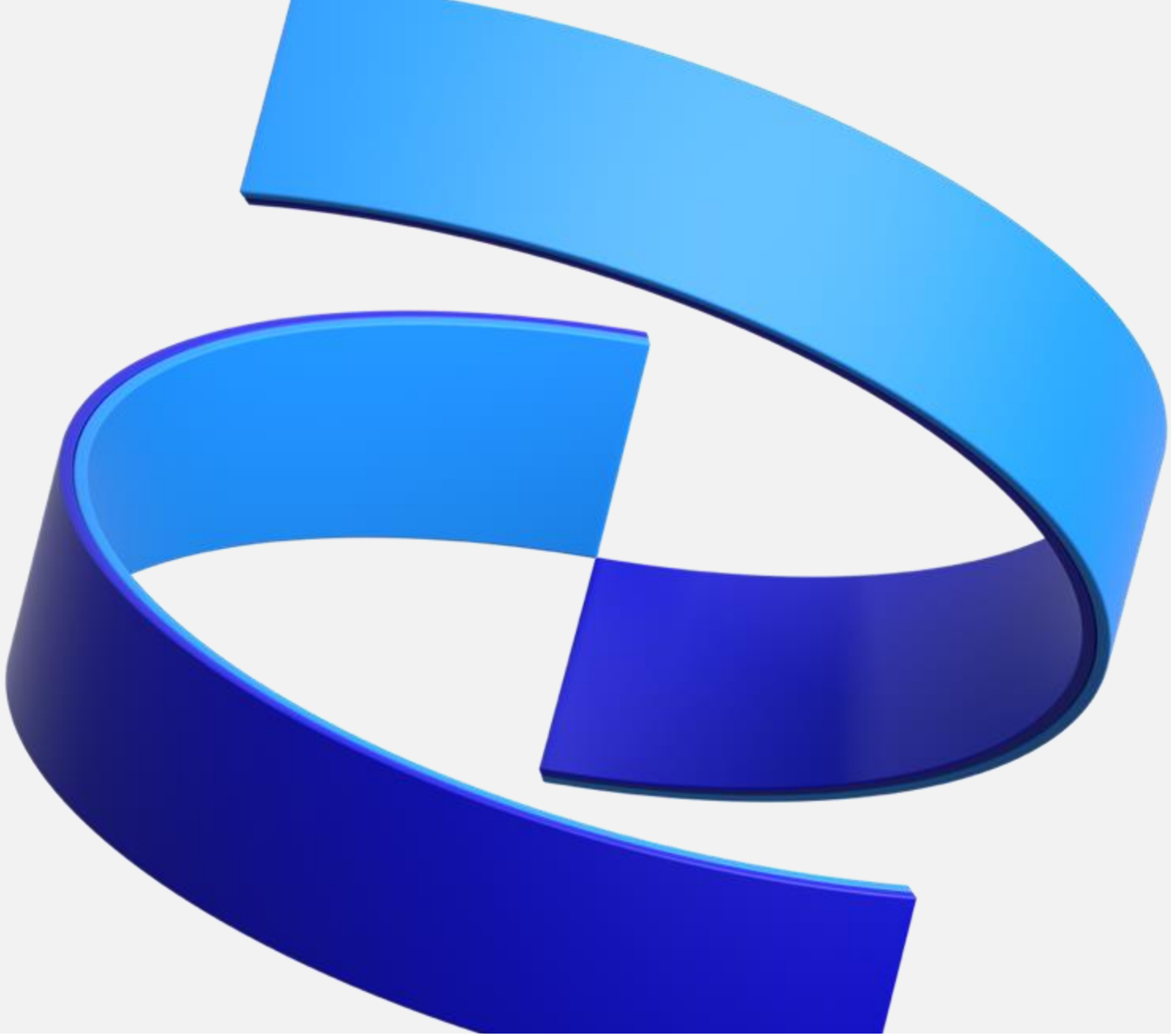
Motivation to define co-processed API as a drug substance and overview of current regulatory landscape



