Regulatory Considerations on Pharmaceutical Solids: Polymorphs/Salts and Co-Crystals

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*Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

Overview

1. **Regulatory Scheme on Polymorphs/Salts**

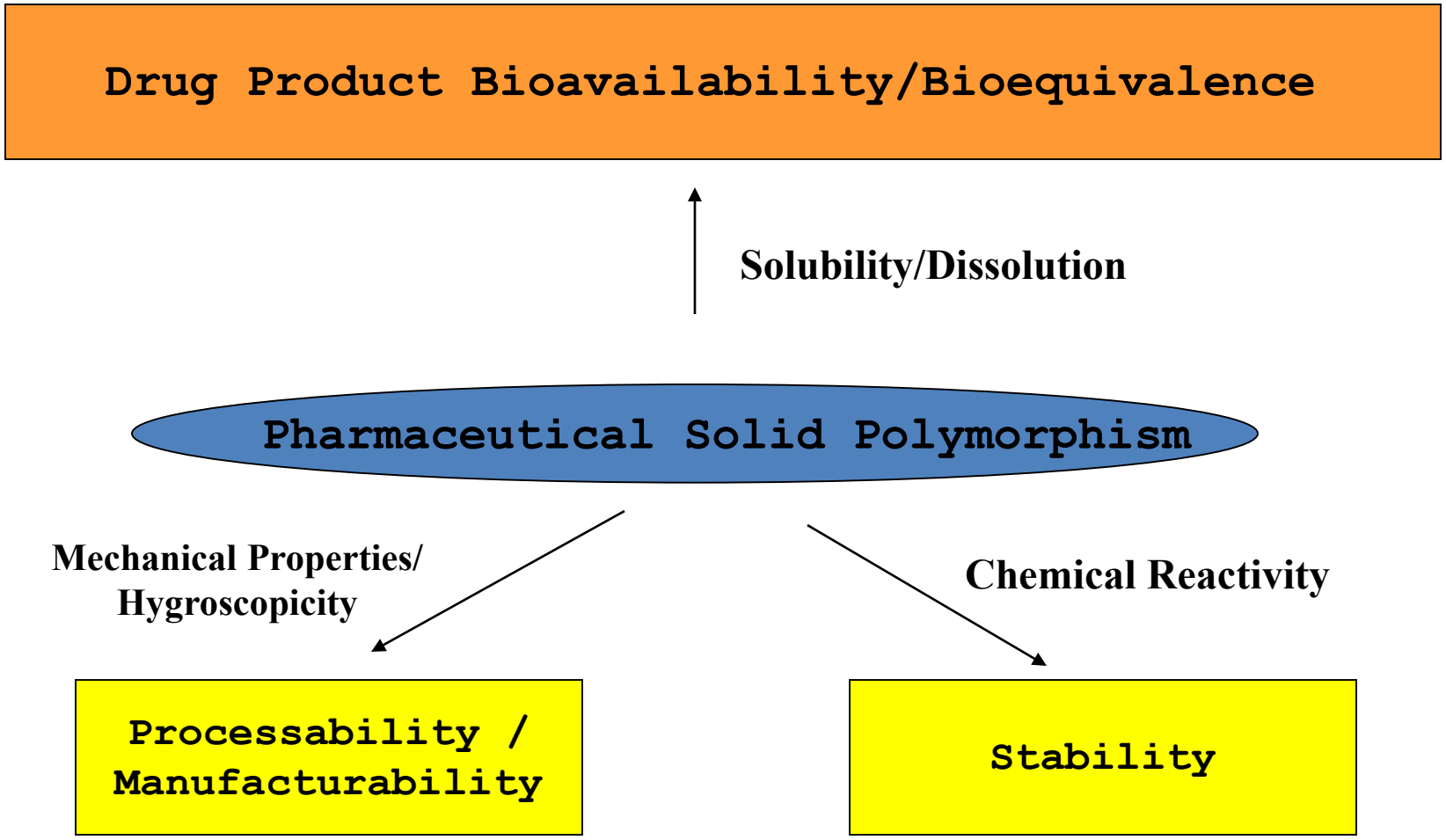
2. **Regulatory Scheme on Co-Crystals???**

Part IA
Regulatory Scheme on Polymorphs

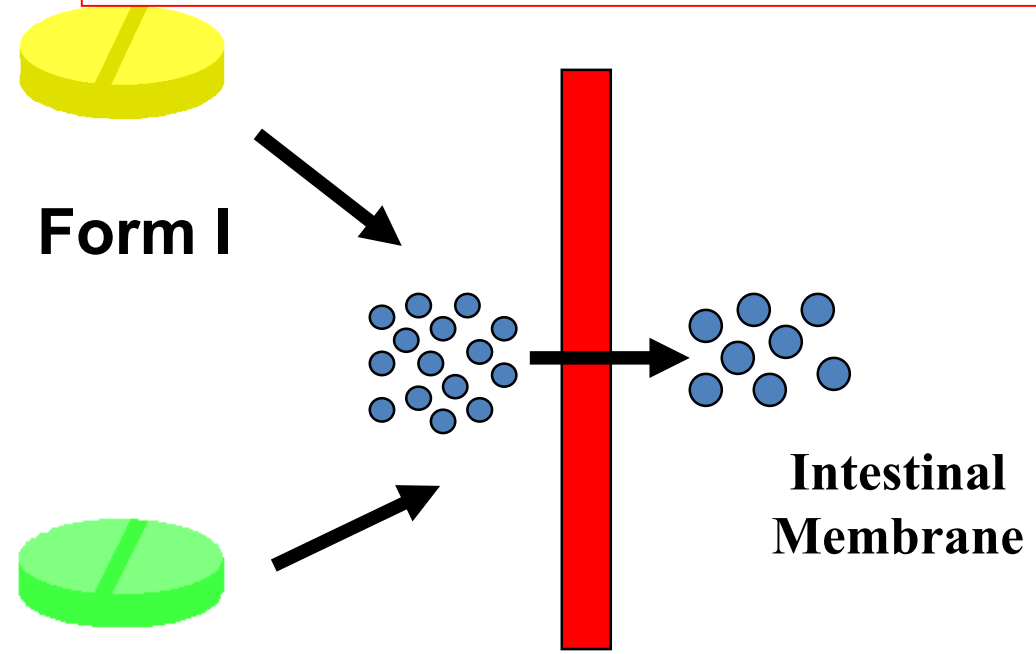
Solid-State Polymorphism

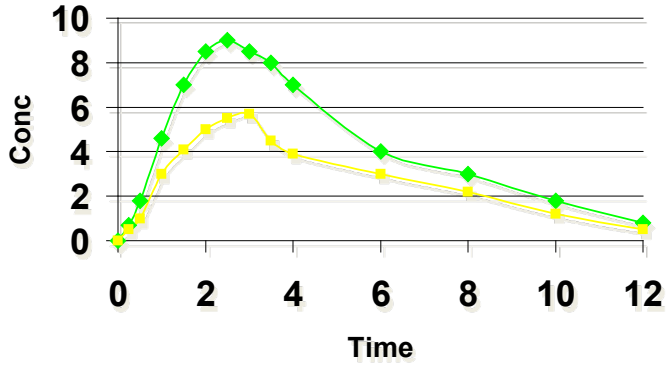
Different crystalline forms of the same drug substance (ICH Q6A)

- **Crystalline forms**
- **Solvates (Hydrates)**
- **Amorphous forms**

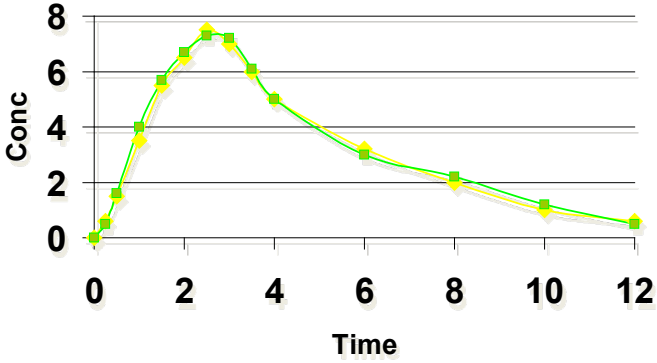

Drug Product Bioavailability/Bioequivalence
Solubility/Dissolution
Pharmaceutical Solid Polymorphism
Mechanical Properties/
Hygroscopicity
Chemical Reactivity
Processability /
Manufacturability
Stability

Polymorphism and the Effect on Bioavailability





Dissolution/Solubility Limited Oral Absorption (e.g. chloramphenicol palmitate)



Gastric Emptying or Permeation Limited Oral Absorption (e.g. ranitidine HCl)

