APOTEX
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Control Strategies for NDSRIs Originating from Impurity Amines in APIs

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Control Strategies for NDSRIs originating from impurity amines in APIs

- Raw materials are not often direct sources of nitrosamines themselves-
  a. APIs are important, but mostly sources of **simple** and **NDSRI** amine precursors
  b. excipients are important, but mainly as nitrosation sources

Presented at AAM Tech. Conf. Nov. 2021

- There is still an enormous amount to be understood about the kinetics of inadvertent nitrosation reactions in drug products, especially solid dose drugs

Presented at AAM Tech. Conf. Nov. 2021

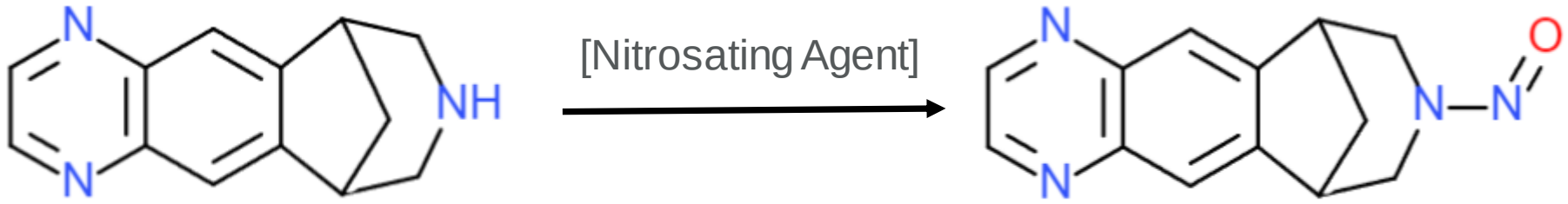
This remains true today!

Introduction

High Level Control Strategy Options

- **Quantify the potency of NDSRIs**
  - presentations/discussion later today will address this topic
- **Introduce additives to drug product formulations to suppress nitrosation**
  - addressed in this session
- **Control precursors to NDSRIs**
  - Nitrosation species (mainly in excipients) > addressed in this session
  - NDSRI secondary amine impurity precursors (mainly in APIs)> **focus of this presentation**

