Co-Processed API

Scientific and Regulatory Considerations

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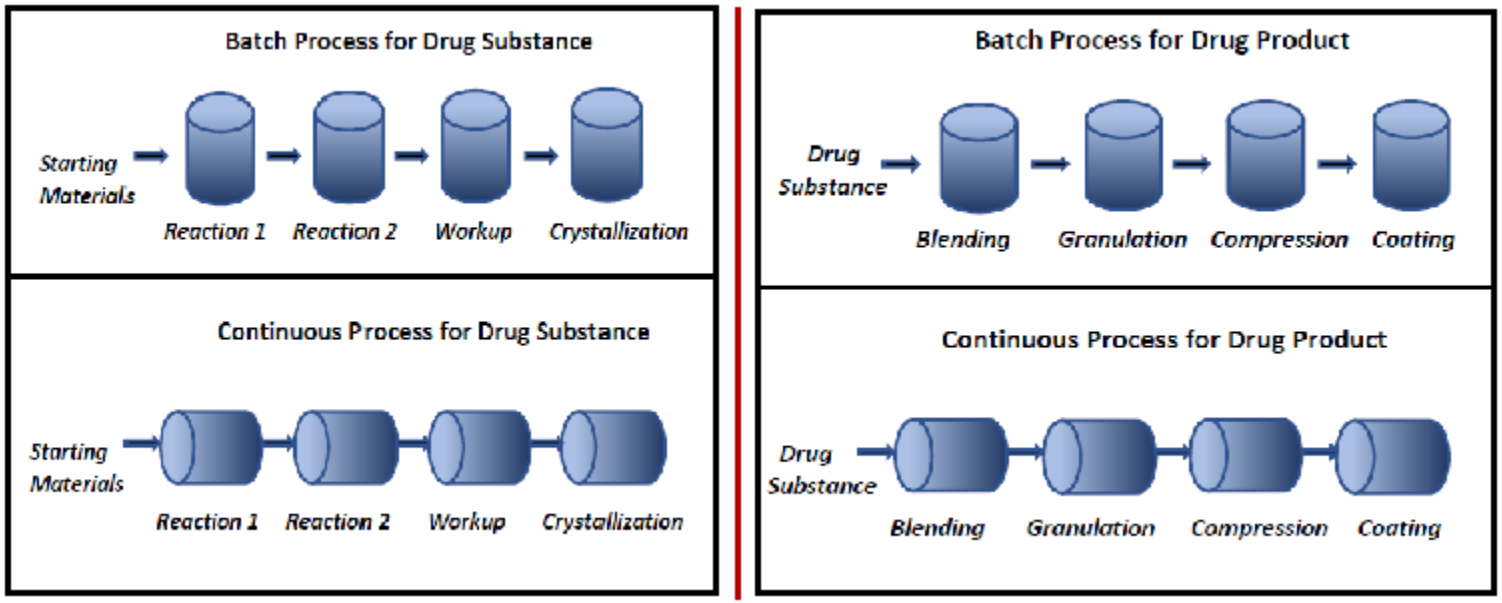
Innovation and the Pharmaceutical Industry

Opportunity: Major advances in science and technology, digital revolution
Customer: New therapies, respond to emergencies, lower cost drug
Globalization: Respond to changing business and political environments
Competition: Develop new products faster
Maintain supply: Drug shortages, product defects and recalls

"The world is changing very fast. Big will not beat small anymore. It will be the fast beating the slow" (Rupert Murdoch).

