 8 – CONTROL - Defines a series of control options

Option 4

- Predicted to be removed by processing based on process understanding – no testing required.

Option 3

- Test at intermediate stage with a higher limit + understanding of process capacity.

Option 2

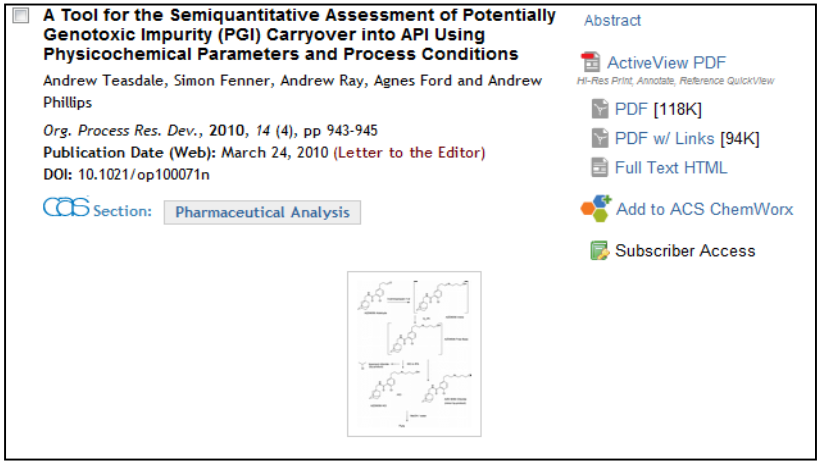
Test for the impurity in the specification for a raw material, starting material or intermediate at permitted level.

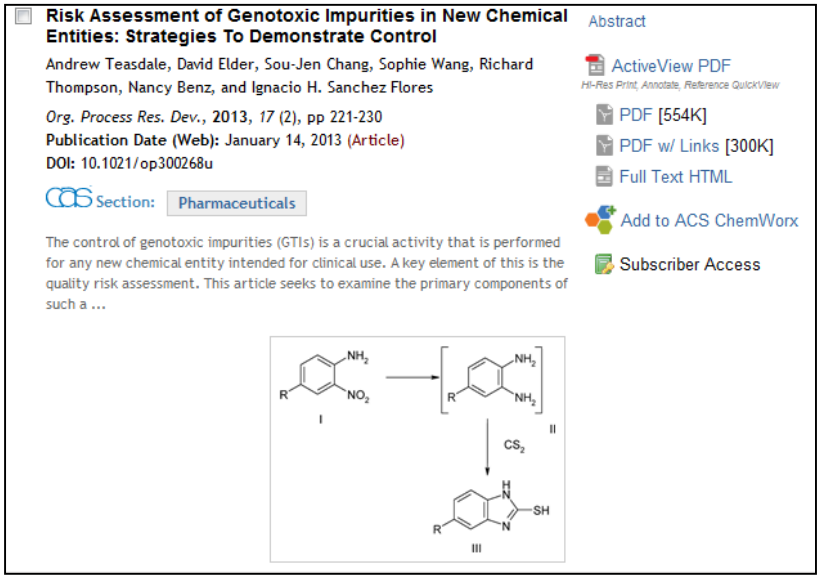
Option 1

Test for the impurity in the drug substance.

Impacted by purge predictions

The principle of relating the physico-chemical properties of the mutagenic impurity to the chemical process is defined in the concept of purge factor calculations.