NDSRIs from Secondary Amine APIs: Varenicline Tartrate

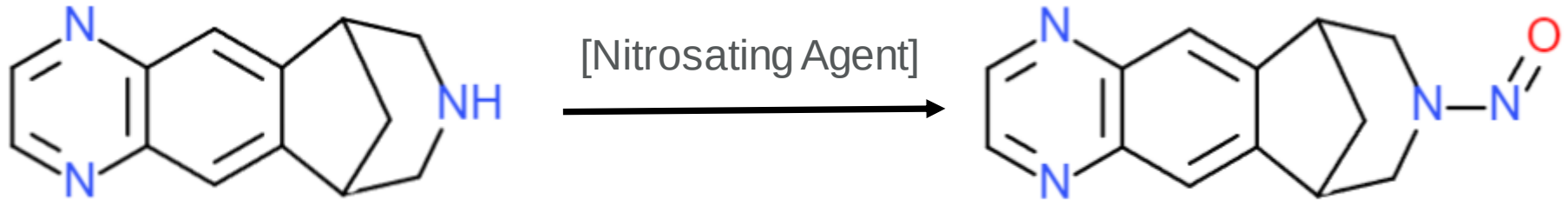


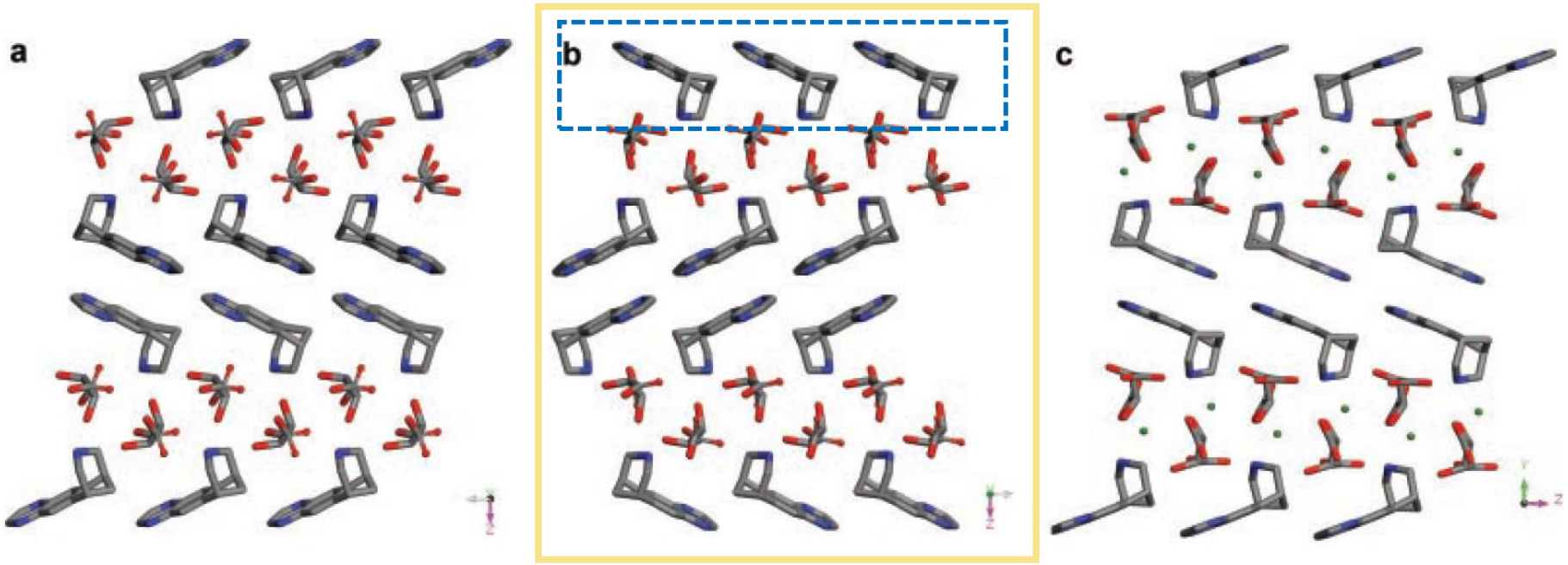
Company (Manufacturer)	Product	Lots Tested	N-nitroso-varenicline level in micrograms/tablet (nanograms/tablet)	N-nitroso-varenicline level in parts per million (ppm)
Pfizer	Chantix (varenicline) 1mg	EA6080, EC9841, EC9847, EC9848, EX2099, DR5086	0.15-0.47 (150-470)	155-474
Par Pharmaceuticals	Varenicline 1 mg	31960807, 31960801	0.003 (3)	3
Apotex	APO-Varenicline Tartrate 1 mg)	TG2183, TG2181, TG2182	0.027-0.044 (27-44)	27-44
Apotex	APO-Varenicline Tartrate 0.5 mg	TG2180, TG2178, TG2179	0.014-0.021 (14-21)	27-42

Published by FDA: Aug. 23, 2021

Current long-term specification: NMT 18.5 ppm

NDSRIs from Secondary Amine APIs: Varenicline Tartrate





Recall from previous slide:

- Highest – 474 ppm
- Equivalent to: **<u>0.042% molar conversion</u>**
- Despite – "[Varenicline FB]" in Form B: **4.04 M**

  API is 58% (w:w) varenicline FB

Murphy, B.J.; Huang, J.; Casteel, M.J.; et al., *J. Pharm. Sci.,* **2010**, *99*, 2766-2776

NDSRIs from APIs with Secondary Amine Impurities

Table 2. Summary of potential nitrosamines that may be formed. The different sources are not mutually exclusive, with some overlap observed. Limited overlap is observed between the USP API and impurity datasets.