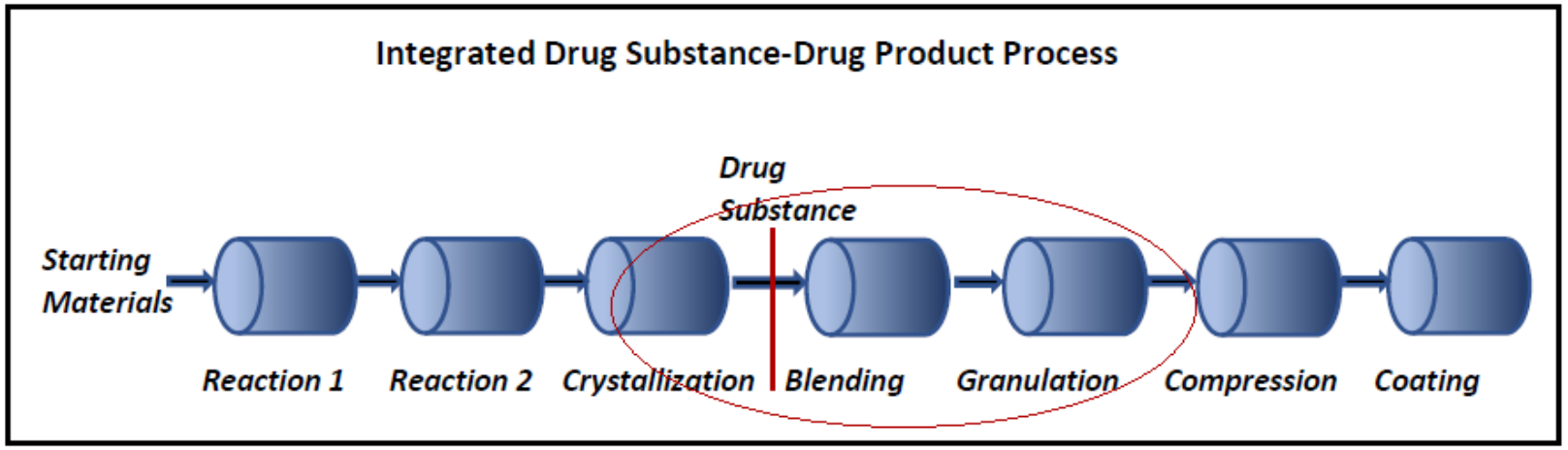
Small Molecules Processes



Both batch and CM processes

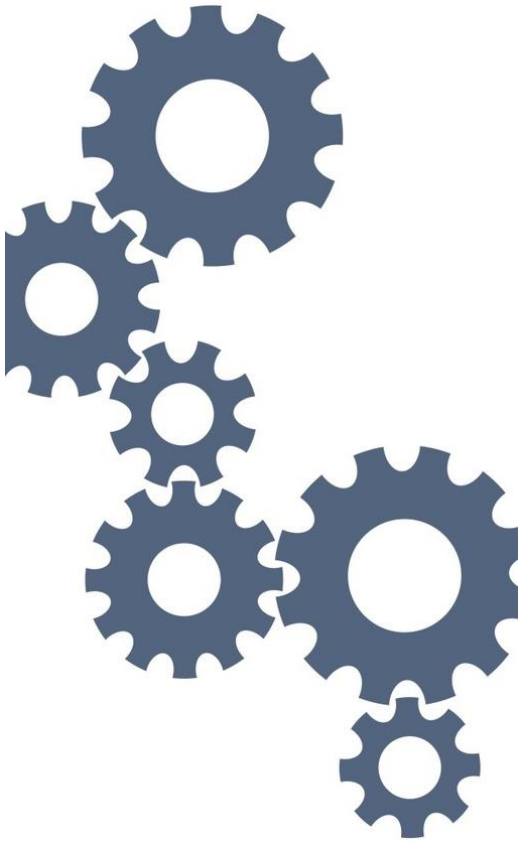
- Use a similar sequence of unit operations.
- Interface between drug product and drug substance.
- Similar challenges in drug product manufacture.
  - *Powder feeding/handling*
  - *Solubility*
  - *Low drug load*
  - *API material properties*
  - *Excipient material properties*
  - *Processability*