OPRD paper referenced directly in ICH M7

Basis of Purge Calculations

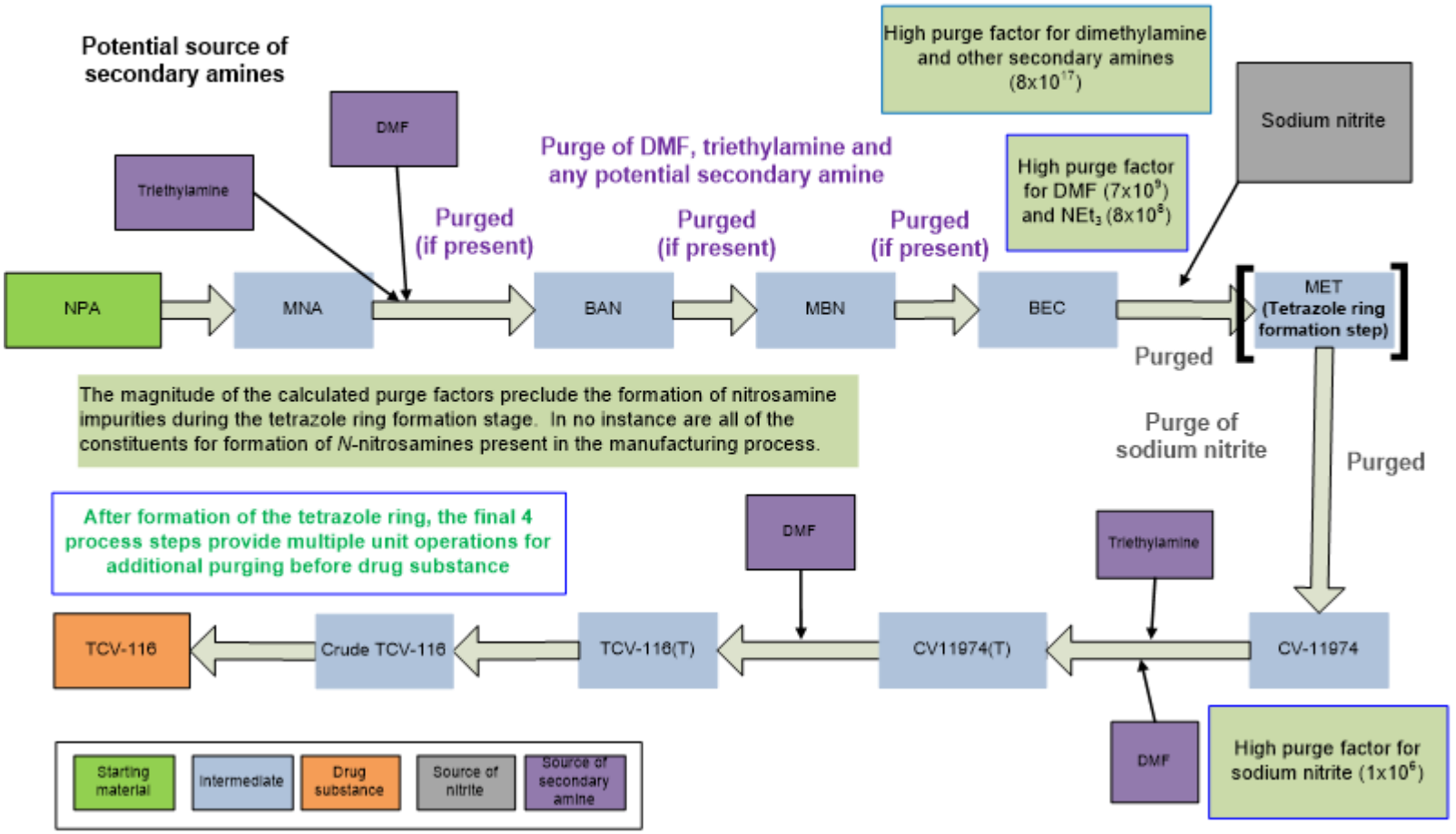
The scoring system was based on basic principles – referred to as "paper" assessment because not automated (manual calculation via spreadsheet).

- Reactivity shown to have largest effect.
- Other factors (especially solubility) would also influence purging.

Physicochemical Parameters	Purge Factor
Reactivity	Highly Reactive = 100
	Moderately reactive = 10
	Low Reactivity / un-reactive = 1
Solubility	Freely Soluble = 10
	Moderately soluble = 3
	Sparingly Soluble = 1
Volatility	Boiling point >20^{0}C below that of the reaction/ process solvent = 10
	Boiling point +/- 20^{0}C that of the reaction/ process solvent. = 3
	Boiling point >20^{0}C above that of the reaction/ process solvent = 1
Ionisability – relates to liquid / liquid extraction	Ionisation potential of GI significantly different to that of the desired product [2]
Physical Processes – chromatography	Chromatography – GI elutes prior to desired product = 100
	Chromatography – GI elutes after desired product = 10
	Others evaluated on an individual basis.

- The entire Sartan process was assessed using this approach focused on the key contributory impurities

Overall Sartan process map – points of control



Conclusion at no point in the process could there be both secondary amines and nitrite present

Outcome of testing

- **Initially > 40 batches of API tested – NDMA not detected Limit 150ppb**
- **DMA Not detected in Stage 5 (tetrazole) <100ppb**
- **Nitrite not detected in Stage 5**
- **Now Option 4 backed up by testing upstream of API for both Nitrosamines and Nitrite,**
  - Subsequently confirmed by over 85 Bx analysis at nmt 5 ppb for NDMA and NDEA
  - including 65 Bx for 5 nitrosamines

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Conclusions

- **To investigate the risk it was first vital to understand the root cause**
- **ICH M7 then provided a systematic, risk based approach to assess the risk.**
- **N-Nitrosamine formation is only possible if BOTH Secondary amines and a Nitrosating agent is present AND there are favourable conditions (low pH / concentration)**
  - Mechanism has been extensively studied
- **Purge calculations, fully aligned to the principles of ICH M7 conclusively showed that there no risk.**
- **This was vindicated by extensive and on-going testing program**