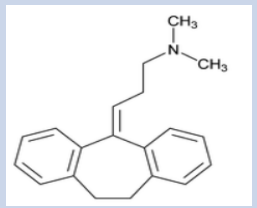
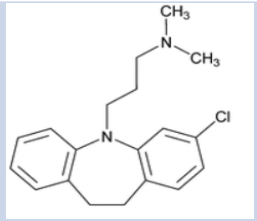
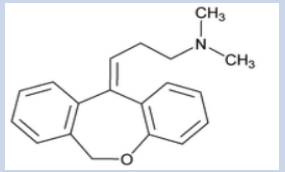
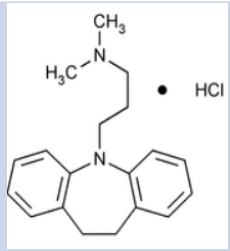
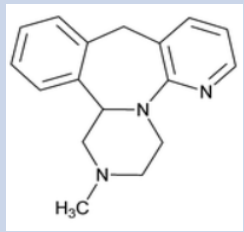
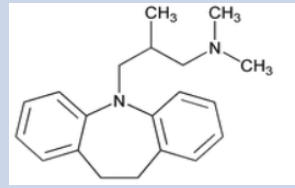
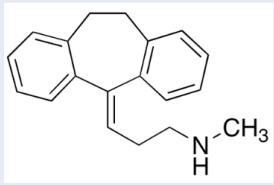
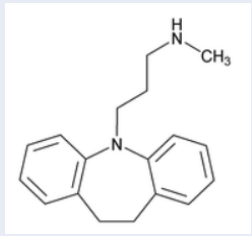
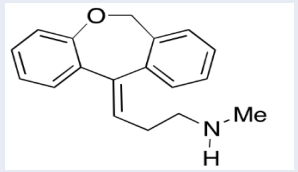
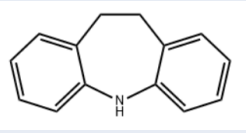
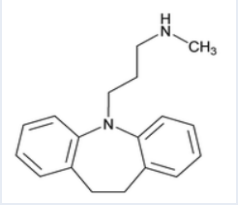
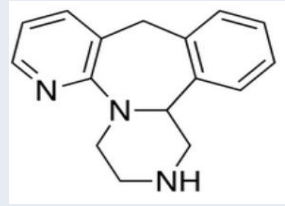
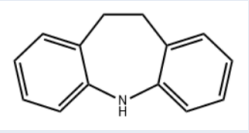
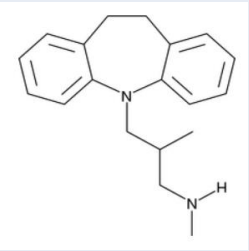
Source	Number of Entries	Structures featuring [Absolute (%)]			Possible nitrosamines		
		2° amine	3° amine	2° and/or 3° amine	Total	from 2° amine	from 3° amine
USP – APIs	8611	1268 (14.7)	2517 (29.2)	3536 (41.4)	7895	2375	5525
USP – Imp	3564	459 (12.8)	681 (19.1)	1077 (30.2)	2213	720	1493
WHO EML	563	58 (10.3)	95 (16.9)	140 (24.9)	287	79	208
Top 200	210	41 (19.5)	43 (20.5)	71 (33.8)	170	81	89
Orange Book	2211	296 (13.4)	526 (23.8)	757 (34.3)	1739	512	1227

Schlingemann, J.; Burns, M.J.; Ponting, D.J.; et al., *J. Pharm. Sci.*, **2023**, *112*, 1287-1304

What about drug products where the API is not a secondary amine, but the API contains secondary amine impurities?

- 720 NDSRIs from 2° amine USP impurities alone!
- Note: numerous 3° amine “precursors” listed, but not much evidence yet that 3° amines lead directly to NDSRIs

USP Listed Tricyclic Antidepressants and their Secondary Amine Impurities

	Amitriptyline	Clomipramine	Doxepin	Imipramine	Mirtazapine	Trimipramine
API Structure						
2° Amine Impurity Potential NDSRI Precursor (USP Acceptance Criteria)	Nortriptyline **(NMT 0.15%)** 	Desipramine **(NMT 0.5%)** 	Related Compound C **(NMT 0.20%)** 	Iminodibenzyl **(NMT 0.1%)**  Desipramine **(NMT 0.2%)** 	Desmethyl mirtazapine **(NMT 0.1%)** 	Iminodibenzyl **(NMT 0.20%)**  Desmethyl trimipramine **(NMT 0.15%)** 

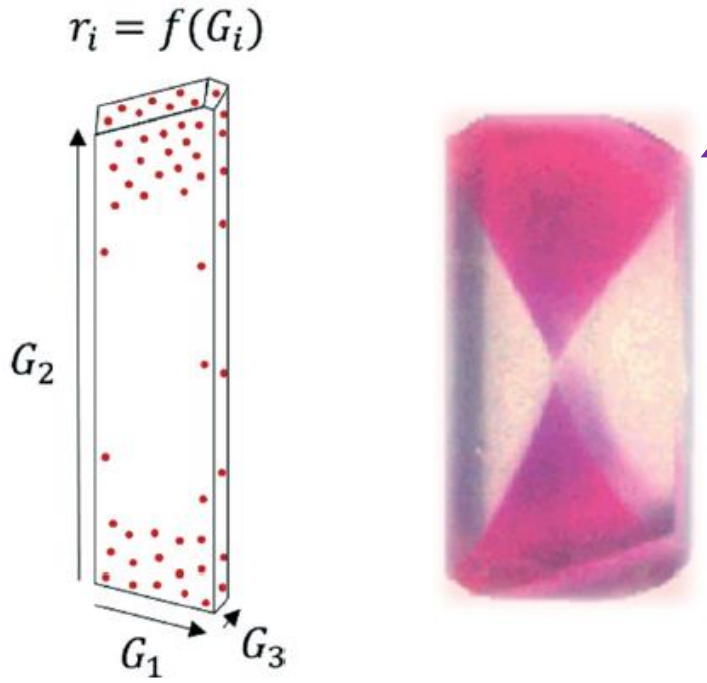
USP Online, May-2023

Analysis of NDSRI Amine Precursors Today

UPLC/HPLC or GC methods, typically with UV detection

- Precursor levels typically allowable today (ICH Q3A/Q3B specifications)
  - NMT 0.1% to NMT 0.2%
  - i.e., **1,500 – 2,500 ppm → ~ 1,500-2,500 ppm** NDSRI if not nitrosation limited
- Solution phase analysis provides only the average content of impurity amine precursors
- No information about the microspatial distribution of precursors in and amongst individual crystallites of the API
- The spatial location of nitrosation-susceptible amine impurities relative to the API could influence nitrosation kinetics

