Formulating for Stability

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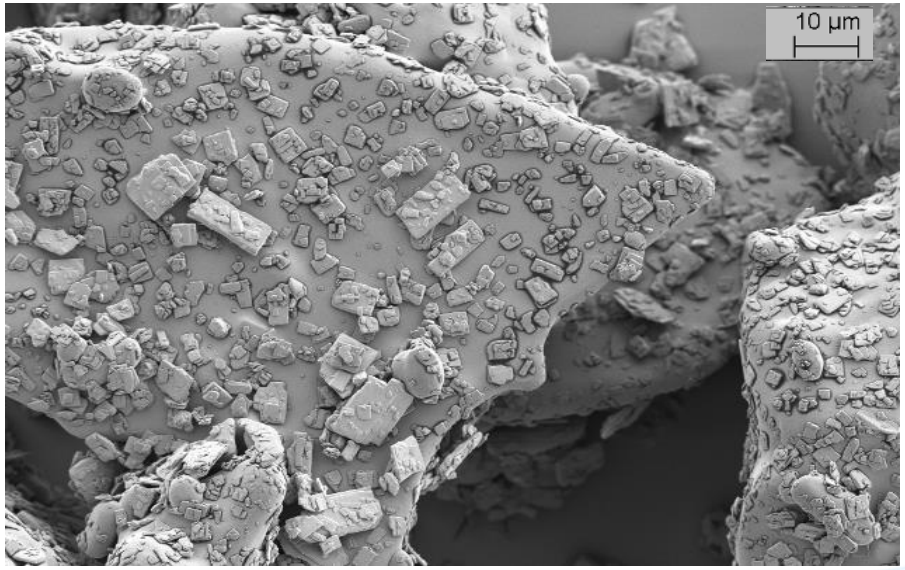
- Practical considerations for designing and executing a tiered formulation screen
- How to assess and handle oxidation

How Excipients Impact Stability: Direct Impact

- Drug substance is typically more stable than drug product
- Degradation can result from direct drug-excipient reactions
  - Relatively uncommon
  - Example: Maillard reaction between secondary amines + reducing carbohydrates (e.g. lactose)
- Degradation can result from reaction of drugs with excipient impurities
  - Peroxides
  - Formaldehyde
  - Acids (e.g. formic acid, acetic acid)
  - Nitrites

How Excipients Impact Stability: Indirect Impact

- Mobility of API increases with loss of crystallinity at drug-excipient interface
- Degradation rates increase significantly with increased mobility



Reaction Rate Dependence on Drug Load

- There is a common relationship between drug load and stability*:

$$k \propto \frac{1}{L}$$

degradation rate

drug load

- Several models assume that degradation is accelerated by contact between drug particles and excipient particles

Lower drug load → more API–excipient interactions → faster degradation → less stable

*Dimerization reactions can be an exception to this relationship

Three Models for Drug-Load Reaction Rate Dependence

1. Waterman et al.[1]

$$\ln(k) = \alpha * \ln\left(\frac{1}{L}\right) + \ln(k_0) \qquad k = k_0 * (\frac{1}{L})^{\alpha}$$

2. Deepika and Dewan[2]

$$\ln(k) = \alpha * \ln\left(\frac{1-L}{L}\right) + \ln(k_0) \qquad k = k_0 * (\frac{1-L}{L})^{\alpha}$$

Power Laws

3. Surface Area Contact Model[3]

$$\frac{1}{k} = \frac{R_{SSA}}{k_{limit}} * \frac{L}{1-L} + \frac{1}{k_{limit}} \qquad k = k_{limit} * \frac{1-L}{R_{SSA} * L + (1-L)}$$

