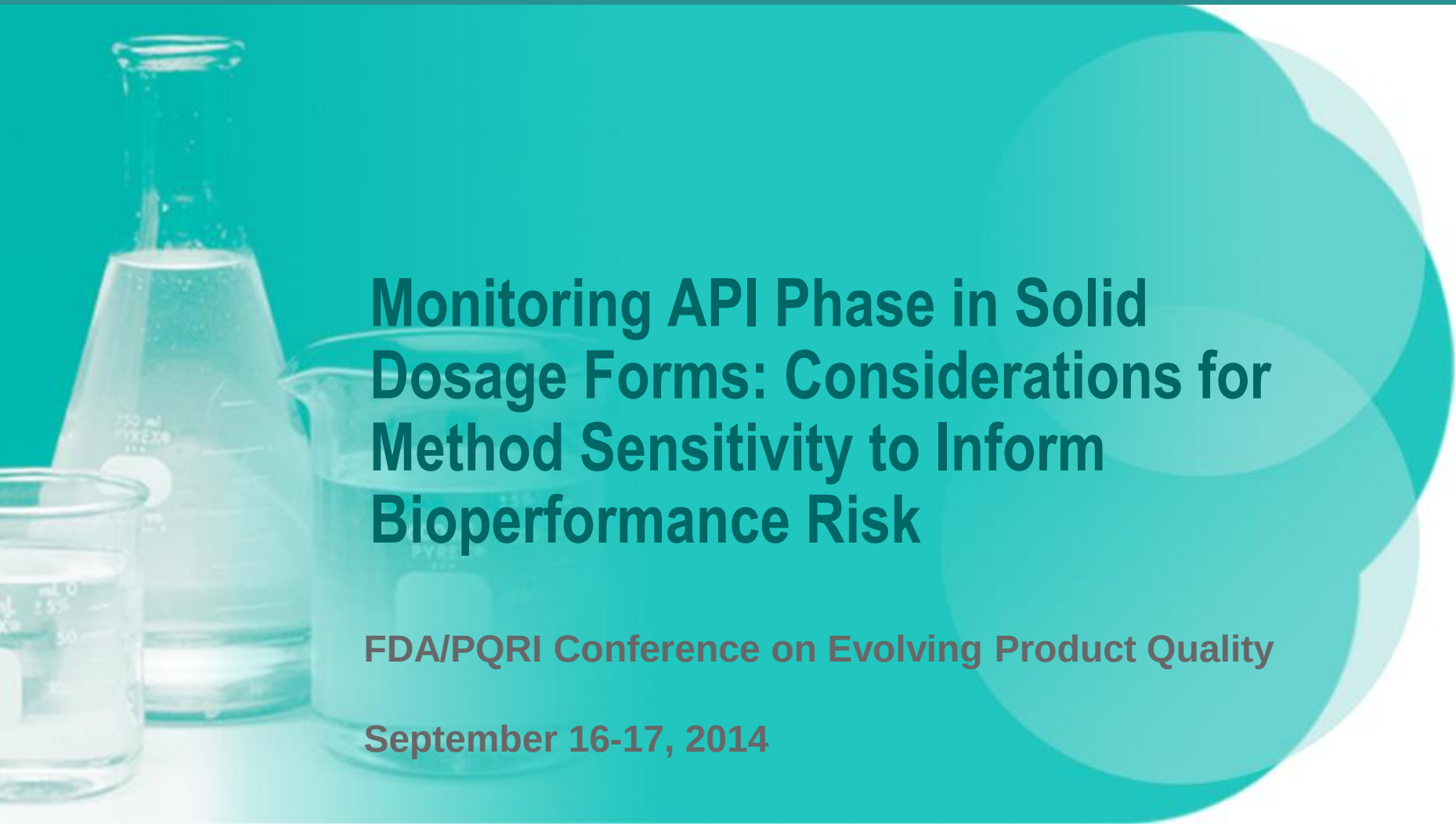

Monitoring API Phase in Solid Dosage Forms: Considerations for Method Sensitivity to Inform Bioperformance Risk

FDA/PQRI Conference on Evolving Product Quality

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Outline

- API phase change in drug product
- Solid-state characterization techniques and method sensitivity
- In vitro dissolution method to detect/quantify API phase change
- Considerations for setting clinically relevant spec for API phase in drug product

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Commonly Encountered API Phase Change in Drug Product

- Crystalline to crystalline
  - Polymorphic conversion
  - Hydration/dehydration
  - Solvation/desolvation
  - Cocrystal to crystalline neutral
  - Crystalline salt to crystalline neutral
- Crystalline to amorphous
  - Crystalline salt/neutral to amorphous salt/neutral
  - Crystal salt to amorphous neutral
- Amorphous to crystalline
  - Amorphous API to crystalline
  - Amorphous solid dispersion to crystalline
- Formation of new phase
  - In-situ salt formation
- Potential Impacts on drug product performance
  - Chemical stability
  - Bioavailability: increased risk for insoluble compound that requires solubilization technique to improve bioavailability

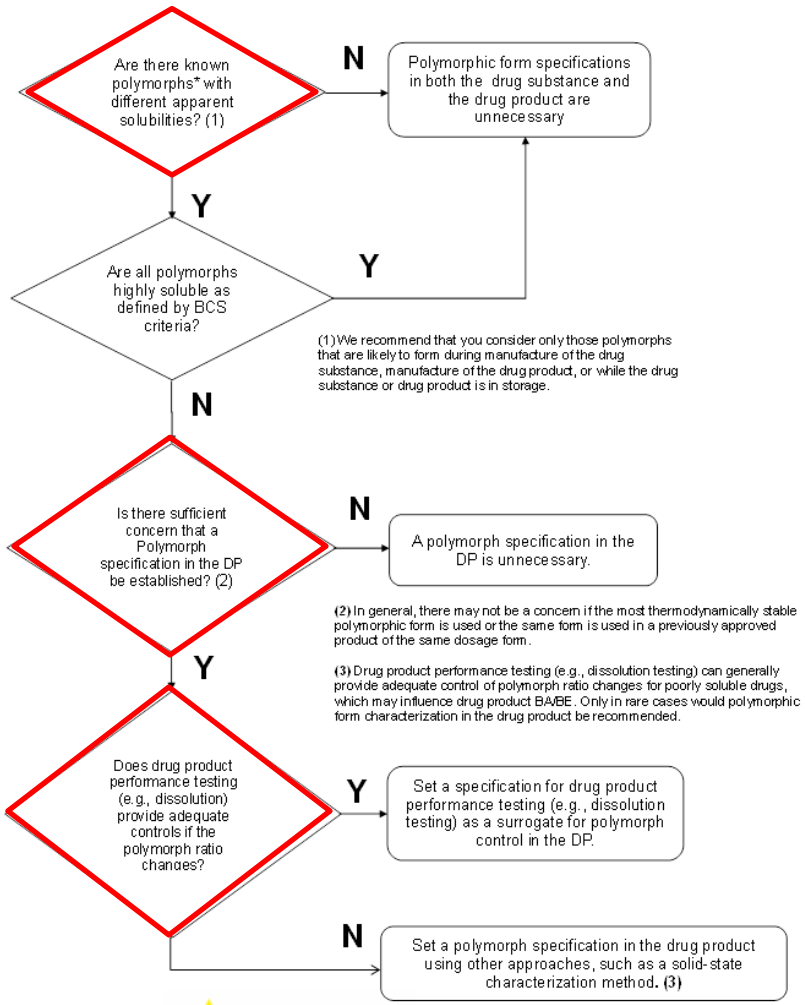
Need to Monitor API Phase in Drug Product