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M-CERSI Co-Processed API Workshop
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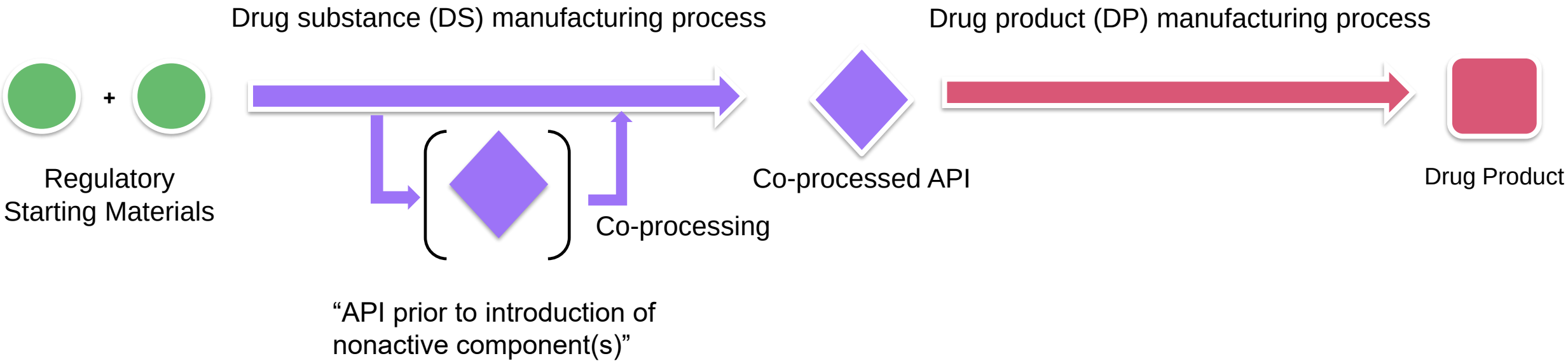
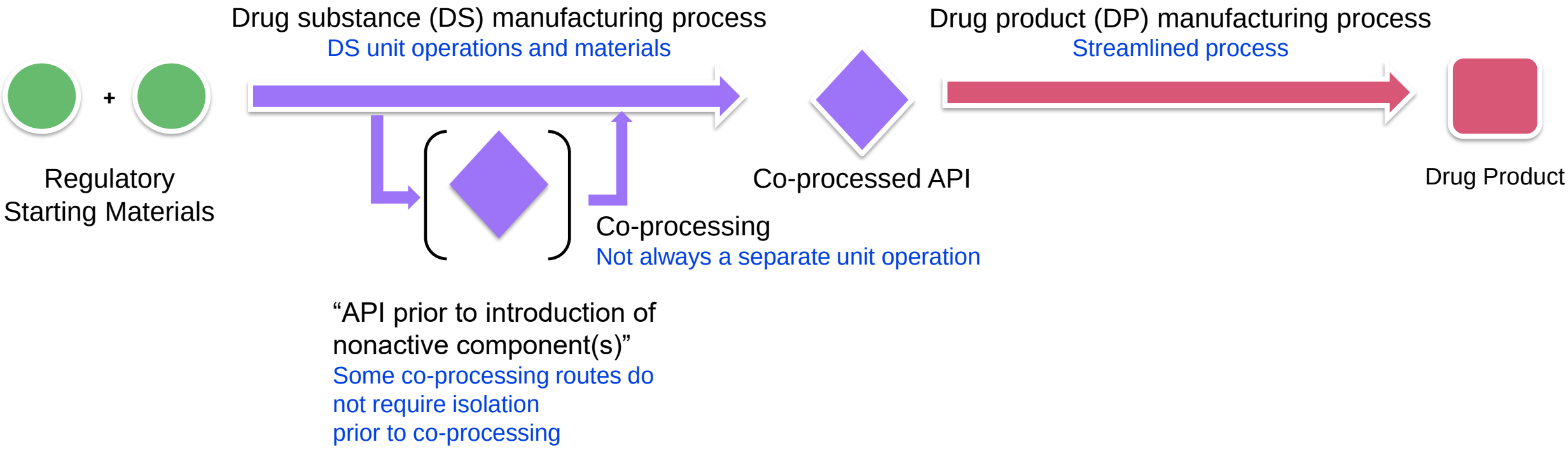
Proposal: Co-processed API may be defined as a drug substance, following API GMPs and principles in ICH Q7



Motivation for Drug Substance Designation Overview



Motivation for Drug Substance Designation Overview

Defining a co-processed API as a DS clarifies these materials should not be considered as:

- In process materials,
- API mix,
- Drug product intermediate (DPI).