Solubility: Form II > Form I

Polymorphism and the Effect on Stability

Crystalline: Degradation: 0.5%
Amorphous: Degradation: 4.5%

Formulation I

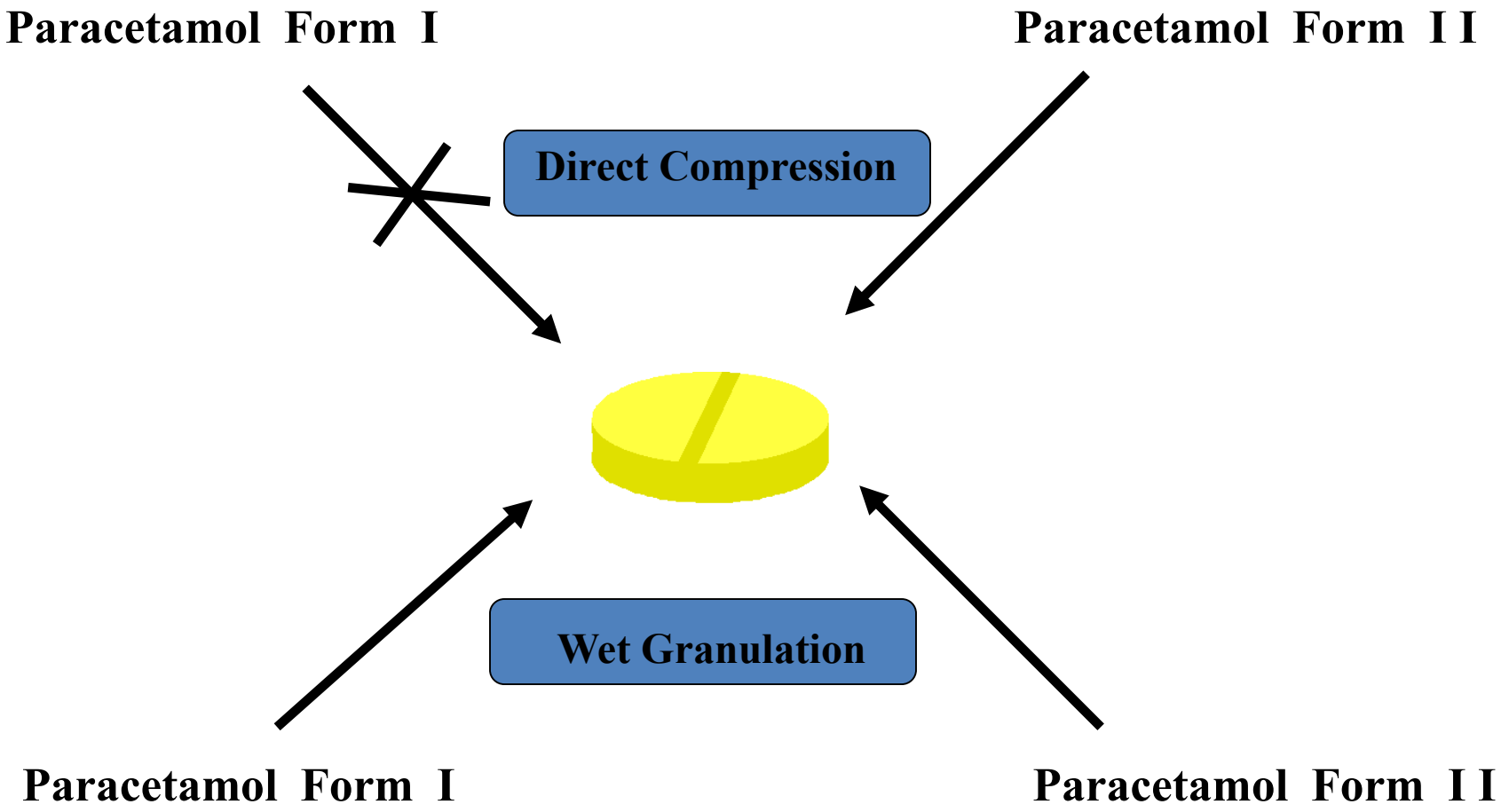
X Crystalline/ Amorphous

Formulation II

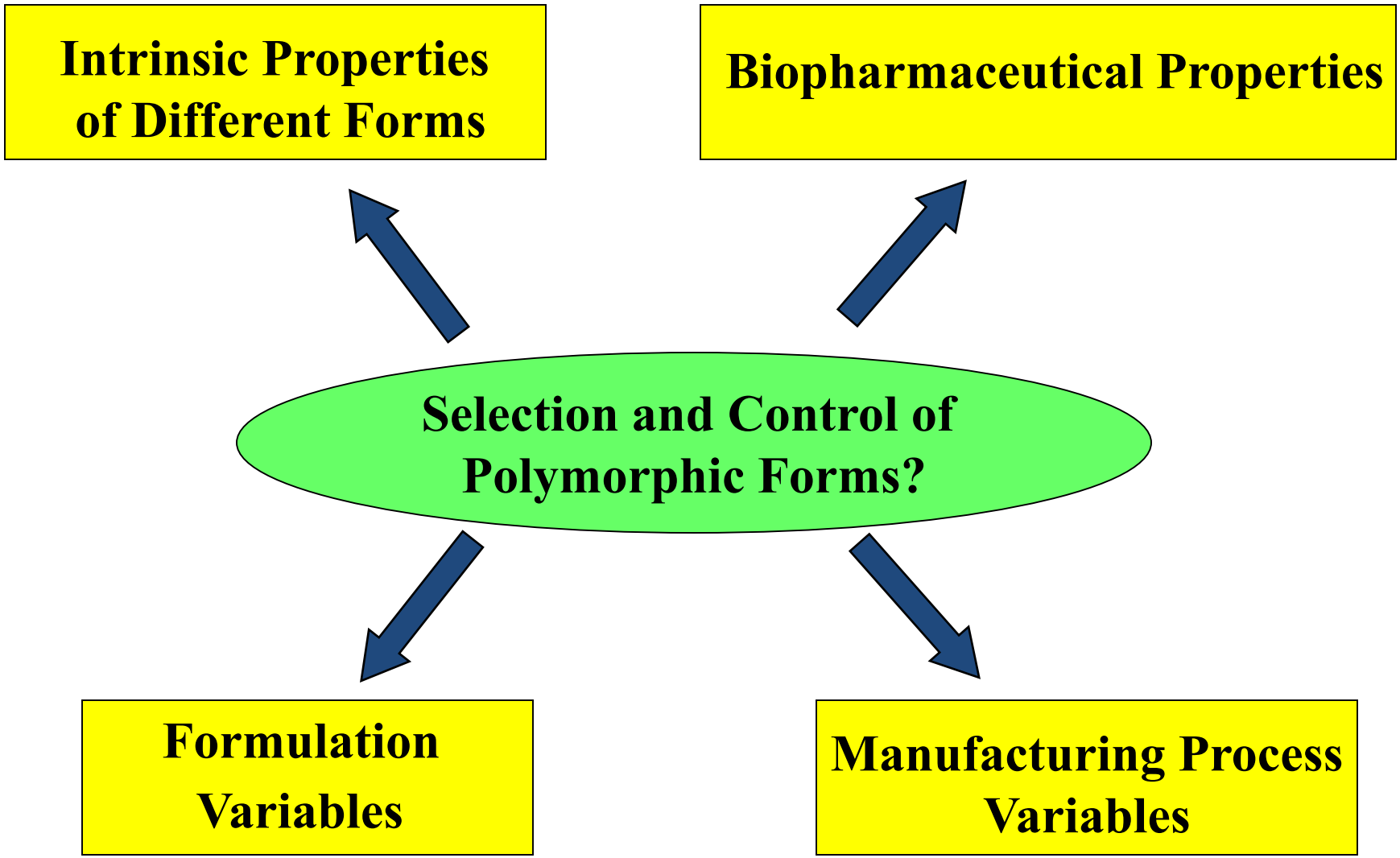
Optimize the formulation mitigate degradation pathways (e.g., adjust pH microenvironment to limit degradation, anti-oxidant to limit oxidative degradation)

Crystalline: Degradation 0.6%
Amorphous Degradation 0.7%

Polymorphism and the Effect on Manufacturability



E. Joiris , Pharm. Res. 15 (1998) 1122-1130


Intrinsic Properties of Different Forms
Biopharmaceutical Properties
Selection and Control of Polymorphic Forms?
Formulation Variables
Manufacturing Process Variables

QbD Paradigm: Polymorphs

From ICH Q8: ***"The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g. solid state properties), should be identified and discussed."***

Expectation that sponsors justify in pharmaceutical development the selection and control of the polymorphic form (as applicable) to achieve drug product performance characteristics, stability and ensure manufacturability