What is the risk for API phase change?
What are the relevant API phases to monitor in drug product?

Could the impact be assessed quantitatively?
Is there an acceptable limit for API phase change?
What is an adequate LOD for a solid-state characterization method?

Could a dissolution method be developed to detect API phase change?
What affects the sensitivity of the dissolution method?
Is it biorelevant?

ICH Decision Tree Q6A #4



Understanding the API Phase Change Risk

- Temperature and humidity induced changes
  - Relative stability of polymorphs/hydrates/solvates over relevant temperature and humidity ranges for
    - Dispensing
    - Manufacturing process
    - Storage
    - In-use
- Process induced changes
  - Granulation (dry and wet)
  - Milling
  - Tableting
  - Spray drying
  - Hot-melt extrusion
  - Film coating
- Excipient induced changes
  - Formation of in-situ salt or co-crystal with excipients
  - Excipient induced disproportionation

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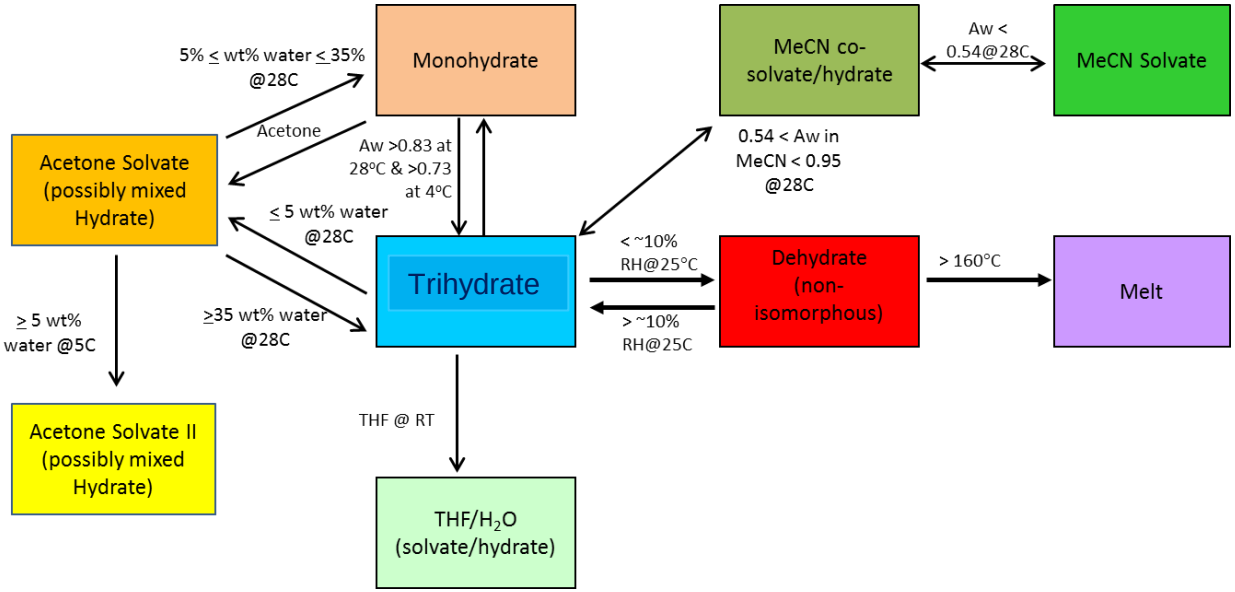
Solid-state Characterization Method Development: Identification of Relevant API Phases

API Phase Diagram for Compound X



- API is delivered as the trihydrate. The API is formulated as an amorphous solid dispersion via the hot melt extrusion (HME) process.
- Crystallization of amorphous API to trihydrate was detected at 40C/75%RH. The monohydrate is the thermodynamically stable phase between 10% and 80%RH at 28C.
- Solid-state characterization methods to detect both the trihydrate and monohydrate in drug product and amorphous solid dispersion intermediate were developed to evaluate the
  - Conversion of the API phase to amorphous by the HME process
  - Physical stability of the amorphous API at different temperature/humidity conditions upon storage

Solid-state Characterization Method Development: Method and Sensitivity

- Commonly used solid-state characterization methods to evaluate API phase in drug product and intermediates

Method	API Phase Change Characterization	Sample Type	Detection Limit for Crystalline Phase (based on total formulation weight)	Practical for Commercial Lot Release
XRPD	crystalline to crystalline amorphous to crystalline	drug product and formulation intermediate	>0.5%	Yes, provided GMP instrument and expertise (quantitative) exist in QC labs.
Vibrational Spectroscopy	crystalline to amorphous amorphous to crystalline amorphous to amorphous	drug product and formulation intermediate	>0.5%	
ssNMR	crystalline to crystalline amorphous to crystalline Amorphous to amorphous	drug product and formulation intermediate	>1% for ^{13}C >0.1% for ^{19}F, ^{31}P	No. GMP instrument and expertise is available beyond R&D
DSC/DMA	crystalline to amorphous amorphous to crystalline	formulation Intermediate (ie. amorphous solid dispersion)	>5%	

- Conversion of amorphous API to crystalline or disproportionation of a salt to its crystalline neutral form is often evaluated more rigorously compared to other types of API phase conversion due to perceived risk on bio-performance.