Anisotropic Impurity Incorporation in Crystals



Sulforhodamine B incorporated in K_2SO_4

Fig. 2 Left: Face-dependent crystal growth (G_i) and impurity incorporation (r_i) in a growing crystal. Right: Example of face-dependent incorporation of sulforhodamine B in a K_2SO_4 crystal [adapted with permission from Kahr and Gurney.[54] Copyright 2001 American Chemical Society].

How will we enable prediction of the extent to which microspatial distribution of precursors will limit their ability to form NDSRIs over the shelf life of drug products?

What other modes of precursor impurity distribution are possible?

Capellades, G..; Bonsu, J.O..; Myerson, A.S., *CrystalEngComm*, **2022**, *24*, 1989-2001

Impurity Retention Mechanisms

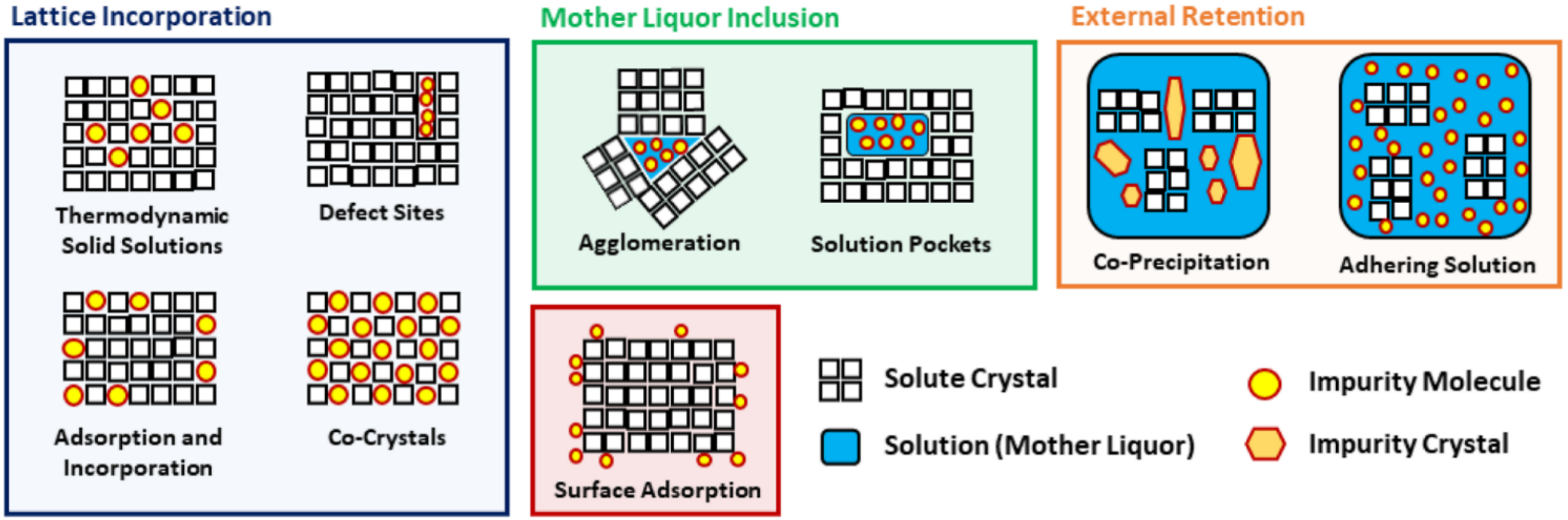
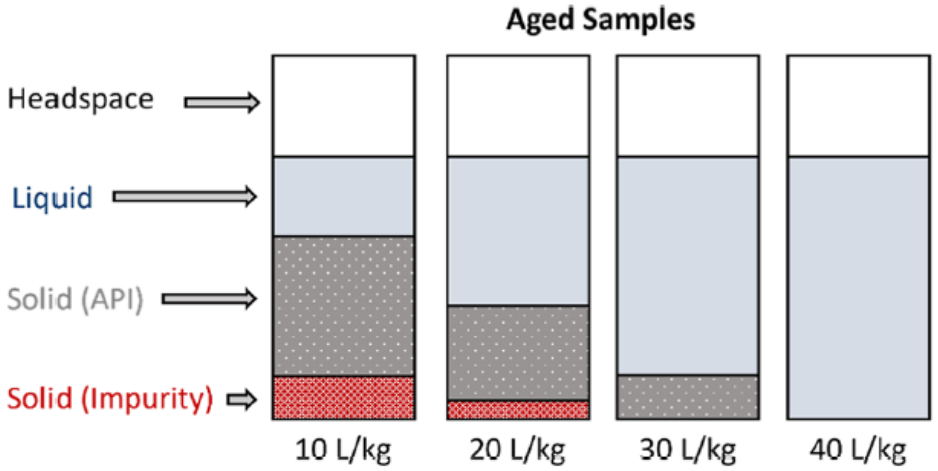
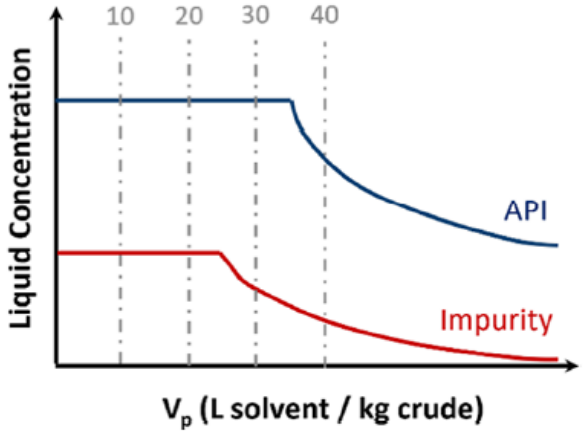