Example QbD MR Tablet
Module 3 Quality 3.2.P.2 Pharmaceutical Development

Quality by Design for ANDAs: An Example for Modified Release Dosage Forms

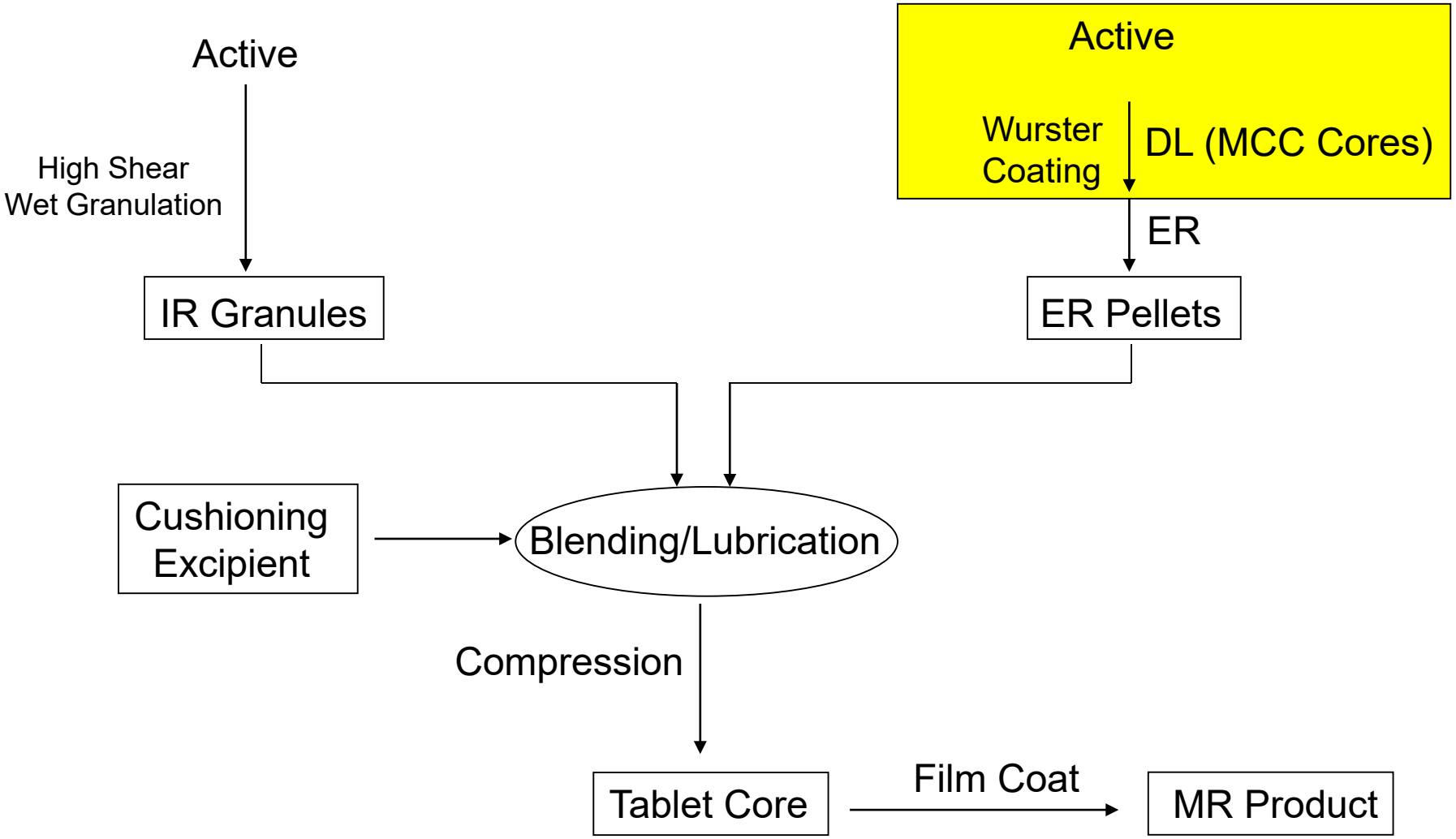
Introduction to the Example

This is an example pharmaceutical development report illustrating how ANDA applicants can move toward implementation of Quality by Design (QbD).

The purpose of the example is to illustrate the types of pharmaceutical development studies ANDA applicants may use as they implement QbD in their development process and to promote discussion on how OGD would use this information in review.

(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf).

Schematic: MR Drug Product



Chemical stability in solid state (crystalline & amorphous) and in solution

Table 10. Stability of drug substance Z under stress conditions

Stress Conditions	Assay (% w/w)	Impurities (% w/w)	Solid State Form
Untreated	99.6	ND	Crystalline
In Solution			
1% solution (Purified Water, RT, 14 days)	99.3	ND	N/A
Acid (0.1% solution, 1.0 N HCl, RT, 14 days)	99.5	ND	N/A
Base (0.1% solution, 1.0 N NaOH, RT, 14 days)	99.2	ND	N/A
Peroxide (0.1% solution, 3% H_2O_2, RT, 7 days)	99.1	ND	N/A
Crystalline Material			
Humidity and heat (open container, 90% RH, 40 °C, 7 days)	99.6	ND	Crystalline
Dry heat (105 °C, 96 hrs)	99.5	ND	Crystalline
Photostability according to ICH Q1B Option 1	99.6	ND	Crystalline
Amorphous Material			
Humidity and heat (open container, 90% RH, 25 °C, 7 days)	99.5	ND	Amorphous
Humidity and heat (open container, 90% RH, 40 °C, 7 days)	99.5	ND	Crystallization observed
Humidity and heat (open container, 90% RH, 60 °C, 7 days)	99.3	ND	Crystallization observed
Photostability according to ICH Q1B Option 1	99.6	ND	Amorphous
Dry heat (105 °C, 96 hrs)	99.4	ND	Amorphous

Active ingredient (solid-state crystalline/amorphous forms) are chemically stable

↓

<u>Low Risk</u>: Potential for Drug Product Chemical Degradation on Stability Therefore No Need to Optimize Formulation Mitigate Potential Degradation

Table 22. Initial risk assessment of the drug layer formulation variables

Drug-layered beads CQAs	Drug Layer Formulation Variables					
	Bead selection (type/size)	DS particle size	Binder type/grade	Binder lot-to-lot variability	DS/Binder ratio	Viscosity of drug layering solution
Assay	Low	Low	High	Medium	High	Medium
Drug Release	Medium	Low	Medium	Low	High	Low

DS/Binder ratio	Assay	The drug substance to binder ratio will impact the adhesion of the drug substance to the beads. The risk of the ratio to impact drug-layered bead assay is high.
	Drug Release	The ratio of drug substance to binder may impact the physical stability of the amorphous form in the drug-layered beads and excessive binder may retard the release of drug substance from the drug layer. The risk of impact on drug release from the layered beads is high.

Solid-State Form of Active Ingredient in MCC Beads Needs to Be Investigated: Potential Impact on Physical Stability and Consequently Drug Release on Stability

<u>Hi Risk</u>: Formulation Needs to be Optimized to Mitigate this Potential Risk Failure Mode

Binder Optimization and Drug Substance Solid-State Stabilization To Mitigate Physical Transformation Failure Mode on Product Stability

Table 24. Drug substance to binder ratio optimization studies for drug layering

Experiment	DS:Binder Ratio	Release in 15 min	HPLC Assay	LOD	Amount of crystalline DS*
		(%)	(% w/w)	(%)	(%)
No binder	100:0	89	99.9	0.1	80
With PVP K30	95:5	89	99.8	0.2	20
With PVP K30	90:10	96	99.7	0.2	ND
With PVP K30	85:15	97	99.6	0.3	ND
With PVP K30	80:20	92	99.4	0.2	ND
With PVP K30	75:25	85	99.5	0.2	ND

*Amorphous-crystalline ratio as determined by XRPD after 6 months storage at 40 °C/75% RH.