Advancing Innovation – DS/DP Interface



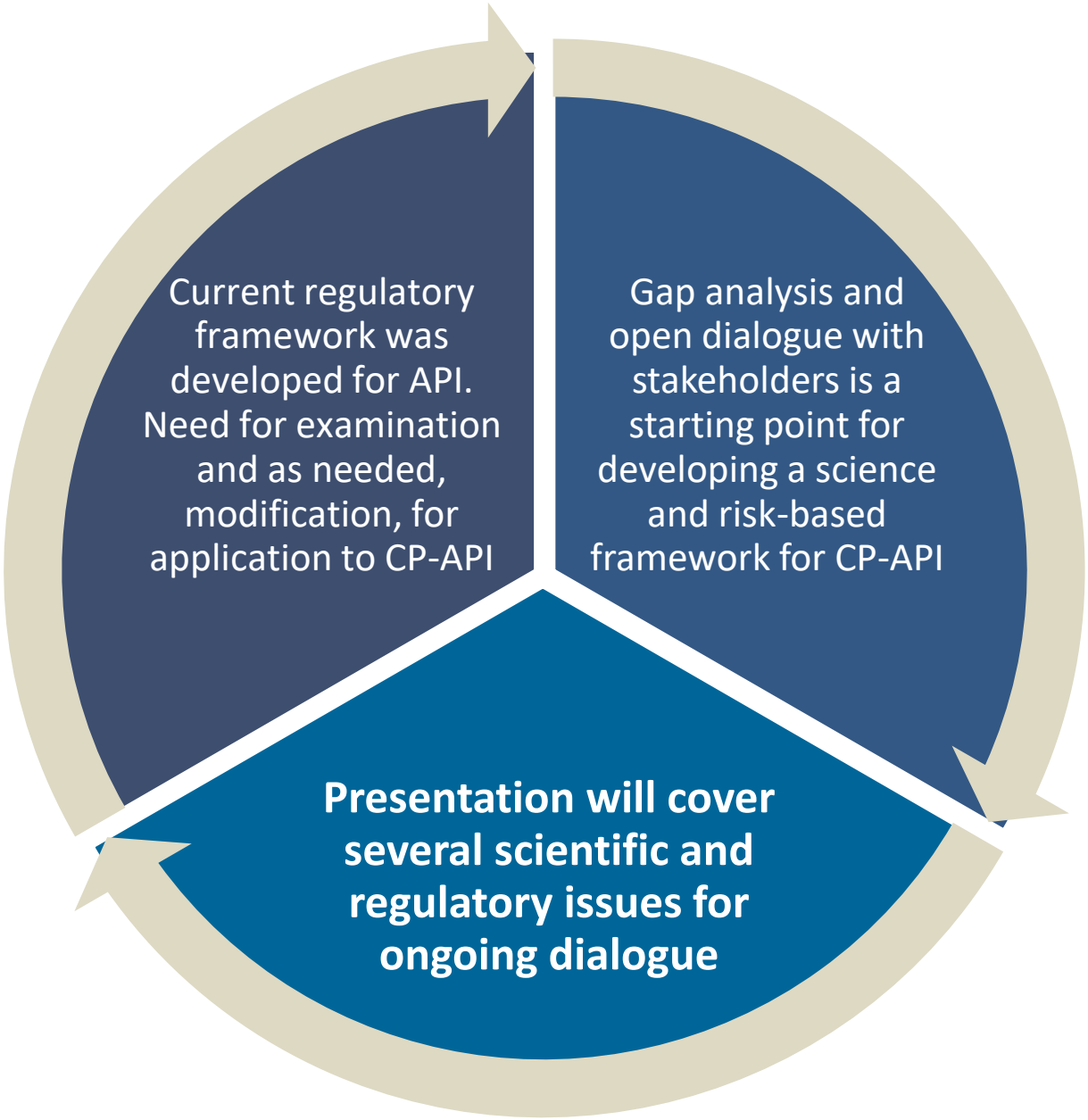
- We haven't yet realized the full potential of process simplification offered by CM.
- Integrated DS/DP or End-to-End (E2E) manufacture has the potential to "rethink" the current approach to drug manufacture and drug delivery.
- Innovations at the DS/DP interface
  - Cocrystals, multicomponent systems, co-processed API (CP-API).

Potential Drivers for CP-API



- Overcome powder flow constraints
- Improve environmental/employee safety
- Modify API or DP characteristics
  - E.g., Improve solubility, stability
- Facilitate novel drug delivery approaches
- Simplify conventional DP unit operations
- Improve DP manufacturability (e.g., BU)
- Reduce manufacturing time
- Facilitate advanced manufacturing
  - E.g., E2E CM, distributed manufacturing

Enabling CP-API



CP-API

A Drug Substance or Drug Product Intermediate?