Definition carries implication for both GMP manufacture and expiry dating.

Option of co-processed API as a drug substance can deliver robust drug substance with bulk powder properties supporting streamlined drug product operations (e.g. continuous direct compression).

Defining as an in process material/API mix/DPI can present significant hurdles to commercializing co-processed APIs.

Motivation for Drug Substance Designation
Manufacturing site licenses and capabilities

Common that pharmaceutical GMP manufacturing sites dedicated to either DS or DP manufacture.

- Very few commercial manufacturing sites have both DS and DP capabilities.
- DS sites typically do not have DP licenses, and it would be complex and costly to license a DS site for DP/DPI manufacture and release with no improvement to product quality.
- Dedicated DPI sites typically have specialized equipment and are external and costly.

Co-processing routes mostly use typical DS unit operations (e.g. crystallization, drying, milling) and organic solvents.

- Most DS facilities have the equipment and controls necessary to handle wet processing in aqueous and organic solvents and dry processing of solids from a quality, plant and worker safety perspective.
- Most DP facilities can handle aqueous solvents and dry powder processing but lack the equipment and controls to handle organic solvents.

Motivation for Drug Substance Designation
Manufacturing Process Efficiency

For many of the co-processing routes, co-processed API can be generated as part of the DS manufacturing process (e.g. during crystallization of the API).

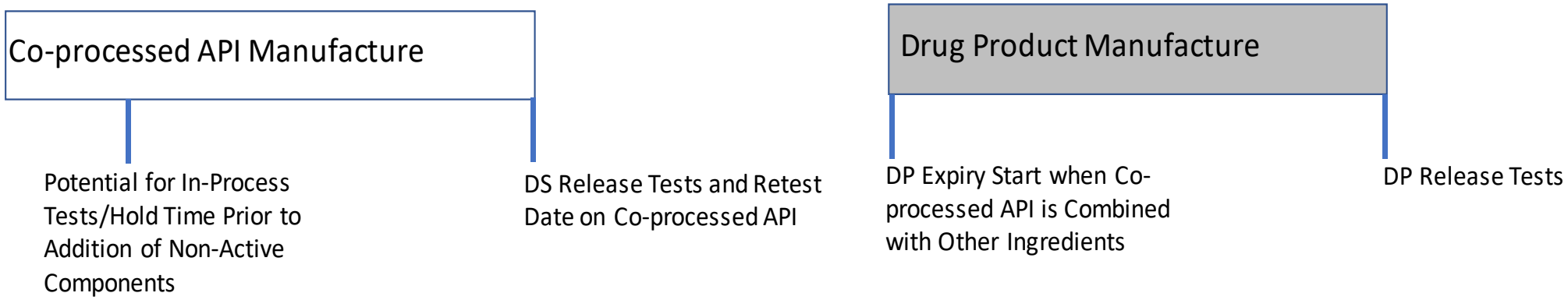
- API prior to addition of nonactive component(s) does not always require isolation. In some instances, isolating the API prior to the addition of nonactive component(s) is impossible or inefficient, and the use of co-processed API allows access to unexplored chemical space.
- Co-processing does not always require added unit operations or extended cycle time and it may improve the DS process efficiency and robustness.
- May allow for stage-appropriate scalability using existing API manufacturing equipment and processes.
- Definition as a DS would allow for potential to support appropriate re-work/re-processing procedures, unlike a DPI.

Incorporation of excipients during solvent-based operations has shown capacity to influence bulk powder properties with lower quantities of excipients as compared to when excipients are added in powder state during typical drug product operations.

Starting the DP process with DS of optimal physical properties may improve DP process robustness and support streamlined drug product operations (both for batch and continuous DP processes).

Potential benefit of improved industrial hygiene and potent compound containment.

Motivation for Drug Substance Designation Expiry Dating



Primary stability studies with stability indicating tests (e.g. physical and chemical stability) to be conducted on co-processed API to support storage of co-processed API with retest period (per ICH Q1A, Q7). DPI would typically not have a retest period.