Figure 1. Summary of impurity retention mechanisms in crystallization and isolation, commonly seen in academic literature. Adapted from Capellades et al.[2] Copyright 2022 Royal Society of Chemistry.

Nordstrom, F.L.; Sirota, E.; Hartmanshenn, C.; et al., *Org. Proc. Res. Dev.* **2023**, *27*, 723-741

Impurity Retention Mechanisms

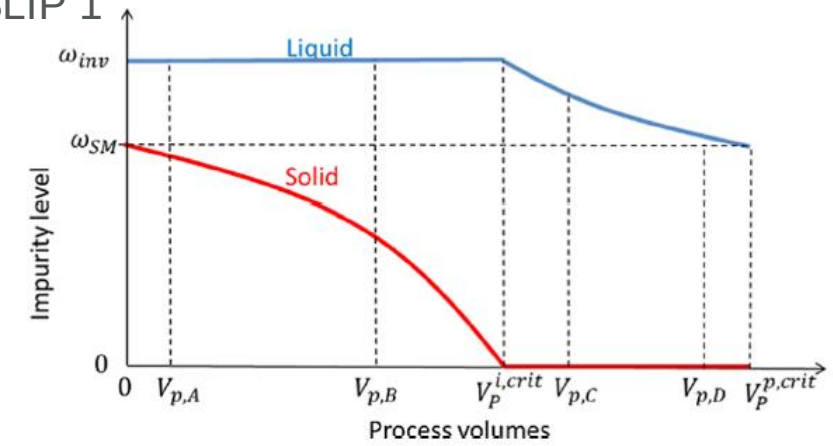




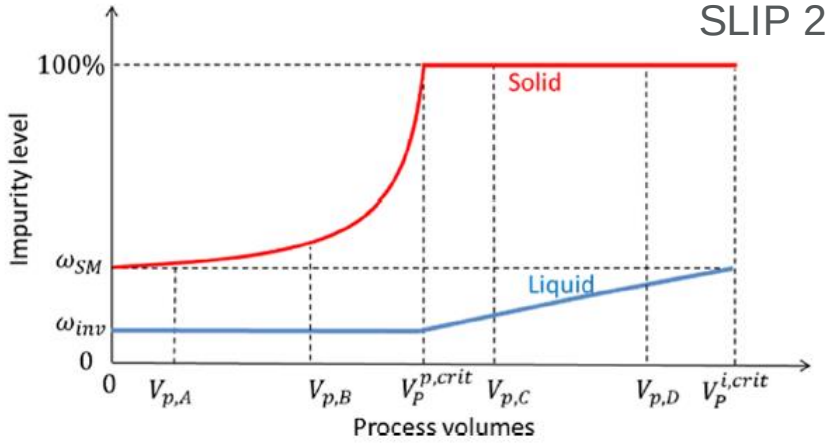
SLIP: Solubility-Limited Impurity Purge

Distinguishes external vs. internal retention of impurities

SLIP 1



SLIP 2



Nordstrom, F.L.; Sirota, E.; Hartmanshenn, C.; et al., *Org. Proc. Res. Dev.* **2023**, *27*, 723-741