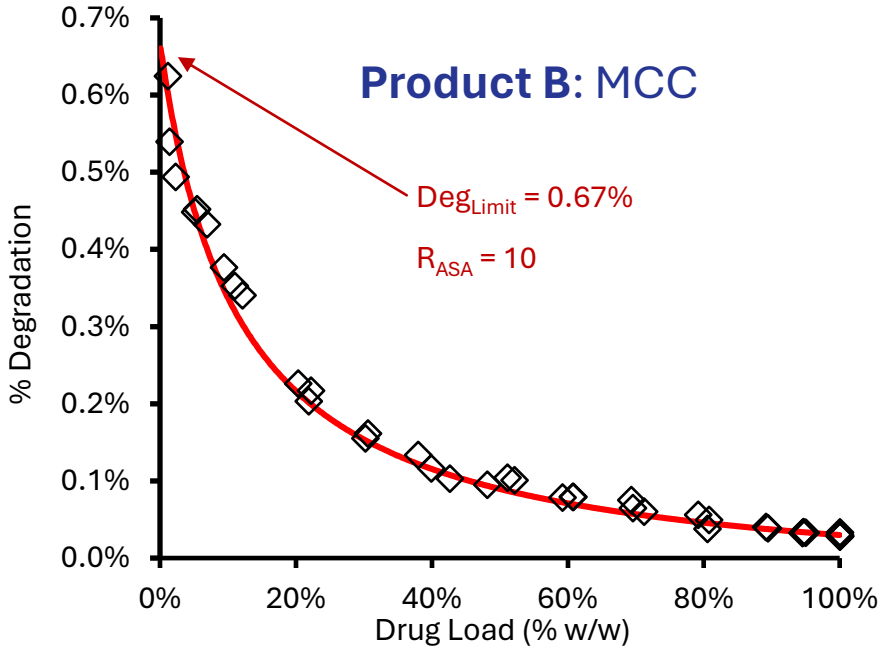
[1]Waterman, K. C. *et al*, *J. Pharm. Sci,* **101 (11)**, pp. 4170-4177 (2012)
[2]Deepika and Dewan, S.K., *Int. J. Pharm. Sci. Heath Care*, **4 (4)**, pp. 109-117 (2014)
[3]Baertschi, S.W. *et al, J. Pharm Sci,* **108**, pp. 1746-1755 (2019)

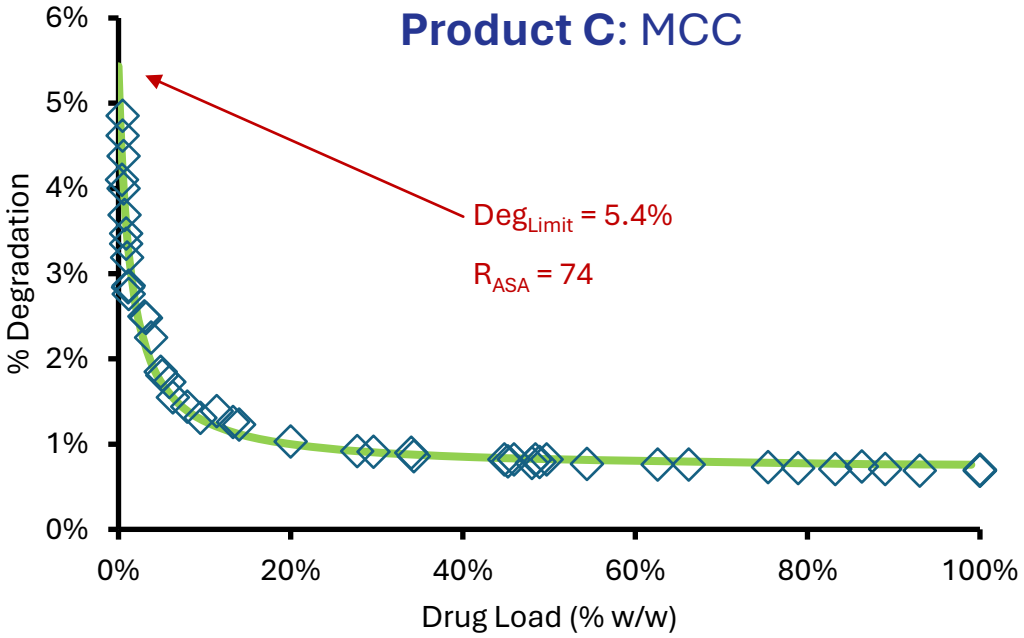
Drug Load Dependence

- In all models, there is a non-linear dependence of stability on drug load

- This dependence is ultimately based on surface contact between the API and the excipients, but does not depend on reaction between API and excipients

Examples of Drug-Load Dependence





Images from 2022 SOS Conference Presentation by Garry Scrivens

Binary Excipient Compatibility

- A drug is mixed with potential excipients
- Each binary combination is stressed and tested (usually for degradant growth)
- Results from all binary mixtures used to inform full formulation

Binary Excipient Compatibility

- Drug:excipient ratio
  - 1:1 ratio most common
  - What is a representative ratio? If API is at 1% and excipient 5%, could use 1:5 or 95:5
- Interactions with low level excipients often exaggerated
  - 1:1 API:magnesium stearate binary studies have led companies to avoid this lubricant, but often no issue if used in the full formulation at ≤1%
- Since excipient effects are non-linear, binary impact is not directly additive