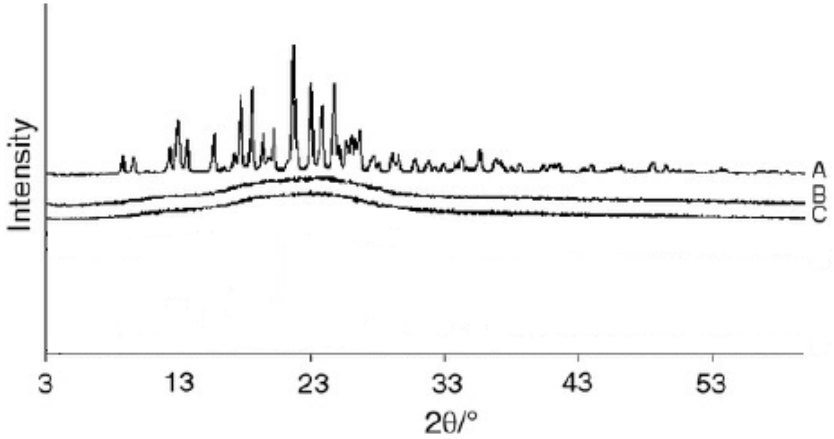


Figure 20. XRPD Analysis: (A) Drug substance crystals; (B) Binder; and (C) Amorphous drug substance with an 85:15 DS:Binder ratio

Formulation (Stability)

Past Paradigm

Stable by Testing
(25 C/60% RH for 24 months)

↓

Limited Testing Sufficient to Ensure Stability on Future Production Batches???

Recall on Stability NDA/ANDAs

QbD Paradigm

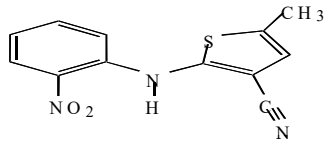
Has the Applicant Optimized the Formulation "Stability by Design"

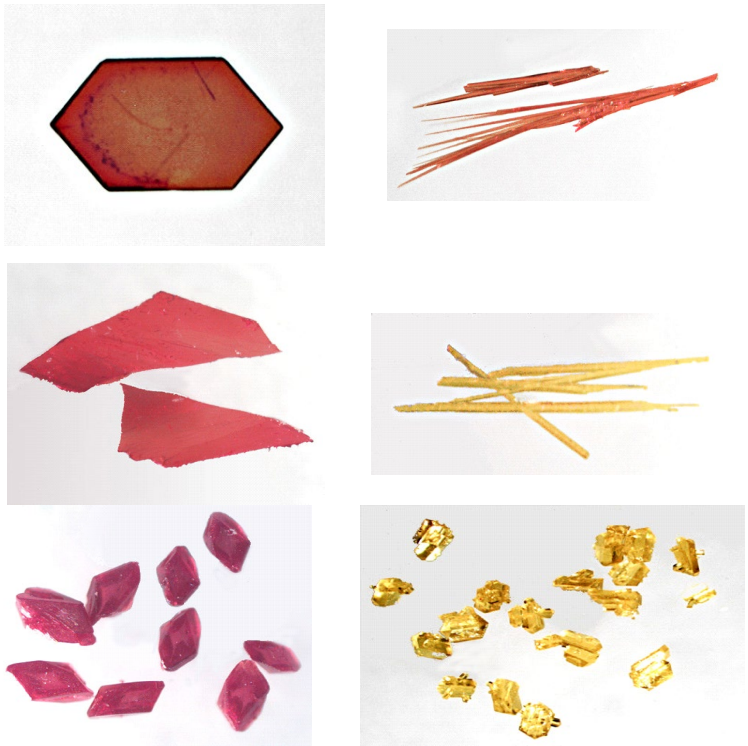
API Chemical Reactivity/ Excipient Compatability?

Amorphous Dispersion (API/Binder) on MCC Core Physically Stable?

Plasticizer Optimal to Minimize Curing

Regulatory Considerations:
Can One Consider Polymorphs to be the Same Active?

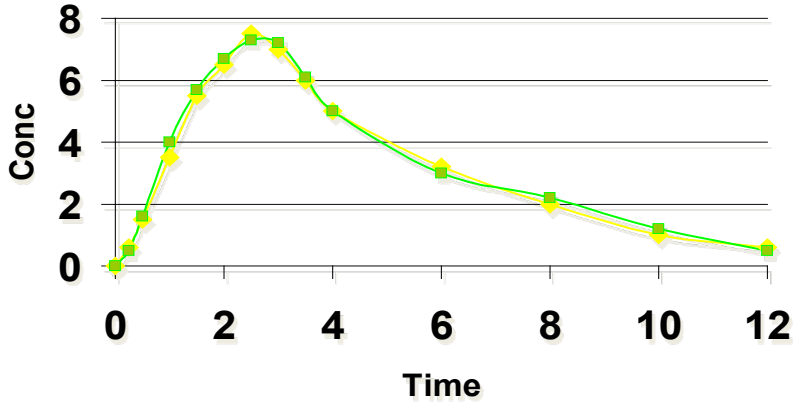




Materials Science

J. Am. Chem. Soc. 122 (2000) 585-591

Form I Form II



Drug Product Safety/Effectiveness

Fundamental Premise for ANDAs for Generic Drug Products

Pharmaceutical Equivalence

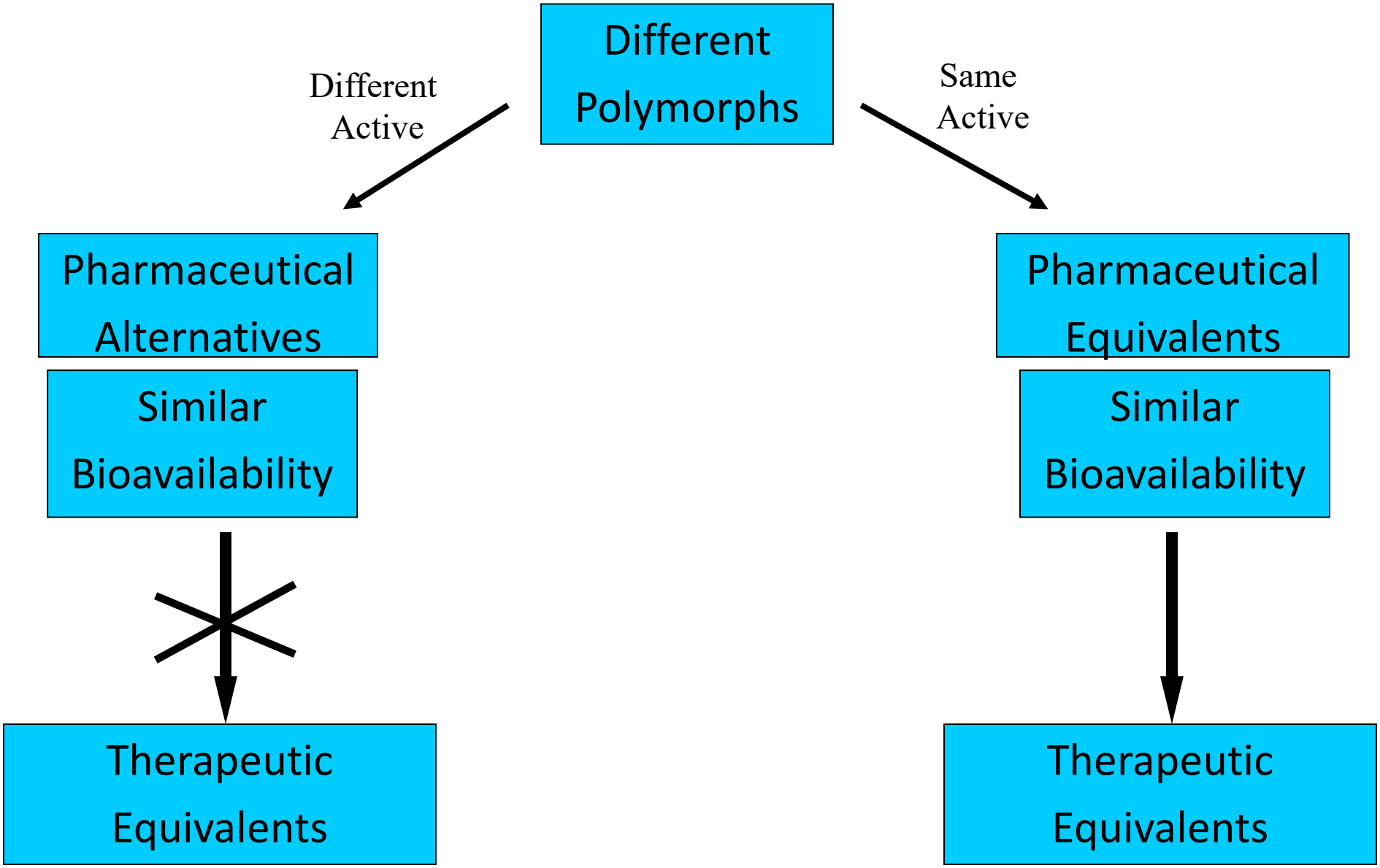
"**Same**" Active Ingredient(s) as RLD (brand product)

Identical in Strength, Dosage Form, Route of Administration. Meet compendial or other applicable standards of Strength, Quality, Purity, and Identity

Bioequivalence

Absence of a statistically significant difference in the rate and extent to which the active ingredient in **pharmaceutically equivalent** products becomes available at the site of action, when administered to subjects at the same molar dose under similar conditions

Therapeutic Equivalence


Different Polymorphs
Different Active
Same Active
Pharmaceutical Alternatives
Similar Bioavailability
Pharmaceutical Equivalents
Similar Bioavailability
Therapeutic Equivalents
Therapeutic Equivalents

Regulation: Solid State Forms

Abbreviated New Drug Application (ANDA) for a Generic Product Must Contain the "Same" Active Ingredient as the Reference Listed Drug (RLD)

⇩

ANDAs May Use Different Polymorphic Forms To Design a Drug Product with Equivalent Performance Characteristics to the RLD

⇩

Preamble 1992 Final Rule: FDA specifically rejected requirement that API in the Generic and RLD product *"exhibit the same physical characteristics … and…solid state forms of the drug have not been altered."*

⇩

Regulatory Scheme for ANDAs: Polymorphic Forms of API are the "Same"

Guidance for Industry

ANDAs: Pharmaceutical Solid Polymorphism

Chemistry, Manufacturing, and Controls Information

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2007
OGD

Part IB
Regulatory Scheme on Salts

Salts

Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound.