Drug Substance (21 CFR 314.3)	• **Drug substance** is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient.
Active Ingredient (21 CFR 210.3)	• **Active ingredient** means any component that is intended to furnish pharmacological activity …….. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
In-process Material [DP] (21 CFR 210.3)	• **In-process material** means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

CP-API Definition

- No regulatory definition of CP-API currently.
  - One proposal (Schenck et al., Mol. Pharmaceutics 2020, 17, 2232−2244).
    - *A drug substance, manufactured in a drug substance facility, that contains the API in addition to one or more non-covalently bonded, nonactive component(s), and differs from salts, solvates and/or cocrystals.*

Regulatory Classification of Pharmaceutical Co-Crystals, Guidance for Industry, 2018, Rev1.

- ***Co-crystals:*** *Crystalline materials composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds.*
- ***Coformer:*** *A component that interacts nonionically with the API in the crystal lattice, that is not a solvent (including water), and is typically nonvolatile.*
- ***Polymorphs:*** *Different crystalline forms of the same API. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same APIs.*
- ***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. Per the current regulatory scheme, different salt forms of the same active moiety are considered different APIs. (See 21 CFR 314.108 and 21 CFR).*

CP-API Definition (contd.)

Need for consensus. Ideally, CP-API definition should,

- Not conflict or overlap with other definitions. Clearly distinguish CP-API from drug product intermediates and API.
- Not be overly broad leading to ambiguity and case-by-case interpretation.
- Long lasting. Not be impacted by change or innovation
- Stand-alone definition not linked to the type of facility used (e.g., multi-purpose modular pods, point of care manufacture, E2E)

Clarity on the following to help align on a definition

- What distinguishes cocrystals, solvates and salts from a CP-API?
  - *Are lack of defined stoichiometry and non-active within crystal lattice the only distinctions?*
- What distinguishes CP-API from drug product intermediate?
  - *Will DP intermediates (e.g., drug coated excipients, API-excipient blend) be re-defined as CP-API?*
- What is the commonality of all CP-API?
  - *API is not isolated separately? No covalent bonds between API and nonactive? Etc.*

CP-API Characterization

- An API is currently characterized through a standard battery of physicochemical characterization tests.
  - NMR, IR, PXRD, TGA, DSC, Solubility, pKa, etc.
- In general, “well-characterized API” knowledge informs the approach to specification, stability, re-test, re-work, reprocess, etc.
  - Commensurate with knowledge.

- What should be the extent of characterization of CP-API?
  - What should be the depth of chemical characterization for CP-API?
  - Should CP-API undergo only physical characterization?
    - *E.g., Surface properties, crystal form homogeneity.*
  - Are specific characterization tests required?
    - *E.g., Transmission electron microscopy for surface properties.*

DS Expiry vs. Retest Date

- Current regulatory framework –
  - Retest date for well-characterized DS (E.g., Small molecule DS).
  - Expiry date for more complex DS (E.g., Biologics).
  - DP intermediates are issued a “hold-time.”

- Knowledge through in-depth characterization informs decisions on retest vs expiry date assignation.
  - What level of characterization is needed to support ‘retest’?

- Is CP-API well-characterized? Or is characterization limited?
  - Lower risk in assigning an expiry date based on CP-API stability data.
  - Higher risk perceived with a retest date approach.
  - Is retest associated with re-process? What would re-process entail?

DP Date of Manufacture and Stability

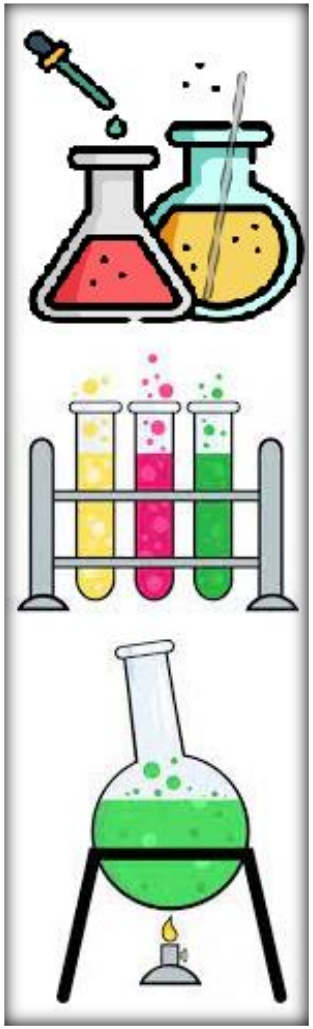
- Current regulatory framework –
  - Expiry/shelf-life for DP. Hold time for DP intermediates.
  - DP date of manufacture (DOM) typically starts when DS is first introduced into the DP manufacturing process.
    - *Rare exceptions: For a few highly stable amorphous solid dispersions, DP DOM may be based on use of intermediate in the manufacturing process.*
      - Intermediate is issued a hold time.
      - Stability data for intermediate, and stability data for DP made with maximum-aged intermediate.