Statistics of impurity incorporation in APIs/intermediates

- Based on 48 product/impurity studies

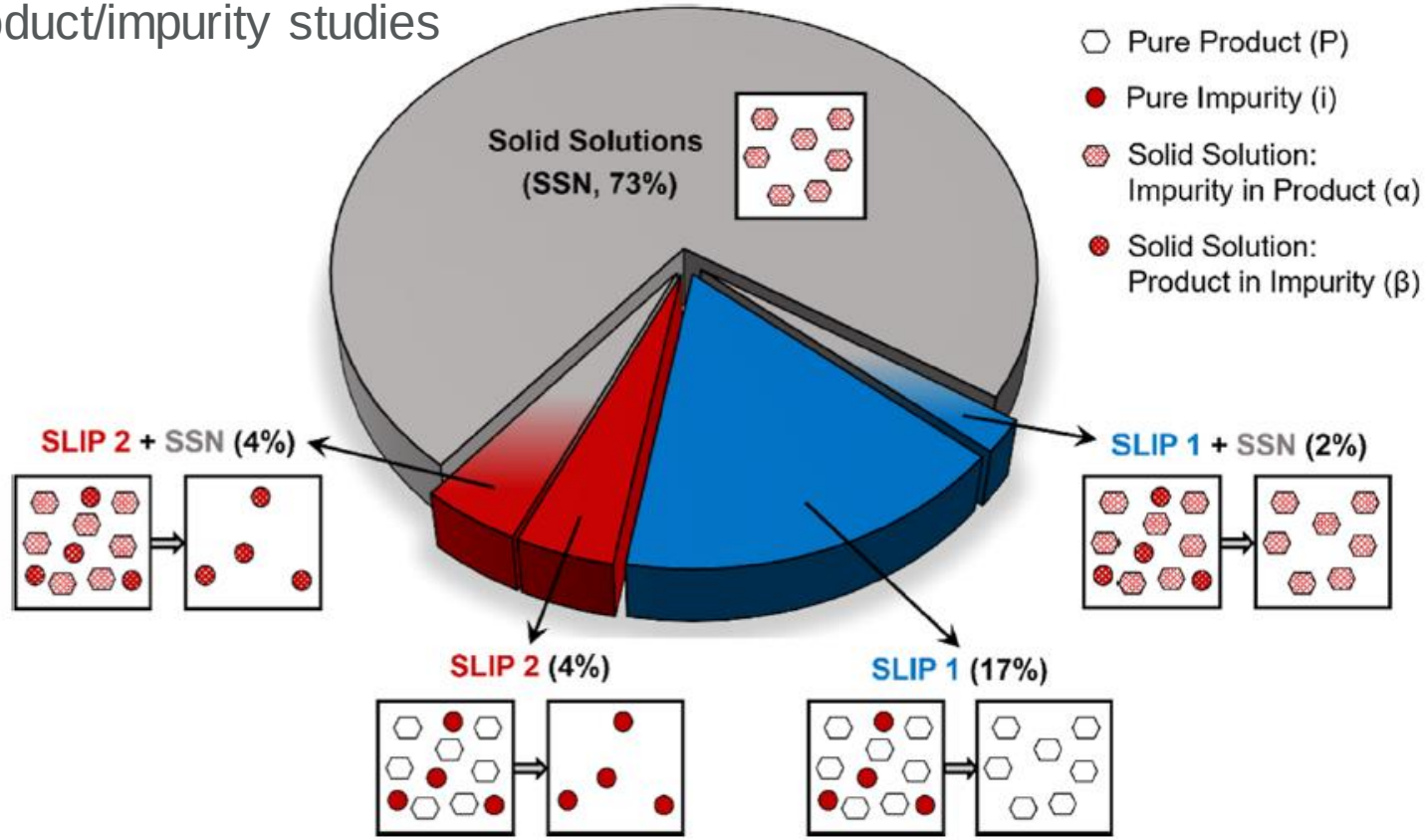
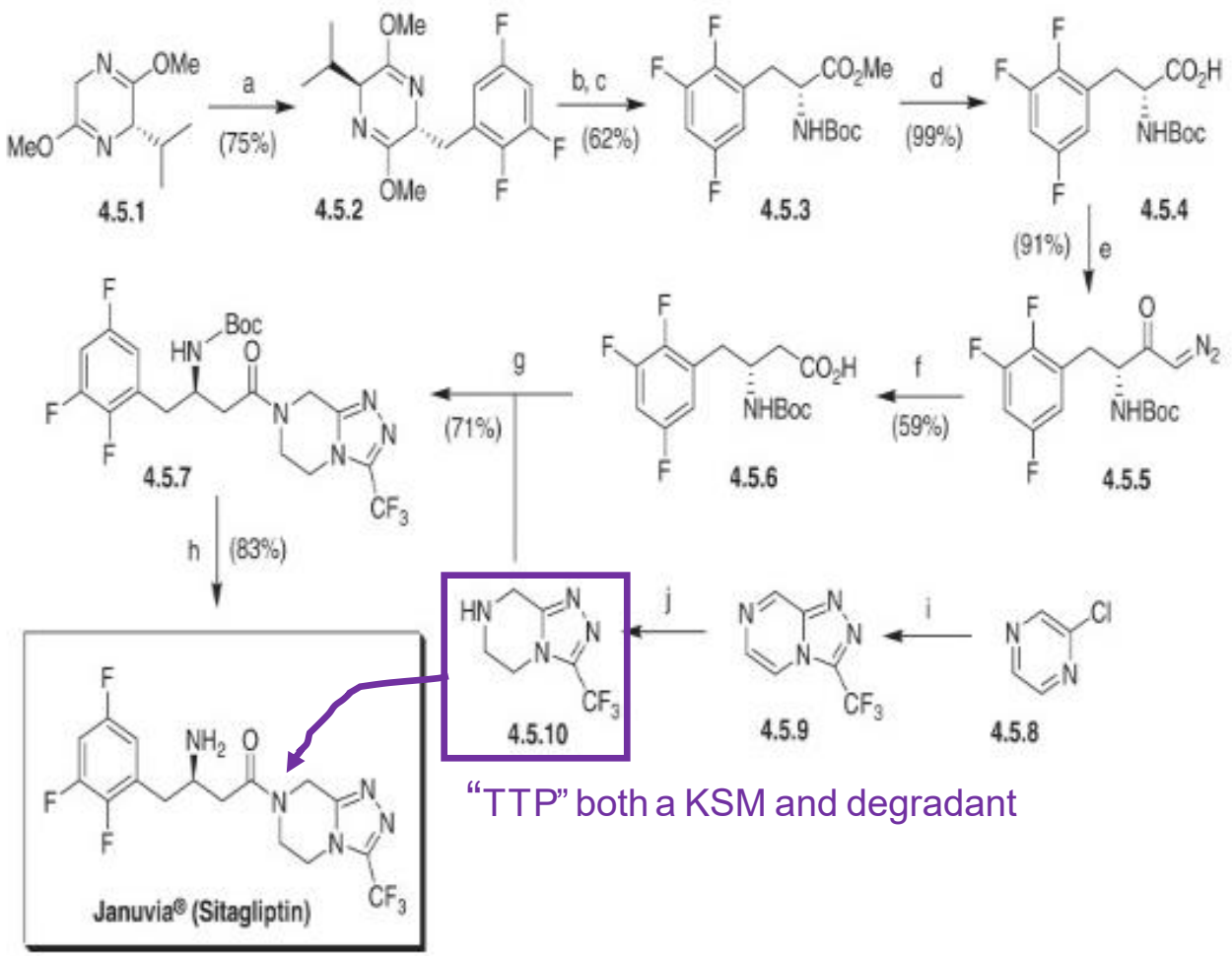