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Salts

May or May Not Enhance Performance Characteristics

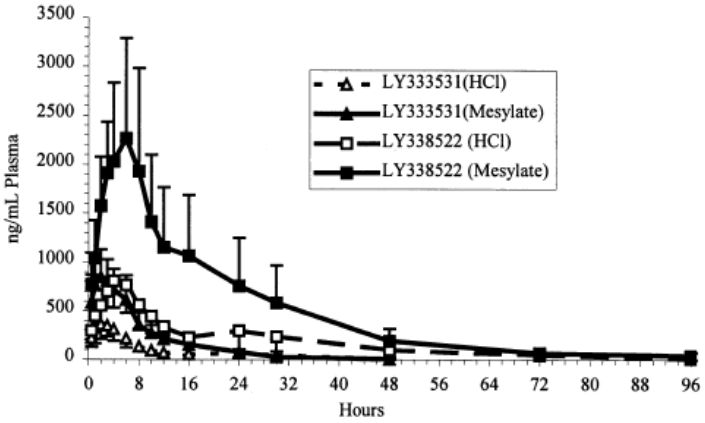


Fig. 7. Mean plasma concentrations of LY333531 and LY338522 in male beagle dogs orally administered LY333531 HCl LY333531 mesylate (20 mg LY333531/kg).

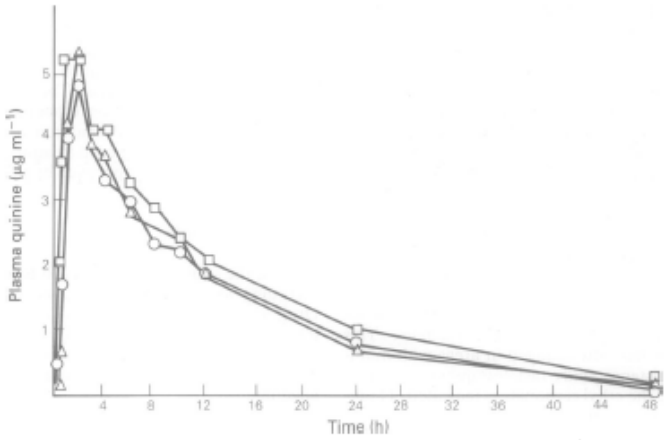


Figure 1 Average plasma concentrations of quinine after oral administration of single doses of three salt forms (600 mg base equivalent) to healthy adult males (○ quinine ethyl carbonate, □ quinine hydrochloride and △ quinine sulphate).

Differing Bioavailabilities for LY333531 Salts (Mesylate/Chloride)

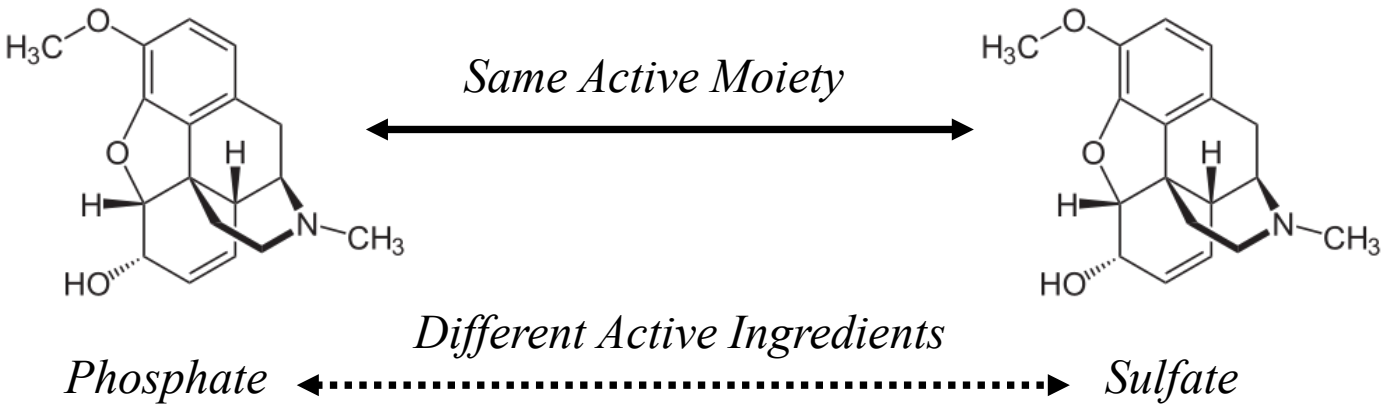
G. Engel, Int. J Pharmaceutics 198 (2000) p. 239-247

Similar Bioavailabilities for Quinine Salts (Ethyl Carbonate/Chloride/Sulfate)

A. Jamaludin, Br J. Clin. Pharmac 25 (1988) p. 261-263

FDA Regulatory Scheme

21 CFR 320.1(c), Food and Drugs, Definitions: *Pharmaceutical equivalent means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety…; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency.*



FDA Regulatory Scheme: Pharmaceutical Alternatives
No Possibility for Therapeutic Equivalence for Different Salts

EMEA Regulatory Scheme

- Article 10.2.b of Directive 2001/83/EC: The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

  In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant

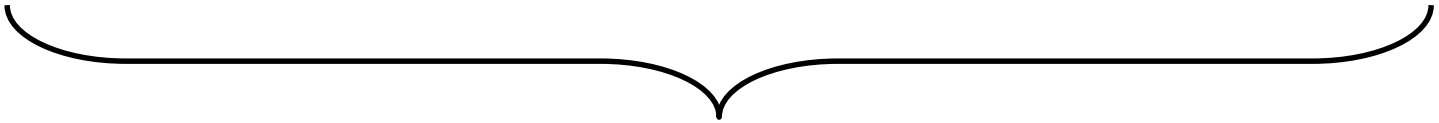
EMEA Regulatory Scheme: More Flexible and Possible Therapeutic Equivalence for Different Salts with Supporting Data

Part II
Regulatory Scheme on Co-Crystals???

What are Co-Crystals

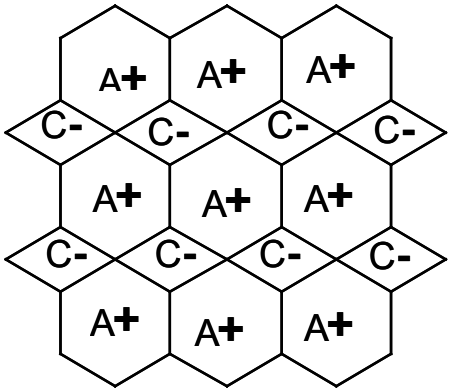
"Multiple Component Crystal in Which All Components are Solid Under Ambient Conditions" (M.J. Zawarotki)

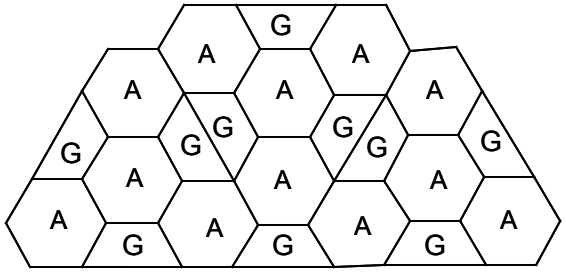
"A Molecular Complex that Contains Two or More Different Molecules in the Same Crystal Lattice" (G.P. Stahly)