Solid-state Characterization Methods to Detect Crystallization in Amorphous Solid Dispersion Formulations

	Method of Choice (Also evaluated)	DL in DP	LOD in DP (API conversion)	DL in Intermediate	LOD in Intermediate (API conversion)
A	FT-Raman (XRPD; ssNMR)	8%	2% Form I 4% Form II	20%	5% Form I, 10% Form II (XRPD)
B	XRPD (Reflectance Raman)	16.7	3%	25%	3%
C	XRPD (Transmission and Reflectance Raman)	10%	5% Form III 6% Form IV	30%	3% Form III 4% Form IV
D	XPRD (Reflectance Raman; ssNMR)	10%	3% Form I 8% Form II	20%	1.5% Form I 3% Form II
X	XRPD (Reflectance Raman; ssNMR)	10%	3% monohydrate, 3% trihydrate	20%	<3% monohydrate <3% trihydrate
C+Y Fix Dose Combination	XRPD (Transmission Raman)	6% for C	8% Form III of C 9% Form IV of C	20% for C	3% Form III of C 5% Form II of C

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Impact of Drug Loading on Method Sensitivity for Solid-state Characterization

Drug Loading	20% LOD	10% LOD	5% LOD
40%	8	4	2
20%	4	2	1
10%	2	1	0.5
5%	1	0.5	0.25
2.5%	0.5	0.25	0.125

- The detection limit of a solid-state characterization method is dependent on API/excipient properties as well as drug loading in the formulation.

Considerations for Solid-state Characterization Method Sensitivity

- A solid-state characterization method can often achieve ~5% LOD for crystalline phase (based on API conversion) when the drug loading is >10%.
  - Is it generally accepted that <5% API phase change is deem low risk for bio-performance?
- When the drug loading is <10%, the probability for a solid-state characterization method to achieve ~5% LOD is low with routine analytical instrumentation in pharmaceutical labs.
  - What if the LOD is between 5 and 10%? Is it acceptable for drug product with tight control on assay (+/-5%)?
  - What if the LOD is greater than 10%?
- Could dissolution experiments be explored to detect API phase change with potential impact on bioavailability?
  - QC method vs method customized to detect API phase change
- Will such dissolution method be bio-predictive?
- What else can be done to assess the bioperformance risk when a sensitive method to detect API phase change could not be achieved for the drug product?

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In Vitro Dissolution to Detect API Crystallization in an Amorphous Formulation: A Case Study Based on Simulated Dissolution Profile

- Model System
  - An amorphous formulation developed to improve the bioavailability of an insoluble compound
  - The crystalline and amorphous solubility in FaSSIF is 0.005mg/mL and 0.05mg/mL respectively

- Hintz-Johnson Dissolution Model is used to simulate the dissolution of a 45mg tablet (mixtures of amorphous and crystalline API at different ratios) in 900mL of media. The impact of tablet disintegration/erosion on the dissolution profile is not considered.

- The sink conditions as well as the particle size of the crystalline and amorphous API are varied in the simulation to assess the impact of these variables on the dissolution profile and the method sensitivity to crystallinity
  - Sink condition
    - 1x, 3x, 10x of amorphous solubility to mimic media selection
  - API particle size
    - Crystalline: 35um, 10um, and 1um to mimic the particle size of crystalline reference material and crystalline phase formed in the amorphous formulation after crystallization
    - Amorphous: 35um and 10um to provide different dissolution rate as amorphous drug with different effective particle size

Hintz-Johnson Dissolution Model to Simulate Dissolution Profile

$$\frac{dM_{diss}}{dt} = \frac{3DM_{0,xtal}{}^{2/3}M_{xtal}{}^{1/3}}{\rho r_{xtal}{}^{2}} \times \left(Sol_{xtal} - \frac{M_{diss}}{V}\right) + \frac{3DM_{0,amor}{}^{2/3}M_{amor}{}^{1/3}}{\rho r_{amor}{}^{2}} \times \left(Sol_{amor} - \frac{M_{diss}}{V}\right)$$

- D: drug diffusivity
- ρ: drug density
- r_{xtal} or r_{amor}: particle radius of crystalline or amorphous API, single radius value used (no particle size distribution)
- Sol_{xtal} or Sol_{amor}: solubility of crystalline or amorphous API
- $M0,_{xtal}$ or $M0,_{amor}$: starting amount of solid crystalline or amorphous API
- M_{xtal} or $M_{amor:}$ amount of solid crystalline or amorphous API at any time
- V = dissolution volume
- Model assumes no interaction in dissolution between amorphous/crystalline other than both being simultaneous source of drug in solution (i.e crystals don't induce crystallization of amorphous)

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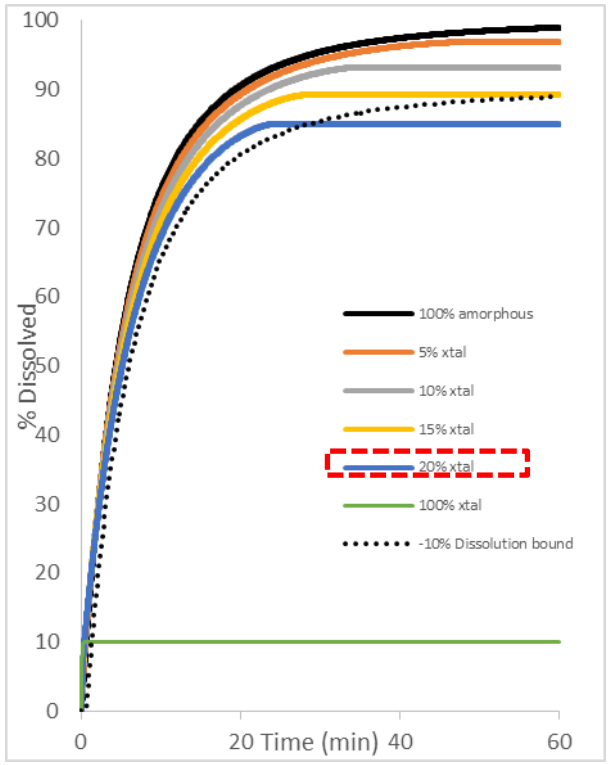
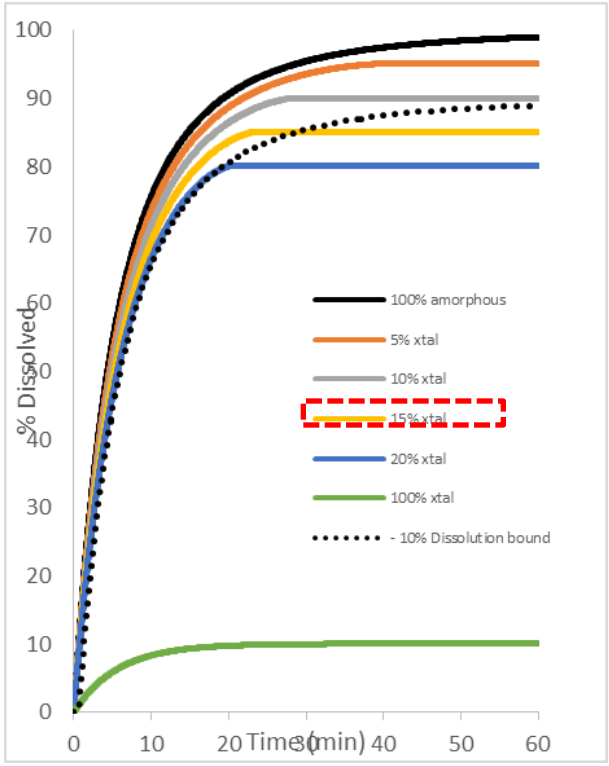
Simulated Dissolution Profile
(Sink = 1x Amorphous Solubility)