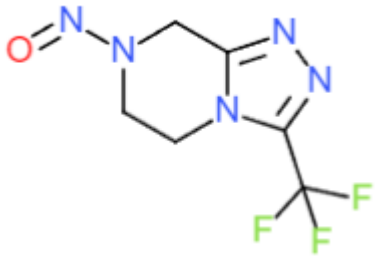
Figure 9. Distribution of impurity retention mechanisms in pharmaceutical crystallizations. Results include 48 solute-impurity systems classified into categories using the SLIP test. SSN stands for solid solutions.

Nordstrom, F.L.; Sirota, E.; Hartmanshenn, C.; et al., *Org. Proc. Res. Dev.* **2023**, *27*, 723-741

Specific Case: Sitagliptin Phosphate



"TTP" both a KSM and degradant



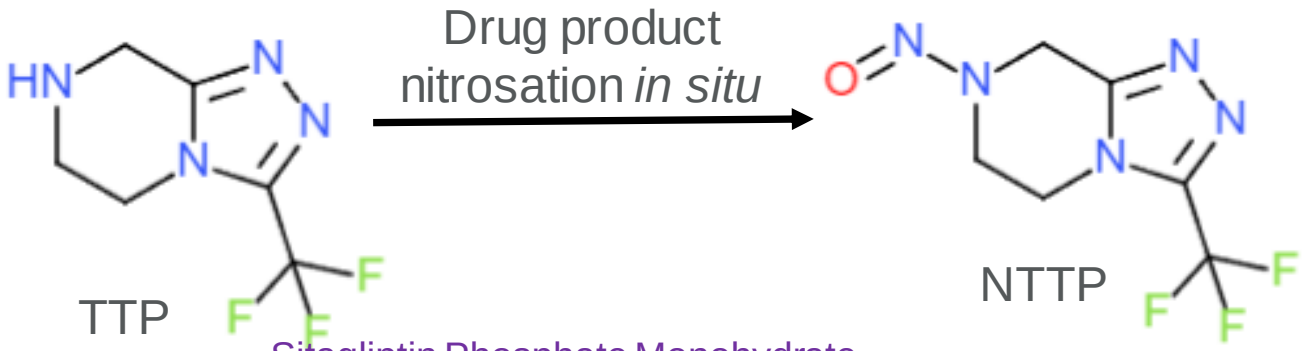
NTTP

Published by FDA:
Aug. 9, 2022

- Long term AI: 37 ng/day (0.37 ppm)
- Temporary AI: 246.7 ng/day (2.467 ppm)