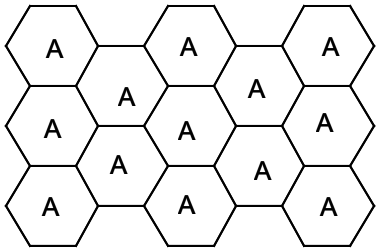


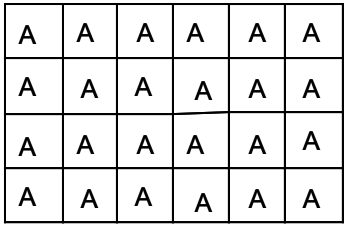
Definitions Generally Distinguish Co-crystals From Salts

Co-Crystals







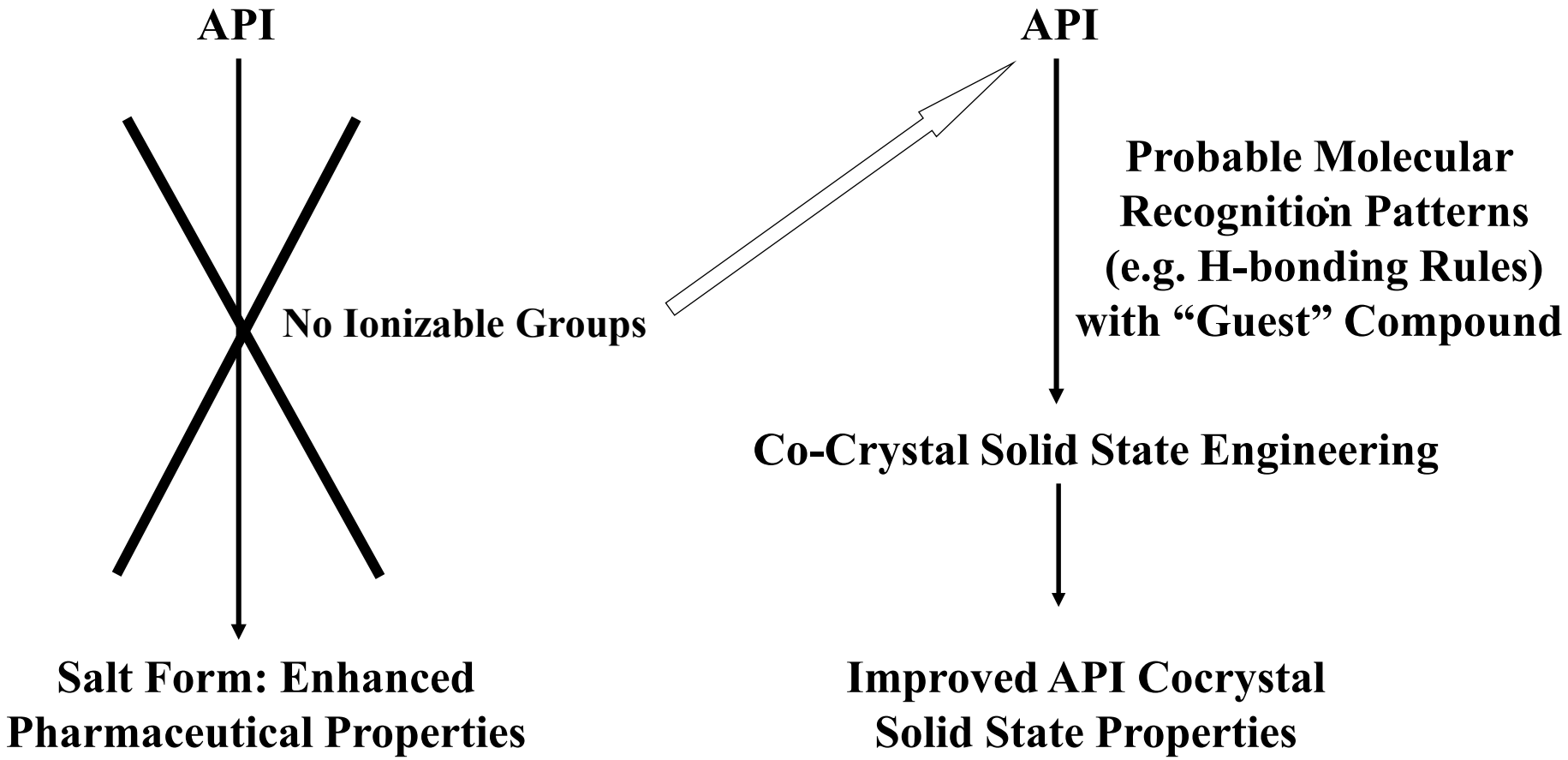


Salts — **Co-crystals** — **Polymorphs**

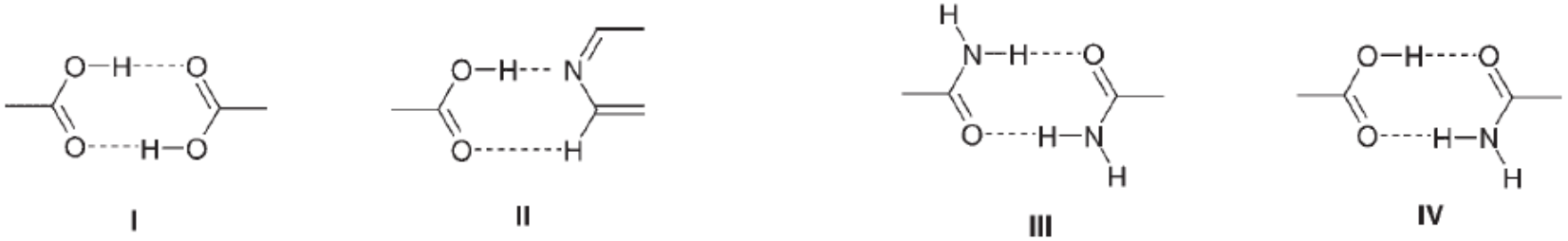
Crystalline Molecular Complexes: Co- Crystal / Salt Continuum

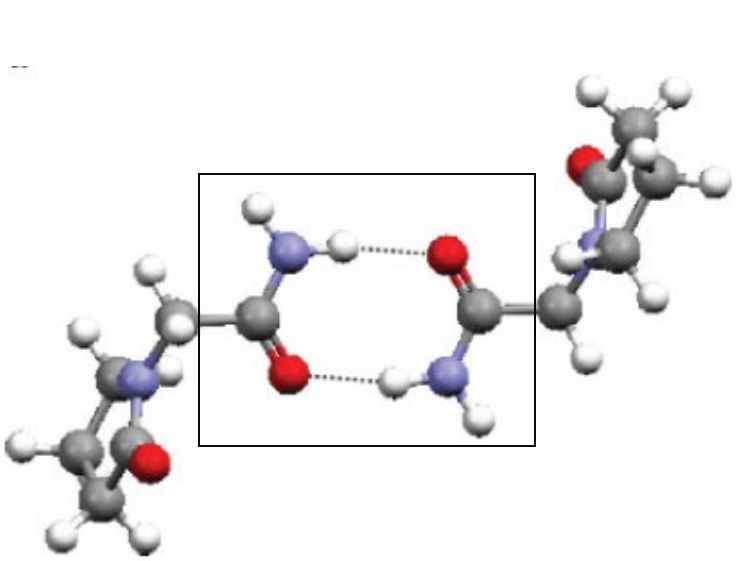
Crystalline Molecular Complexes: Analogous to Polymorph Solvate (Except other Component in Crystal Lattice is a Solid (not Liquid))