Rank Order Screening from Single Condition

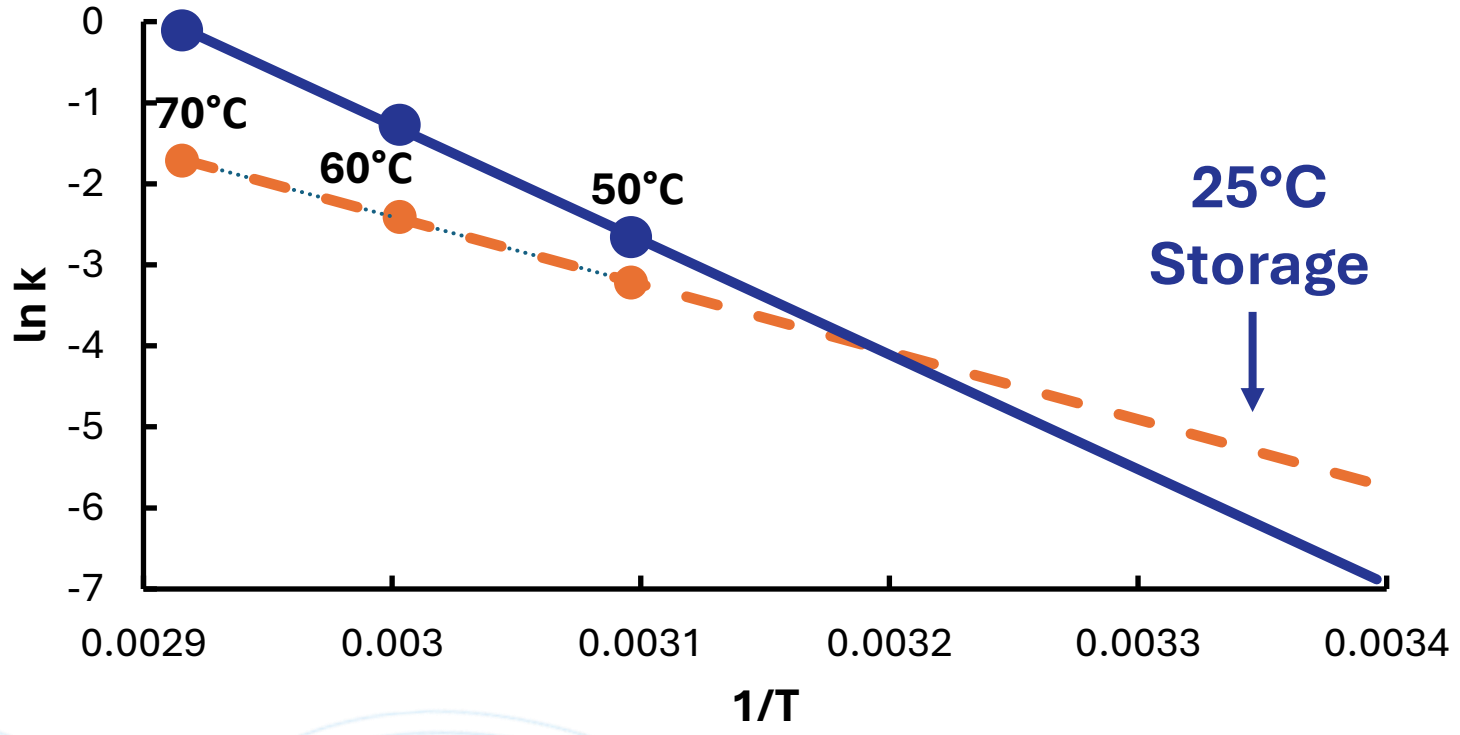
- Rank order testing from a single condition: often used with binary compatibility or with full formulations
- Example: Two formulations stressed at 70°C/75% RH/2 weeks

Formulation	% Degradant after stressing
A	0.18
B	0.90

- Which formulation do you proceed with for 25°C/60% RH storage?

Rank Order Screening from Single Condition

- While **B** is less stable at 70°C, it has a greater slope with temperature (larger E_a), making it more stable than **A** at 25°C



Rank order at high temperature is often the reverse of rank order at room temperature!