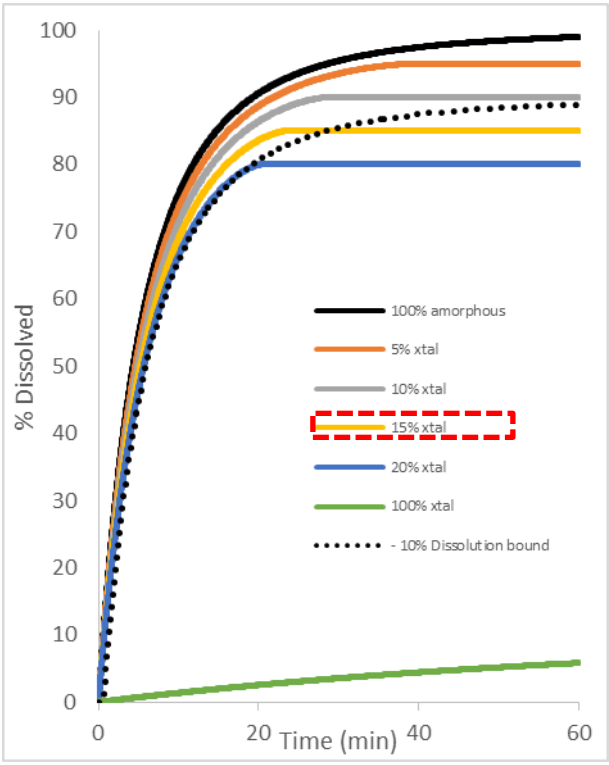
10 um particles for amorphous
1 um particles for crystalline



10 um particles for amorphous
10 um particles for crystal



10 um particles for amorphous
35 um particles for crystal



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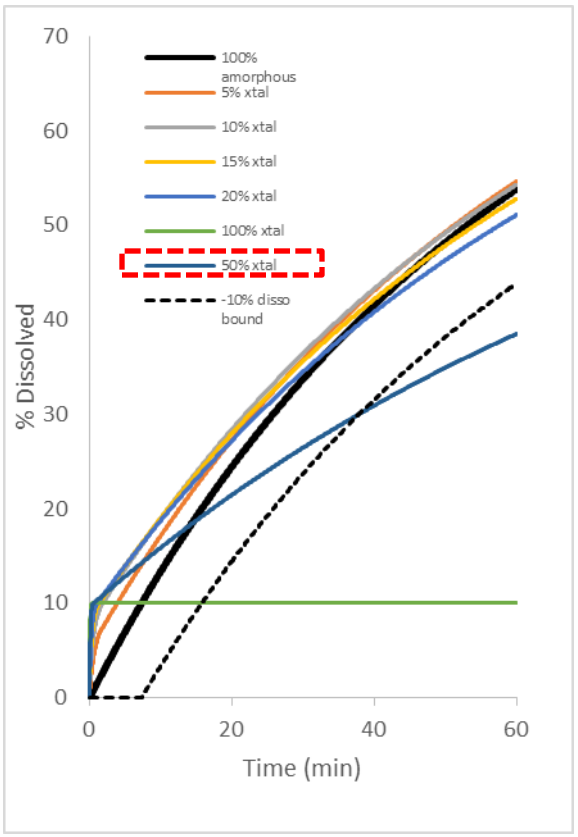
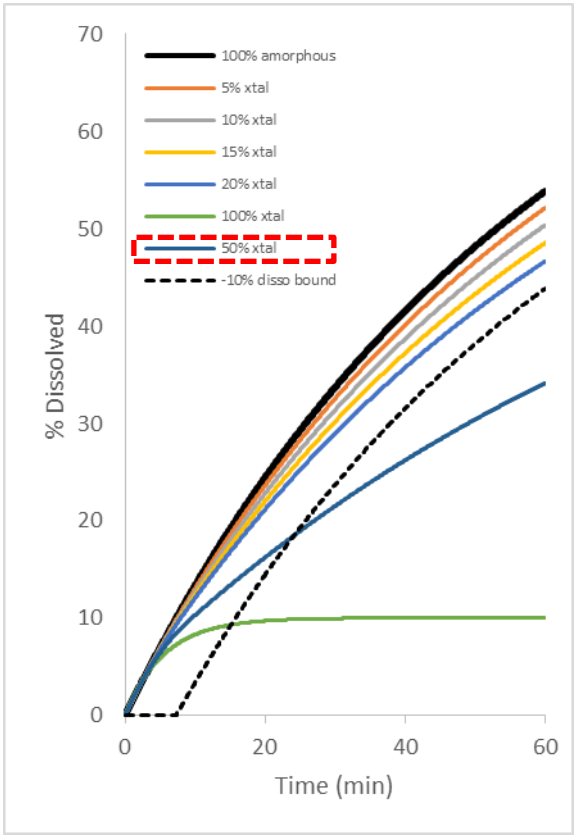
Simulated Dissolution Profile
(Sink = 1x Amorphous Solubility)