Potential Utility of Co-Crystals

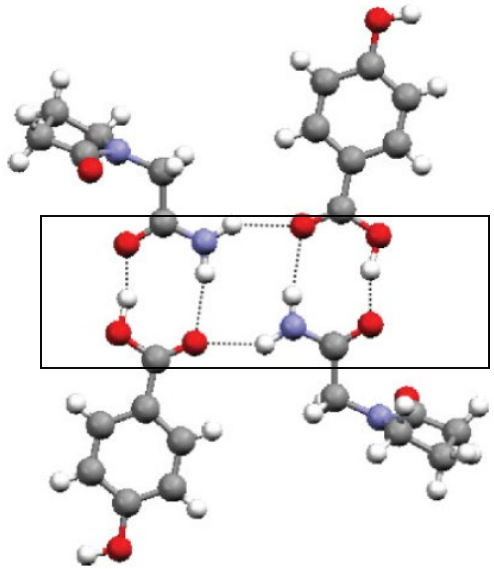


Crystal Solid State Engineering Based Upon H-Bonding Motifs





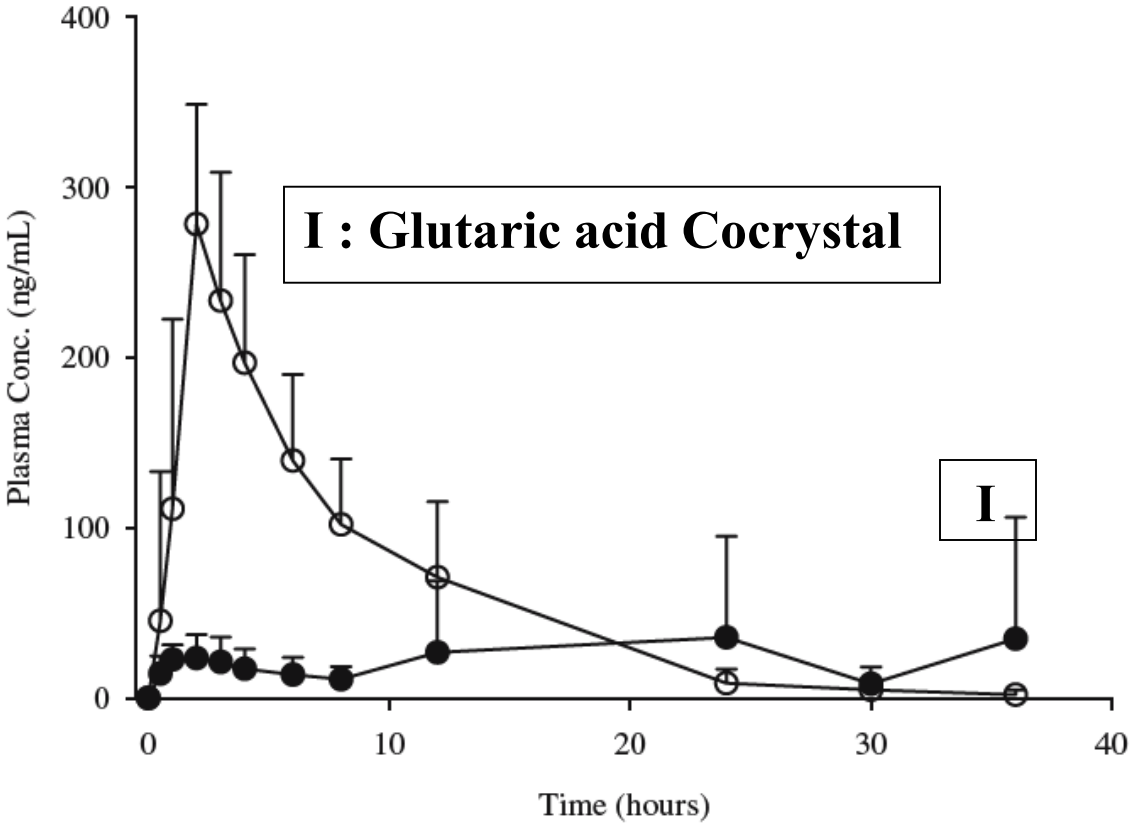
Piroxicam
Amide H-Bonding Network (III)

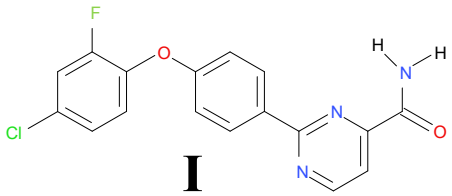


Piroxicam-Hydroxybenzoic Acid Co-Crystal
Carboxylic Acid-Amide H-Bonding (IV)

P. Vishweshwar, J. Pharmaceutical Science, 95(3) 2006, p.499-516

Co-Crystals May Enhance Drug Product Properties: Bioavailability





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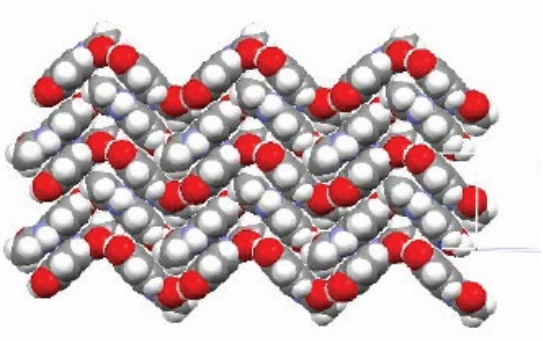
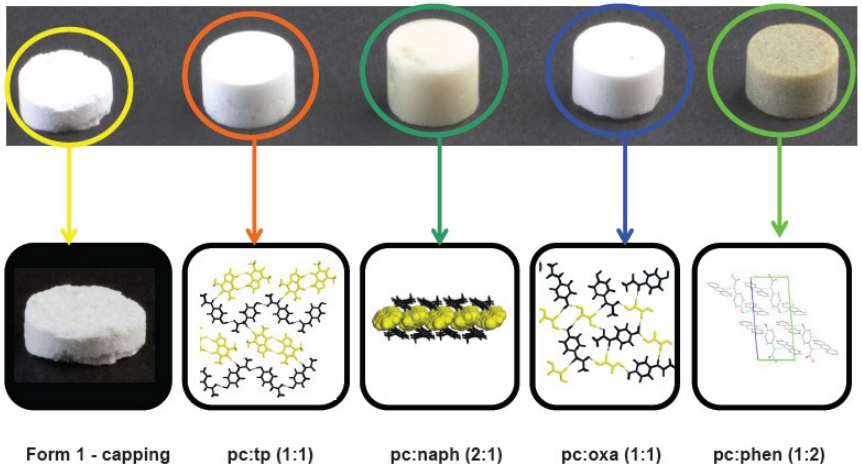
Candidate Drug I (Low Solubility– 0.1 µg/mL – pKa of conjugate acid (-0.5))

D. McNamara, Pharmaceutical Research 23 (2006) p. 1888-1897.

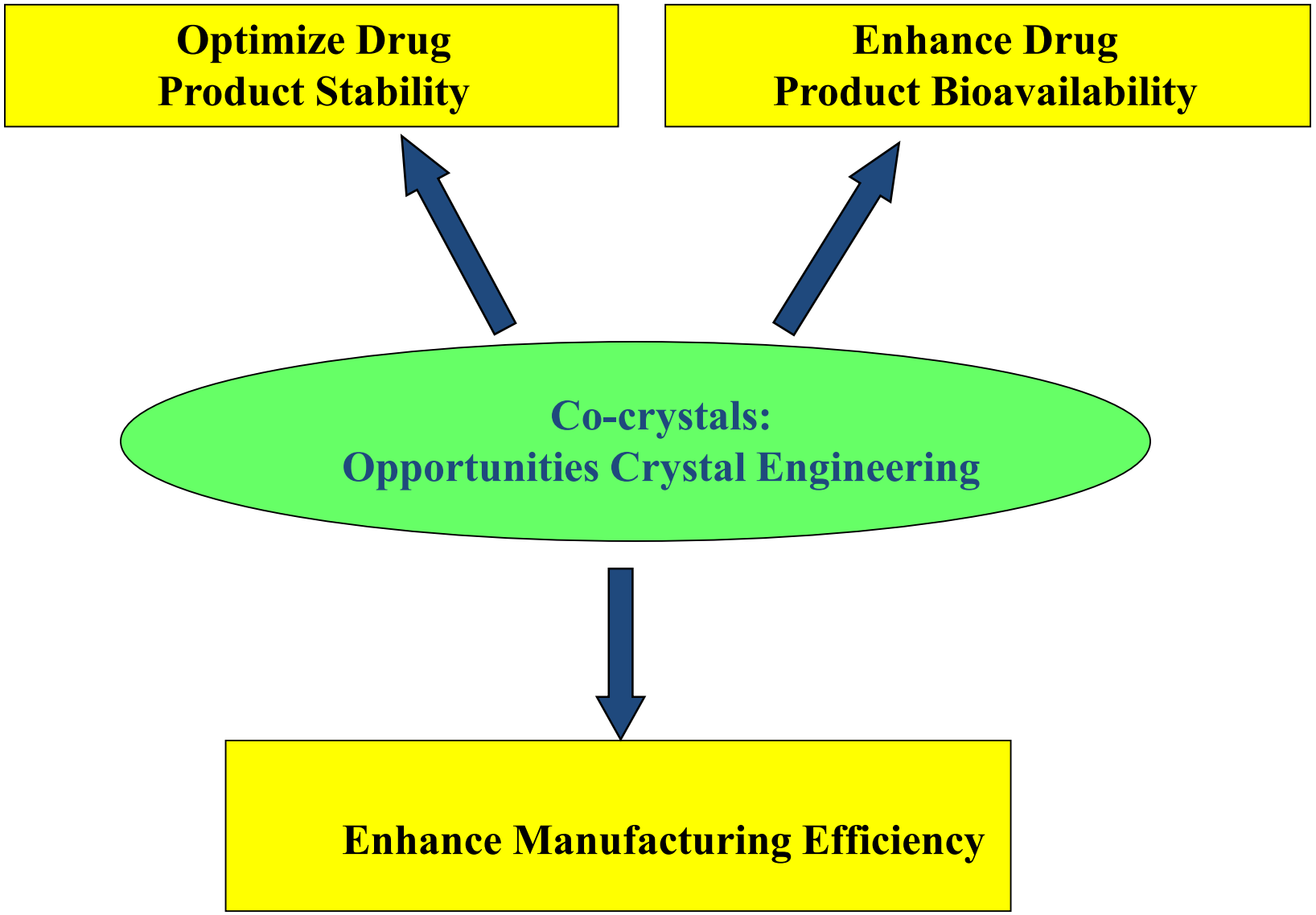
Co-Crystals May Enhance Drug Product Properties: Processability