Beyond Rank Order: ASAP

- Need to understand formulation behavior at the storage condition, not the accelerated condition
- To relate the storage condition to accelerated conditions: measure slope with temperature (and %RH)
- Employ ASAP: Accelerated Assessment Stability Program
  - ASAP*prime*®: software program to model ASAP data

Beyond Rank Order: ASAP

- Stress formulations at several T/open %RH conditions and measure the amount of degradation over time
- Calculate time-to-fail at multiple T/% RH conditions
- Fit data to moisture-modified Arrhenius equation. Use model to predict time-to-fail at long term storage conditions

Spec. limit/
(time-to-fail)

Activation energy

$$\ln k = \ln A - E_a/(RT) + B(RH)$$

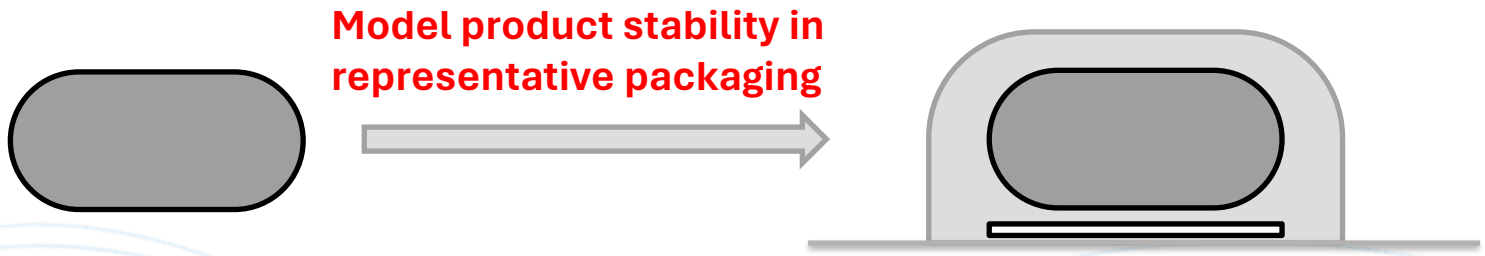
Pre-exponential factor,
~collision frequency