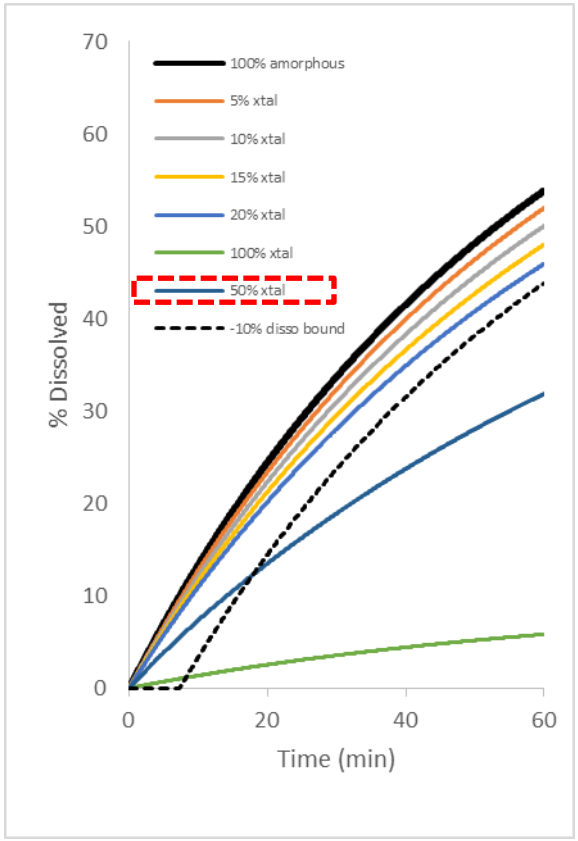
35 um particles for amorphous
1 um particles for crystalline



35 um particles for amorphous
10 um particles for crystalline



35 um particles for amorphous
35 um particles for crystalline



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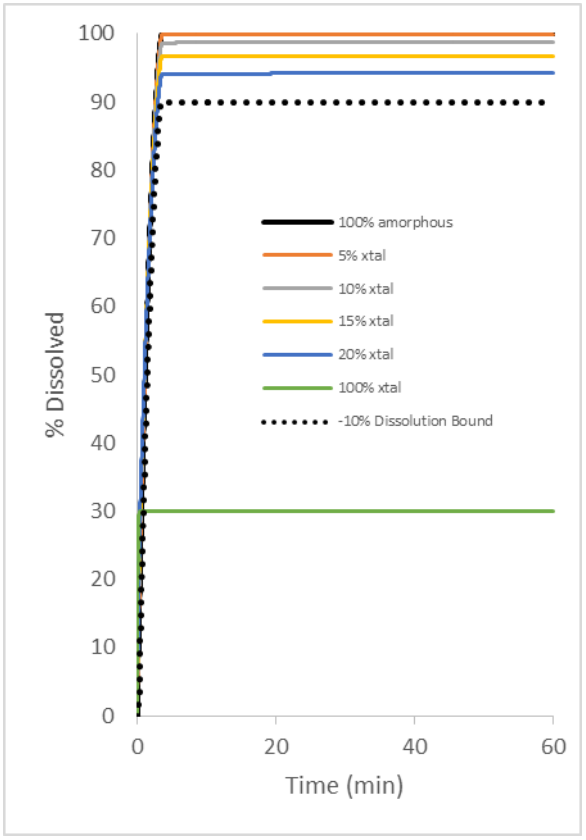
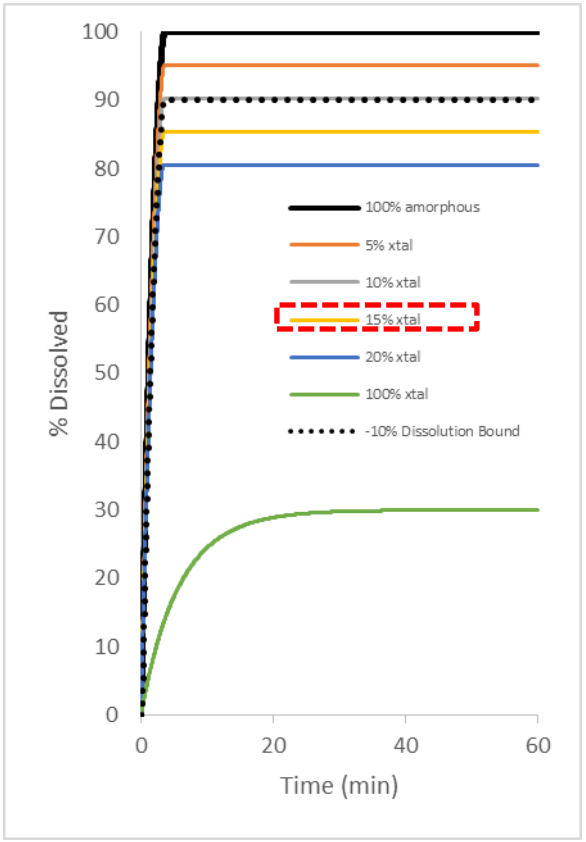
Simulated Dissolution Profile
(Sink = 3x Amorphous Solubility)

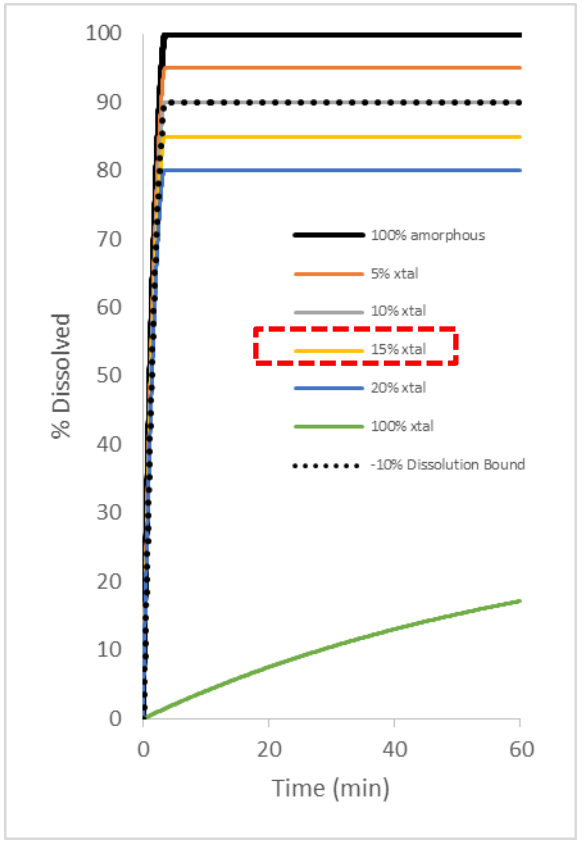
10 um particles for amorphous
1 um particles for crystalline