- For DP made with CP-API,
  - Could the same approach be used for CP-API?
  - Potential challenges with implementing a retest date?

CP-API Consistency/Reproducibility

- How is CP-API lot to lot consistency and within batch consistency ensured?
  - Is reprocessed CP-API the same as the original CP-API?
- What is the rationale for the lack of a defined stoichiometry between API and nonactive components in the CP-API?
- What would be impact of variability on drug product manufacture, stability, and performance?
- Potential impact on,
  - CP-API tests and specification.
  - Sampling (for testing conformance to specification) approach.
  - Appropriateness of retest or reprocessing.

CP-API Manufacture and Controls



- For API, large focus on chemical reactions, impurities and impurity clearance.
- CP-APIs may have increased risk comparative to API.
  - More complex. Closer to the product used by the patient.
- Information need to support intra- and inter-batch consistency of quality attributes and demonstrate the ability to manufacture at commercial scale.
- What should be the level of detail provided on –
  - Process development?
  - In-process tests and controls?
  - Scale-up for commercial manufacture?
  - Should the level of information currently be comparative to the information currently submitted for manufacture and control of DP Intermediate or API?
- Is CP-API made directly from starting materials or is it a separate process with API and excipient as inputs?

Facility and CGMP

- DS and DP are subject to the statutory CGMP requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.
  - DP CGMPs are in 21 CFR Part 210 and Part 211.
  - DS CGMPs are in ICH Q7(R1) Guidance for Industry, September 2016.
    - *> If classified as API: "should be manufactured in accordance to this guidance."*

- CGMP requirements for DS and DP are essentially the same.
  - CP-APIs should also comply with CGMP regardless of where made.
- Facility inspection/regulatory oversight is same for DS and DP.
  - Based on complexity, risk of product, product and process knowledge, submission content, prior experience, CGMP history, etc.

- Facility profile codes.
- Could API and CP-API manufacture be non-contiguous, including use of different facilities?
  - Is the CP-API then a DP intermediate?

CP-API Submissions and Exclusivity

NCE

21 CFR 314.108(a)

- A drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

Issues to address when the API is already approved

- Whether or not CP-API qualifies for NCE status.
  - Patent/exclusivity issues.
  - In most cases, CP-API may not qualify as NCE.
- If performance of CP-API is the same or differs from API?
  - E.g., Bioavailability, safety, efficacy.
- Plans for bridging a change from API to CP-API, including the need or lack thereof, for new clinical, non-clinical or bioequivalence studies.
- If the CP-API is in a new NDA, is the submission a 505(b)(1) or (b)(2)?
  - For generic applications, refer to the Dr. Graham's presentation.
- For an approved API submission, is a change to CP-API a supplement or a new NDA/ANDA?

Established Name & Labeling

21 CFR 201.50 drug labeling requires a statement of identity, strength, etc.,

- Statement of identity is based on the established or compendial name of drug.
- U.S. Adopted Names Council assigns established name (§ 299.4).
- Nomenclature, monograph, etc., have significant impact on generic drugs.

Is the established name of a CP-API the same as that of the API?

Labeling example for a DP with API-inactive (not considered co-processed).

- –Established name is that of API alone.
- –DP strength is in terms of established name.
- –Chemical name, molecular formula, molecular weight and structural formula is for API alone.
- –Description mentions, "X <*API name*> is adsorbed onto Y <*excipient name*>. X on Y is a white to pale yellow solid with a solubility of ……."

CP-API Implementation

Scientific Knowledge Base

Significant knowledge of API manufacture and crystallization. Principles of crystallization, composite manufacture, etc., are well-established.

Scientific knowledge base is applicable for CP-API manufacture.

Complexity

Increased complexity, inexperience with CP-API, and varying skill levels in organizations require staff re-training.

Potential implications for global implementation.