Humidity sensitivity factor

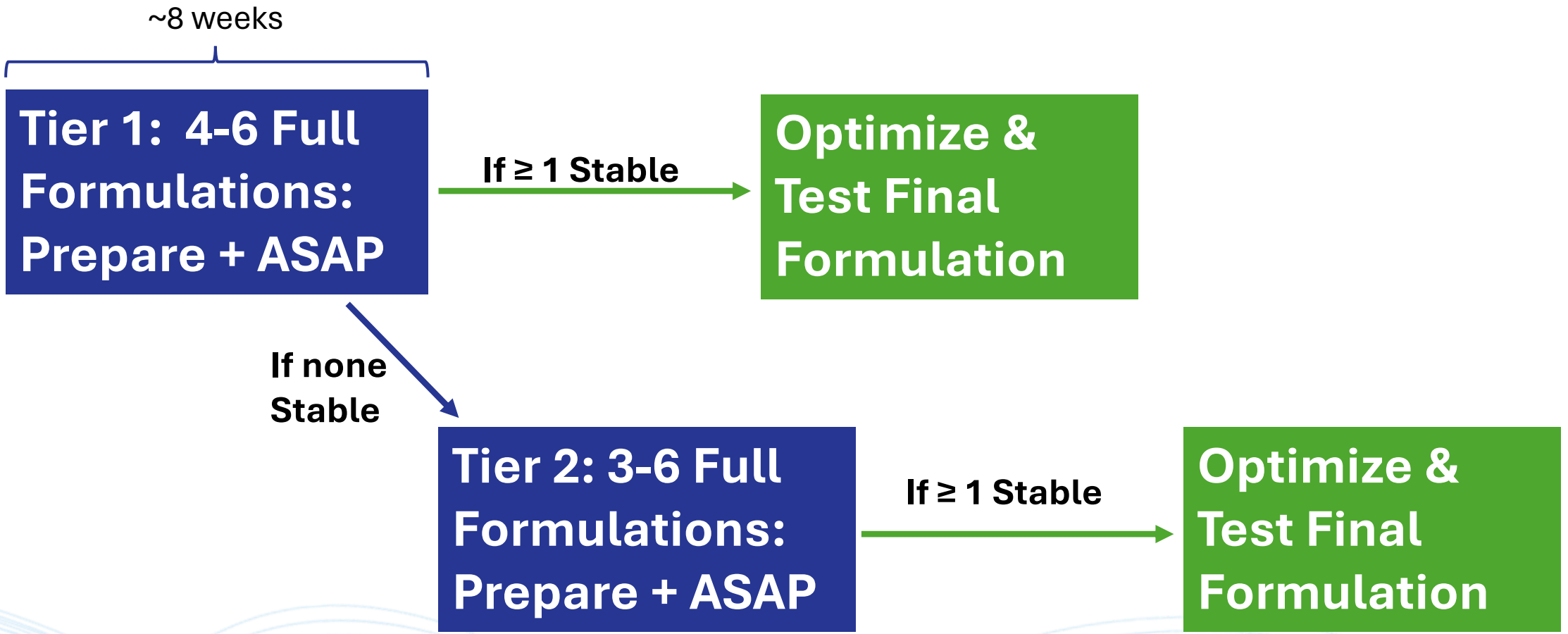
Equilibrium relative humidity

Use of ASAP with Tiered Formulation Screen

- Conduct ASAP stability study on full formulations (compacts, blends)
- Build a predictive model that gives product shelf life in representative packaging
  - Often model with low and high RH to mimic protective and non-protective packaging
- Optimize and retest final formulation



Tiered Formulation Screen



Results of Tiered Formulation Screen

- Result: **Acceptable** or **Unacceptable** for targeted storage condition
  - Can evaluate several climate zones
  - Can evaluate different representative packaging options
- If multiple formulations acceptable, can choose formulation based on characteristics other than stability – see Target Product Profile (TPP)
  - Selection can be based on manufacturability or other considerations

Results of Tiered Formulation Screen: Next Steps

- Second tier formulations needed infrequently
  - Even with a second round, formulations can be developed in a short time
- Re-evaluate stability once final formulation is refined
  - Early API lots often vary in stability (usually improve over time)
  - Changes in excipient grade or processing methods may impact stability

Tiered Formulation Screen Design

- Control test of pure API gives baseline stability
- Potential characteristics to cover:
  - Wet and dry processing
  - Addition of acids or bases
- Choice of API drug load
  - If dose is set in TPP, use target drug load
  - If dose unknown, use lowest likely drug load
- Check specialized characteristics of concern for API (e.g. compression)

Example of Tier 1 Formulations (Immediate Release Tablet)

Function	Component	% Composition (mg)			
		Formulation 1	Formulation 2	Formulation 3	Formulation 4
Active	API	15	15	15	10
Ductile diluent	MCC	50	50	50	50
Brittle diluent	Lactose	25	25		
	Mannitol			25	25
Disintegrant	Croscarmellose sodium	5		5	
	Sodium starch glycolate		5		5
Binder	HPC	4		4	
	PVP		4		4
Lubricant	Magnesium stearate	1		1	
	Stearic acid		1		1

Example Formulation Screen Results

Formulation	% Probability of Passing after storage at:	
	25°C/35% RH/2 y	25°C/60% RH/2 y
Formulation A (Base formulation)	97	95
Formulation B (Alternate diluent)	88	86
Formulation C (Alternate diluent)	90	87
Formulation D (Acidic environment)	100	100
Formulation E (Basic environment)	74	63

Formulations A and D can both be advanced

ASAP Study Considerations

- For formulation screen, design smaller study for stability “bucketing”
- To test final formulation, design larger study for refined shelf life
- Shelf life-limiting degradant may vary by formulation

Advantages of a Tiered Formulation Approach

- Information beyond rank order
  - Get **acceptable**/**unacceptable** result for stability of all formulations
  - Possible outcomes: all acceptable or all unacceptable
- Material sparing approach
  - Under 1 g works for low dosage strength formulations
- Rapid approach
  - Tier 1 study length ~ 8 weeks

Handling Oxidative Degradation: Role Unknown

- Include sample comparison with +/- oxygen at same stress condition to look for effect
  - When degradation responds to oxygen level → oxidative degradant
- Will indicate if shelf life-limiting degradants are oxidative

Handling Oxidative Degradation: Known Issue

- Include formulations with antioxidants in screen
- Use relatively high % of antioxidant to assess impact (e.g., 1%)
- Use antioxidants with different mechanisms of action[4]
  - Chain terminators
  - Sacrificial reductants
  - Chelators

[4]Waterman, K. C. *et al*, *Pharm. Dev. Tech*, **7 (1)**, pp. 1-32 (2002).

Options for Stabilizing Oxidative Degradation

- If antioxidants work, optimize level in formulation
- Minimize excipient impurities that cause oxidation (e.g. peroxides)
- Consider protonation of API (oxidations are hindered when the API already is positively charged)
- Consider oxygen-protective packaging
  - Low oxygen permeability packaging
  - Oxygen absorbers
  - Flushing with nitrogen

Summary: What Was Covered

- Advantages of using a tiered formulation approach with ASAP*prime*® for rapid, material sparing drug product development
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Questions?