10 um particles for amorphous
10 um particles for crystal



10 um particles for amorphous
35 um particles for crystal



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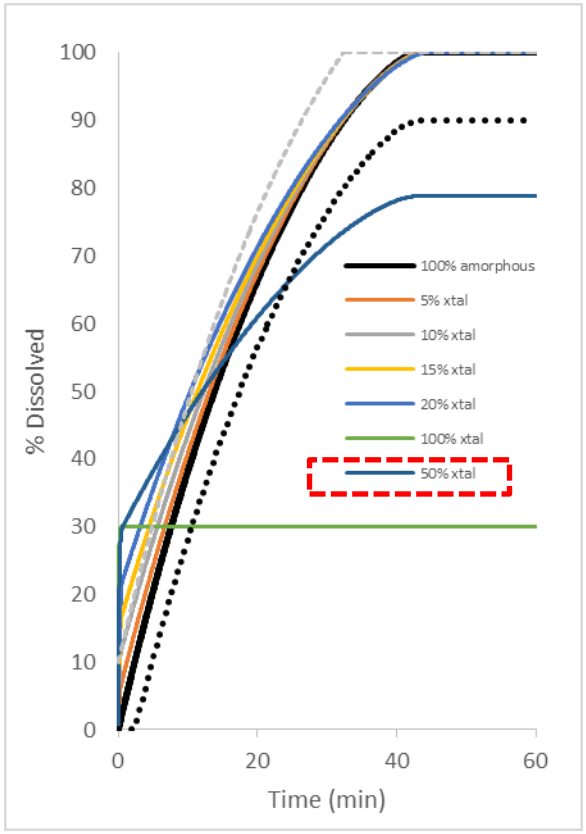
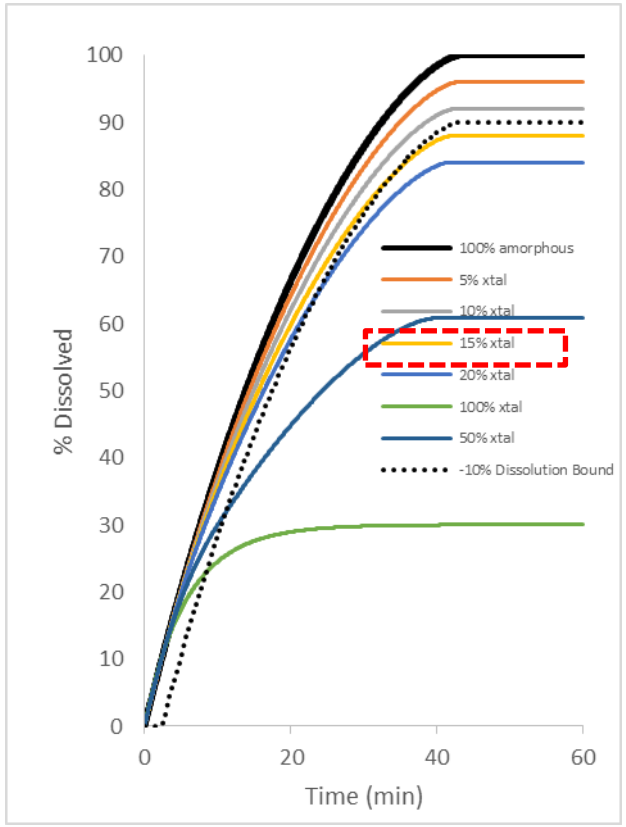
Simulated Dissolution Profile
(Sink = 3x Amorphous Solubility)

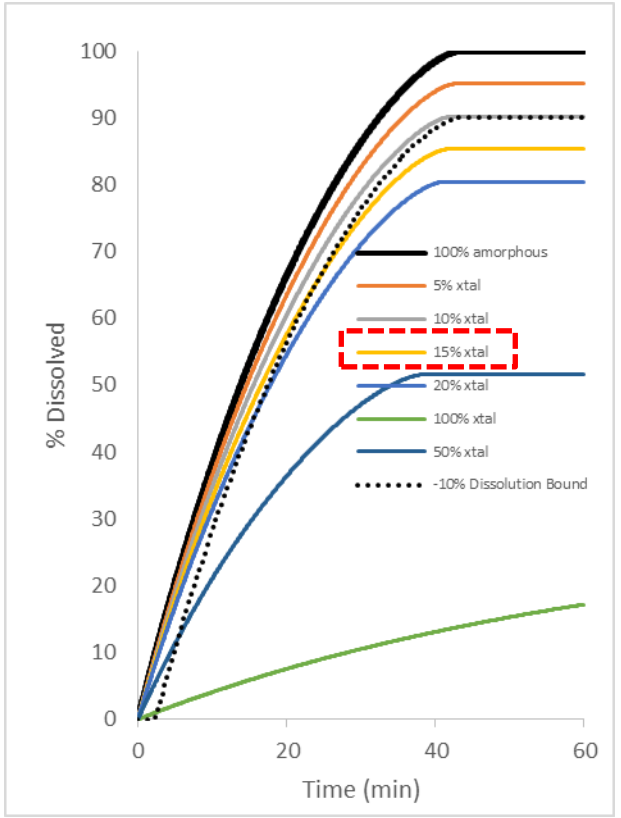
35 um particles for amorphous
1 um particles for crystalline