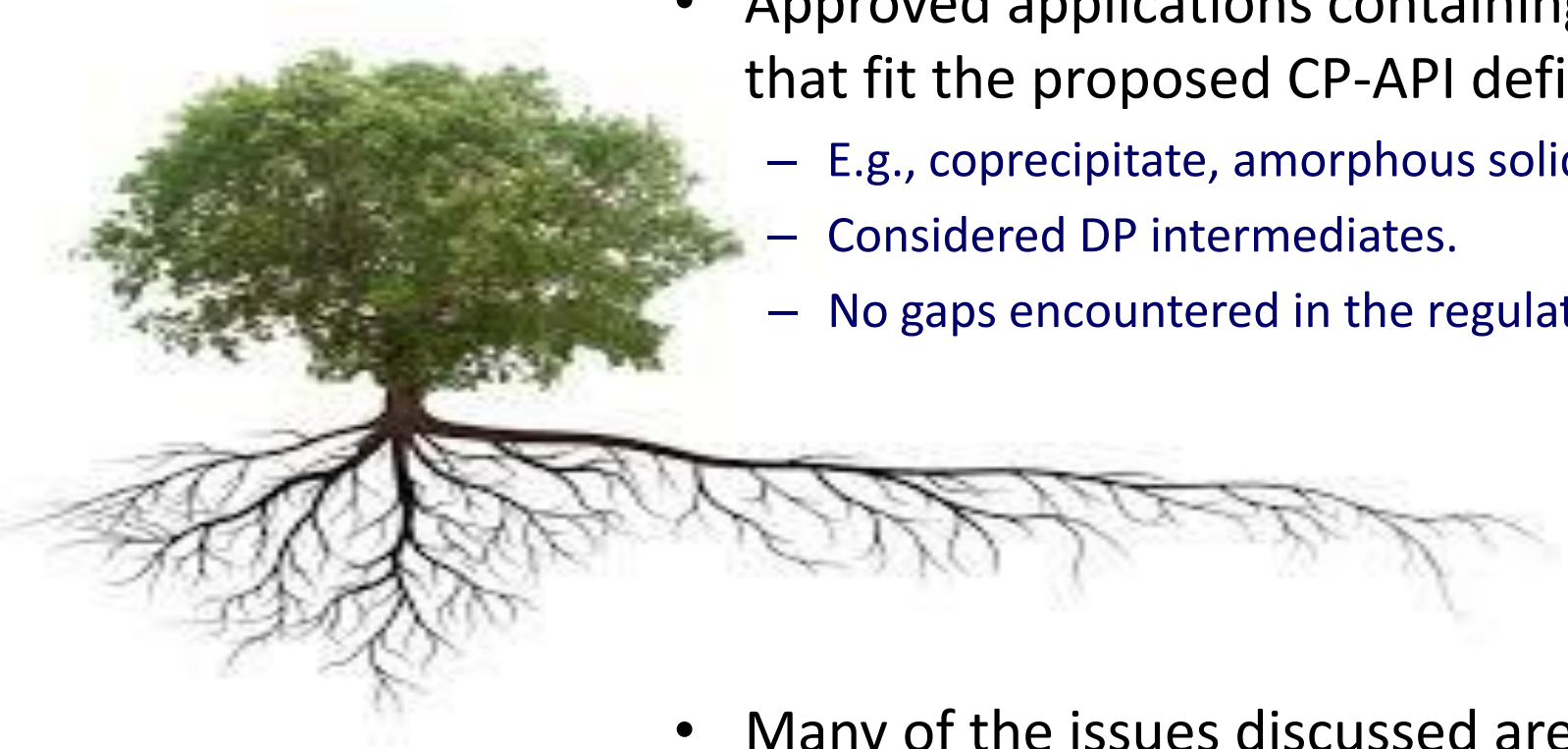
Failure Modes

Incomplete understanding of CP-API failure modes.

E.g., Intramolecular interactions, degradation kinetics, contributors to quality variability, scale up for commercial manufacture.

Need for open dialogue to understand failure modes to enable the development of a robust control strategy and regulatory framework.