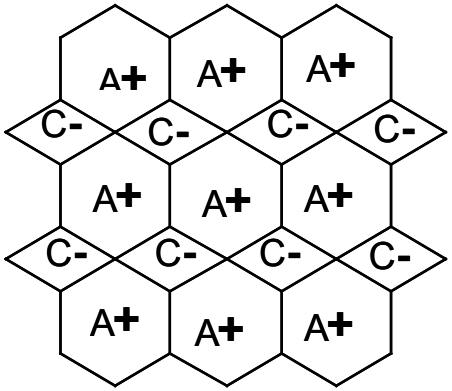
Paracetamol Form I (Stable Form)
Crystal Lattice Compact
Currugated Layers
Difficult to Compress



S. Karki, Advanced Materials, 21 (2000) p. 3905-3909.

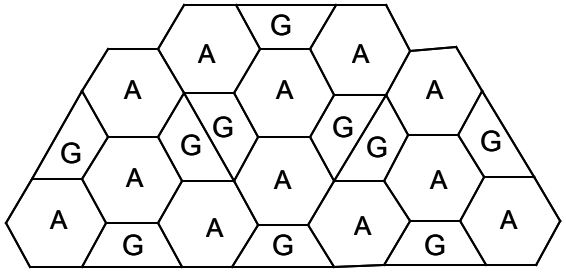

Optimize Drug Product Stability
Enhance Drug Product Bioavailability
Co-crystals: Opportunities Crystal Engineering
Enhance Manufacturing Efficiency

Where Do Co-Crystals Fit in Our Regulatory Scheme?



Salts

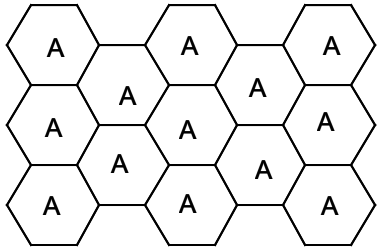
Same Active Moiety
Different API

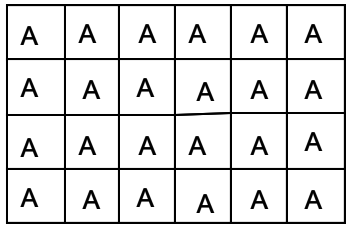


Co-crystals??

Where Do Co-Crystals Fit?

Is a New Regulatory Class of Solids Needed?





Polymorphs

Same API

Analysis: Formulating Regulatory Policy

21 CFR 210.3(b)(4): A drug product is a finished dosage form (e.g., tablet; capsule; or solution that contains an active pharmaceutical ingredient generally, but not necessarily, in association with inactive ingredients (excipients)).

Association of Active Ingredient with Excipients in Drug Product

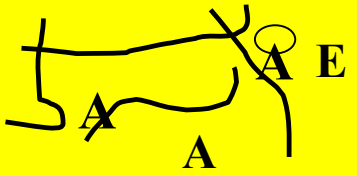
Physical Association (API – Excipient)

API with Lactose Dry Blend

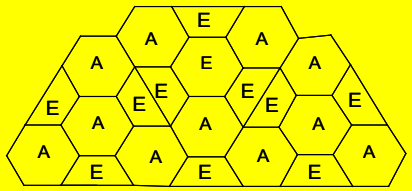
Molecular Association (API – Excipient)

API Inclusion Complexes (e.g. Cyclodextrin)

API – Molecular Dispersions

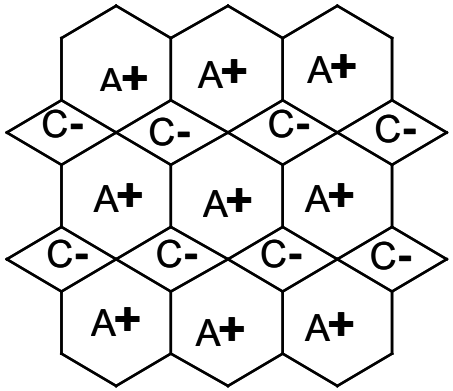


API-Co-Crystals

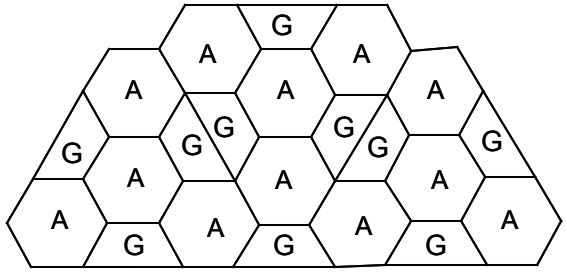


Distinguishable by Having a Crystal Lattice

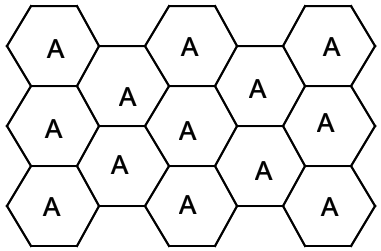
Co-Crystal Regulatory Scheme

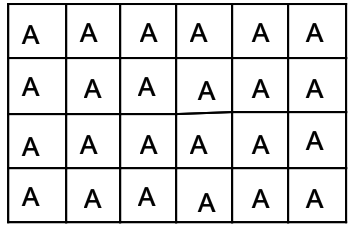


Salts



Co-crystals





Polymorphs

No Need to Create New Category Of Solid-State Form

Fits Nicely Within Our Framework As an Active Ingredient Drug Product Intermediate

Considerations in Review of CoCrystals

1. **Determine whether, in the crystalline solid, the component API with the excipient compounds in the co-crystal exist in their neutral states and interact via nonionic interactions, as opposed to an ionic interaction, which would classify this crystalline solid as a salt form.**

   a. **Generally speaking, if API and its excipient(s) have a ΔpKa (pKa (base) - pKa (acid)) < 0, there will be negligible proton transfer and the molecular complex will be a co-crystal.**

   b. **If the ΔpKa > 3, there will be complete proton transfer resulting in complete ionization and formation of a salt as opposed to a co-crystal.**

   c. **In instances where the ΔpKa > 0 and ΔpKa < 3, the extent of proton transfer and ionization is generally not predictable. Rely on Spectroscopic tools to resolve this.**

2. **For pharmacological activity, ensure that the API dissociates from its excipient prior to reaching the site of action.**

Guidance for Industry

Regulatory Classification of Pharmaceutical Co-Crystals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER/OGD) Andre Raw at 240-276-8500, or (CDER/ONDQA) Richard Lostritto at 301-796-1900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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CMC

Common Themes from Docket (Not Comprehensive List)

1. Co-crystals be new alternative APIs: Some reasons cited

- **Fixed phases of defined stoichiometry**
- **Co-crystals have different properties from the API.**
- **API co-crystal is typically fully characterized for solid-state properties, not API.**
- **Drug substance release and stability testing is performed on the co-crystal, not API**

- **Co-crystals are manufactured at API facilities (not drug product facilities).**
- **API is typically not isolated during synthesis but rather isolated as a co-crystal.**
- **Drug product manufacturing facilities do not typically generate co-crystals intermediates**

Common Themes from Docket

2. Classify co-crystals as salts: Conceptually no different than salts.

a. The approach to distinguishing co-crystals from salts is flawed

- **pkas are from the solution state and not representative of "true" pka in a co-crystal lattice.**
- **Determining the location of the proton by spectroscopic tools is difficult if not impossible.**
- **Distinguishing between a salt and co-crystal would place undue burden to the industry.**
- **This would also result in endless debate among industry/reviewers on classification**

b. This would cause confusion. Many putative approved "salts" are actually co-crystals.

c. Classify the co-crystals as salts but take the broader approach of changing the FDA regulations in relation to salts to be similar to the EMEA approach

3. For pharmacological activity of co-crystals, what are the data requirement expectations to ensure the API dissociates from its excipient prior to reaching the site of action?

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Co-Crystals

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