35 um particles for amorphous
10 um particles for crystalline



35 um particles for amorphous
35 um particles for crystalline



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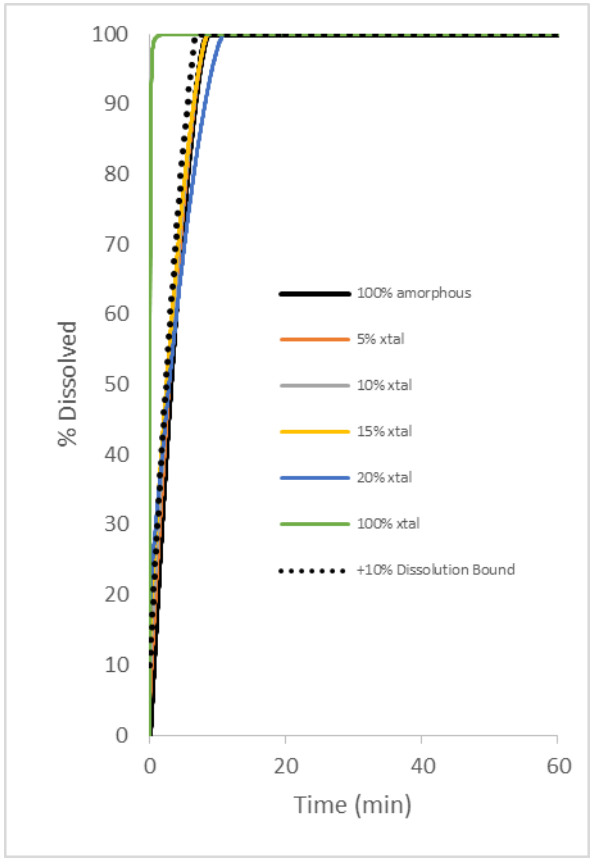
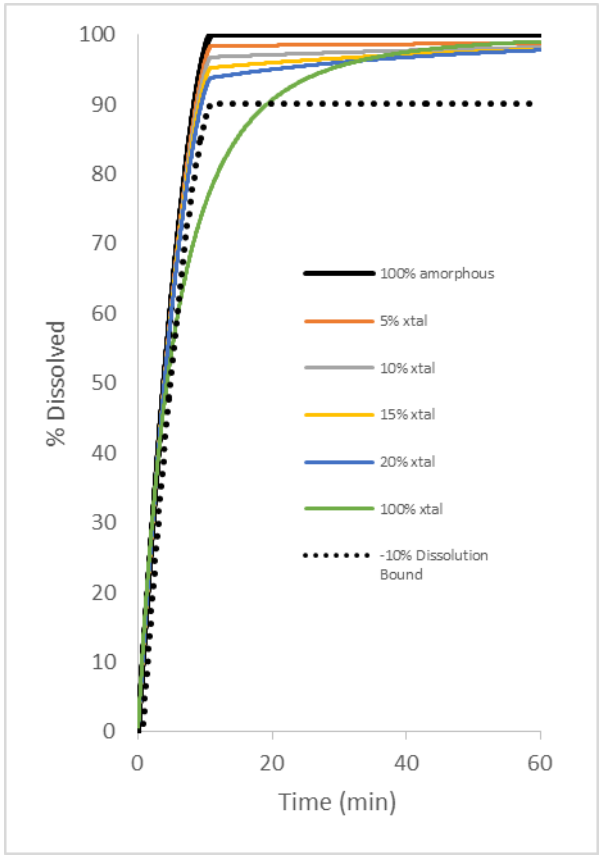
Simulated Dissolution Profile
(Sink = 10x Amorphous Solubility)

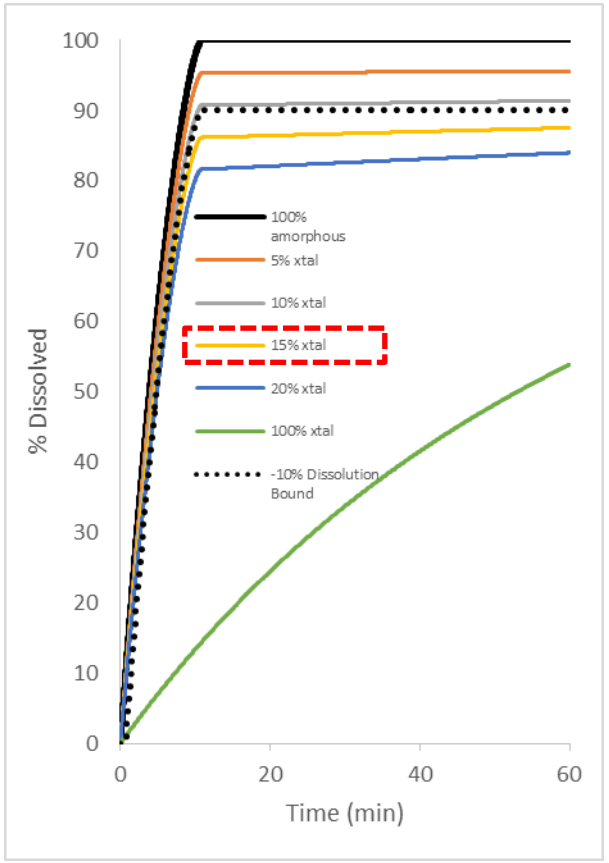
35 um particles for amorphous
1 um particles for crystalline



35 um particles for amorphous
10 um particles for crystalline



35 um particles for amorphous
35 um particles for crystalline



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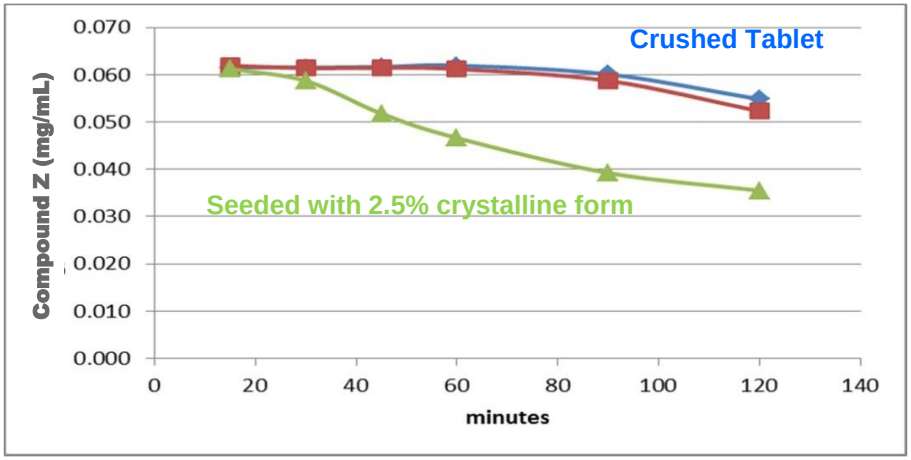
In Vitro Dissolution to Detect API Phase Change: The Effect of Seeding



Sink Condition: 1x amorphous solubility
Amorphous solubility: 0.06mg/mL
Crystalline solubility: 0.006mg/mL
Particle size of crystalline: 50um

- Under certain dissolution conditions, the presence of a low solubility crystalline form can induce phase change during dissolution. This seeding affect can be observed at <5%.
  - Degree of supersaturation relative to the solubility of the stable phase
  - Relative dissolution rate of the two API phases (PSD)
  - Inherent crystallization property of the API
- Caveat of applying the seeding method to detect low level of the crystalline phase of interest
  - Nucleation is stochastic and other substance may induce nucleation.
  - Representative seed material (particle size) is not readily available.
  - May not be quantitative
  - Very difficult to be implemented as a QC test
- Concern over undetectable crystalline seed to induce crystallization in vivo
  - The effect of low level of crystalline seed on PK is largely unexplored.