Current Regulatory Experience

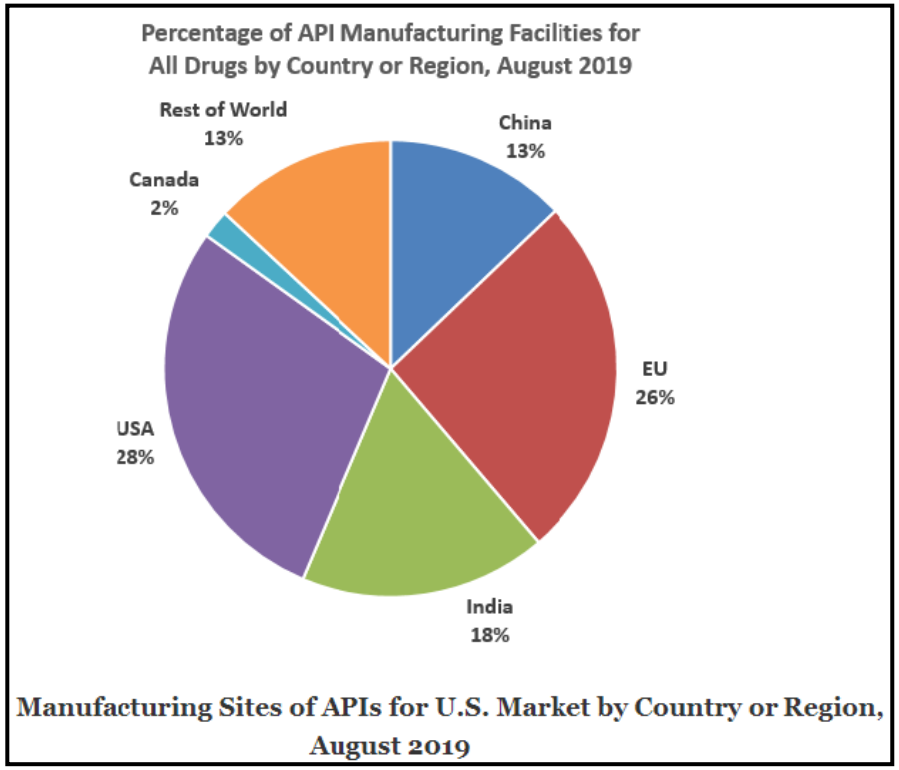


- Approved applications containing entities that fit the proposed CP-API definition.
  - E.g., coprecipitate, amorphous solid dispersions
  - Considered DP intermediates.
  - No gaps encountered in the regulatory pathway.

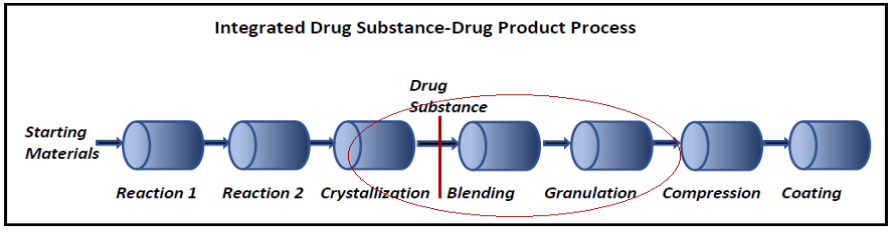
- Many of the issues discussed are associated with the designation of CP-API as a drug substance.

Supply Chain Considerations

- *2019 U.S. Congressional Testimony, Dr. Woodcock:* 72% of APIs in US drugs (and 79% of APIs in US drugs in the WHO 2019 essential medicines list) are manufactured overseas.
- Significant API supply chain interruptions observed recently.
- National interest in shoring up US drug supply.
  - Advanced manufacturing expected to promote domestic manufacture (e.g., Integrated continuous process with CP-API/DP)
  - Will CP-API follow the conventional API approach of overseas manufacture?
  - How will CP-API improve API supply chain and domestic manufacture?



Manufacturing Sites of APIs for U.S. Market by Country or Region, August 2019



Conclusions

Innovations at the DS-DP interface could pave the way for new approaches to drug manufacture and drug delivery. Implementation of DS-DP interface innovations require re-examination of the current regulatory framework and modification, as appropriate.

National interest in ensuring drug supply chain and domestic manufacture. CP-API coupled with other advanced manufacturing technologies seen as one promising option.

CDER Emerging Technology Program is an avenue for obtaining early feedback on new technologies. Early discussions with FDA greatly facilitate the development and first cycle approval of new technologies.

FDA strongly supports the advancement of pharmaceutical manufacturing technologies.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