- **TTP precursor** could be present as:
  - Impurity in API
  - Continue to form in drug product as degradant

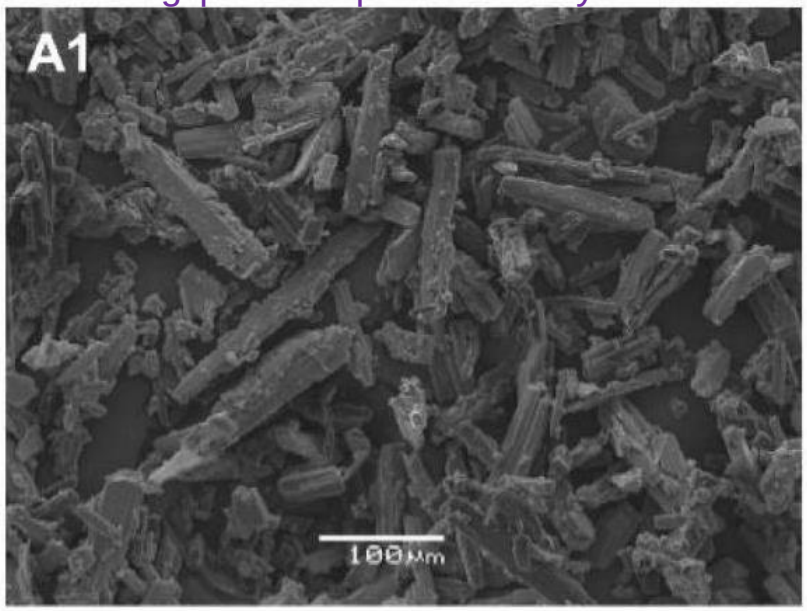
Specific Case: Sitagliptin Phosphate



Published by FDA:
Aug. 9, 2022

- Long term AI: 37 ng/day (0.37 ppm)
- Temporary AI: 246.7 ng/day (2.467 ppm)

Sitagliptin Phosphate Monohydrate



- **TTP precursor** is both synthetic impurity and potential degradant:
  - Likely API TTP spec.: NMT 0.15% (~1000X the NTTP level)
  - TTP distribution in API- lattice incorporation or external retention or combination? SLIP test candidate.
  - Degradation TTP generated post API mfg., lattice or external? Not a foregone conclusion. SLIP test candidate.

Stofella, N.C.F.; Veiga, A.; Oliviera, L.J.; et al., *Materials* **2019**, *12*, 2531-2547

NDSRI Amine Precursor Control Strategy: Options and Challenges

Confirm the impurity secondary amine precursor (or API) actually forms a stable NDSRI

- Most do, but some do not, e.g., calcium channel blockers
- Attempting to obtain a reference standard will answer this

Limit/reduce impurity secondary amine precursors in APIs (where the APIs are not vulnerable to nitrosation)

- Existing Q3A/B based specifications mean impurity amine precursors can be present in affected APIs at levels 10x - 1,000x greater than likely specifications for fate product NDSRIs. This makes these precursors *prima facie* risks

- Where required, engage current API supplier to evaluate process modifications to reduce amine precursor levels
  - Will increase API cost to varying extents…and may provoke supplier pushback
  - May require development of MS detector-based RC methods for the precursors (if precursor limits need to be in the 1's to 10's of ppms)

NDSRI Amine Precursor Control Strategy: Options and Challenges

Conduct API/excipient binary compatibility studies

- Beneficial, but time intensive studies and may not reflect NDSRI generation kinetics in final drug product formulation trials

Enhance product nitrosamines risk assessments – API SLIP test as a new tool

- Apply SLIP tests and future modifications of SLIP-type tests to APIs to better understand microspatial distribution of impurity amine precursors:
    - Lattice incorporation API/precursor systems should have lower NDSRI risks than external retention systems and the former may tolerate higher precursor levels
    - Nordstrom *et al*. work predicts that the majority of API/precursor impurity systems are lattice incorporation types (i.e., solid solutions)
    - Could differentiate a risk level for NDSRIs when changing an API source or replacing a previously used API process with a new process

Control Strategies for NDSRIs originating from impurity amines in APIs

Thank you.