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Considerations for Using In-vitro Dissolution to Detect API Phase Change

- The sensitivity of a dissolution method to API phase is dependent on multiple factors
  - Solubility difference between the two API phases
  - Particle size of both API phases
  - Sink condition
- The sink condition can be varied to optimize the sensitivity. Simulation can be used to guide the selection of dissolution conditions.
- The PSD of the API phase formed in the drug product is difficult to determine. If the PSD of the reference material is not representative of that in the drug product, the detection limit established based on reference material can be misleading!
- Considering the experimental variability, in-vitro dissolution has low probability to detect <15% API phase change reliably if the solubility difference between the two forms is less than 10x and the particle size of the lower solubility form is less than 10um
- Solid-state characterization method is likely to achieve lower LOD than in vitro dissolution for drug product with a drug loading greater than 10%.

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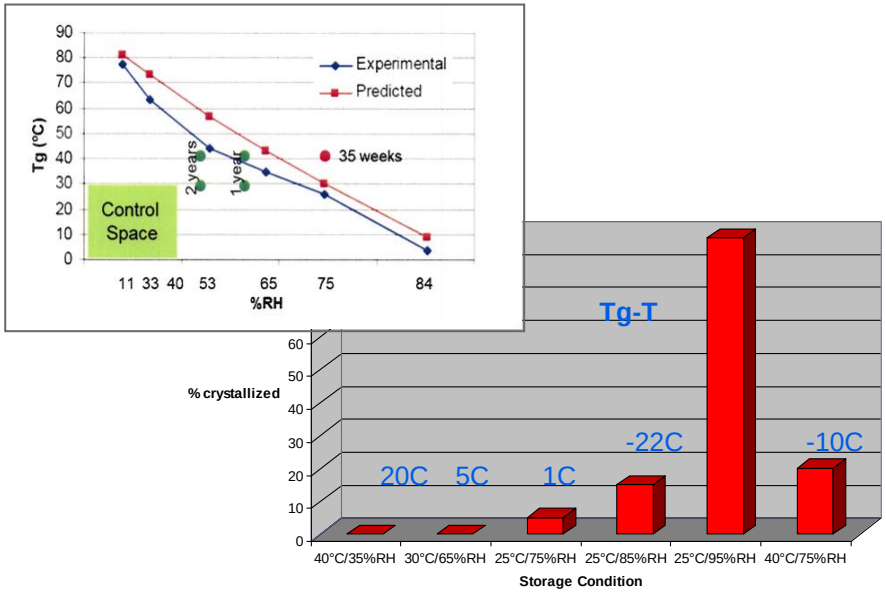
Consideration for Setting API Phase Specification for Drug Product

- Drivers for setting specifications
  - Product quality: bioavailability
  - Process control
- Strategy based on solid-state method sensitivity
  - LOD <5% and API phase change is not detected under relevant process or storage conditions
    - Minimal impact on bioavailability expected, spec may be set based on LOD for process control
  - LOD >5% and API phase change is not detected under relevant process or storage conditions
    - Knowledge based risk assessment
    - Clinical experience: clinical batches manufactured under process conditions in filing
    - Relative bioavailability study to qualify stressed formulation or formulation manufactured at edges of the process space that represent a higher stability risk as needed
    - If LOD is greater than 20%, evaluate in-vitro dissolution as potentially a more sensitive method. Spec is set based on LOD with process control to ensure product quality.
  - LOD >5% and API phase change is detected under relevant processing or storage conditions
    - Establish the level of no PK effect in a relative bioavailability study
      - 100% A vs 100%B
      - Stressed sample

Knowledge Based Risk Assessment on API Phase Change in Drug Product

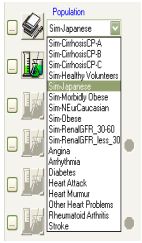
- How can we assess the API Phase change risk in absence of a sensitive solid-state or in-vitro dissolution method?
  - Knowledge of processing and temperature/humidity effect on API and formulation intermediate
  - PK modeling and simulation to evaluate sensitivity of bioperformance to API phase

Tg – T as an Indicator for Physical Stability of Amorphous SDI



- Moisture protection to keep the Tg of the drug product above storage temperature.

Relative Exposure for Different % Free Base in HCl Salt



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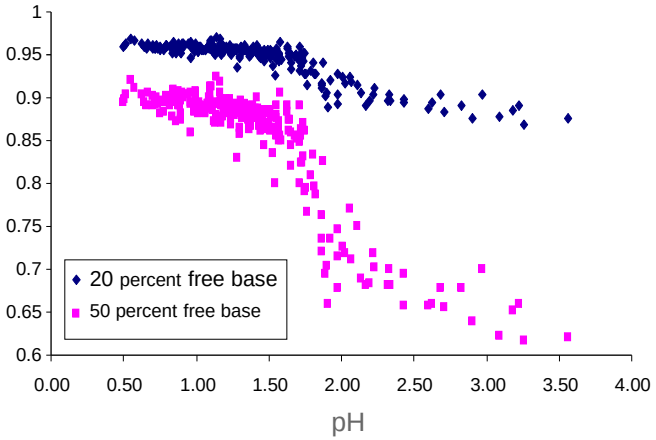

- At 20% free base, a small effect on total exposure is predicted (GMR to HCl salt is predicted at 0.95).
- At 50% free base, the predicted mean relative Fa is 85%.

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Conclusion

- Monitoring API phase is a critical component of drug product development.
- A sensitive solid-state characterization method is desired to minimize the performance risk.
- In vitro dissolution can be explored to detect API phase change in the drug product, but is unlikely to be sensitive to low levels (<15%) of API phase change.
- The LOD of the API phase characterization method is an important consideration for establishing a control strategy to ensure product quality.
  - In vitro method (solid-state and dissolution) only or additional human PK evaluation
- Other risk assessment tools can be leveraged to guide the control strategy.
- A clear guidance on setting API phase specification can help streamline product development.
  - Joint effort between Pharma and Regulatory