DP manufacturing process and expiry period would not include co-processing.

- DP expiry to start when co-processed API is combined with other excipients in the DP process.

Strategy ensures product quality while making the most efficient use of supplies.

Case Study: Quality Risk Assessment of Designating a Co-precipitate as a DS vs DPI

Investigational product with low solubility API co-precipitated with a polymer as part of the DS process. Proposed co-processed API addressed the challenges with API solubility, allowed for stage-appropriate scalability using existing API manufacturing equipment and procedures, and could potentially be used in a continuous direct compression DP process.

Pfizer conducted a quality risk assessment to assess the risk to product quality/patient safety of assigning a co-processed API as a DS and manufacturing in a DS facility. Assessment was intended to align with the principles of ICH Q9 and ICH Q11, ensure that all appropriate DS GMP requirements per ICH Q7 could be met, and assess risk of any differences between DS and DP GMPs.

- Foundational GMP expectations are the same for DS and DP but some expectations for controls are different.
- No high risks were identified during the assessment.
- Most items were low risk, few items were moderate risk. Moderate risks and mitigations summarized on next slide.

Case Study: Quality Risk Assessment of Designating a Co-precipitate as a DS vs DPI

Moderate Risk	Proposed Strategy	Mitigation
Facility designation	Drug substance facility to be used and no update to designation.	For clinical site: Perform internal audit to demonstrate appropriate GMP controls in place. Prepare for agency inspection. For commercial: Internal audit and agency inspection is standard practice; no risk.
QP release	DS is released by Quality Unit and does not require QP release. DP requires QP release.	QP Release of Finished Product checks DS release information including release state, CoA, deviation and CAPA closure, and expiry dating.
Polymer component definition and release	Define polymer as reagent not starting material nor excipient.	Complete full compendial testing for polymer release.
Definition of API prior to the addition of non-active components and control strategy for co-precipitate	Define API prior to the addition of non-active components as API intermediate. Some quality attributes may be on intermediate specification or controlled through IPCs, while others are on the specifications of the co-ppt drug substance. Additional quality attributes may potentially be required for co-ppt specifications for a given co-processed API. Demonstrate homogeneity of co-ppt through standard practices.	During development test all standard DS quality attributes on API prior to introduction of non-active components and demonstrate no change of attributes during co-processing. Demonstrate homogeneity during development, tech transfer and PV.

DS or DP GMPs for co-processing operations are equivalent in terms of risks to patient safety and product quality.

Regulatory Landscape Overview

Current regulations/regulatory guidance documents in major markets allow for:

- Inclusion of non-active components in DS for reasons such as stability or safety.

Inclusion of non-active components in DS for other reasons (e.g. below) generally not accepted or subject to agency review:

- Improving physical stability/physical properties,
- Improving manufacturability/processability.

No clear scientific rationale for why DS designation is only acceptable for limited reasons.

Subjective interpretation risks global regulatory harmonization.

- Industry cannot manufacture the same product at different sites or to different standards/GMPs.
- Clarification and regulatory alignment needed for acceptable justification for DS designation/being able to manufacture at DS site.

Regulatory Landscape
ICH

ICH Q7

Active Pharmaceutical Ingredient (API) (or Drug Substance) **Any substance or mixture of substances** intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

ICH Q7 Q&A (2015)

Does ICH Q7 apply to manufacturing steps for the **addition of substance(s) to an API** (**e.g., to stabilise the API**)?

When a mixture is classified in the regulatory filing as an API in a region or country in which it is used in a drug product, ICH Q7 should be applied to the manufacturing of these mixtures.

The proposed definition of a co-processed API as a DS is aligned to the principles of ICH Q7.

Regulatory Landscape Overview

EMA Quality Working Party Questions and Answers on API Mix (2016)

Under which circumstances can an API Mix [a mixture of an API with one or more excipients] be submitted as part of 3.2.S?

- ✓ In certain circumstances, i.e. **stability or safety reasons**, the applicant can submit data on such a mixture under part 3.2.S…The API mix should comply with the same requirements as for an API with regard to GMP…A re-test period for the API mix can in such cases be accepted, if justified.

Health Canada Quality Guidance for NDS/ANDS (2017)

Drug Product Intermediate is a material that is the result of a drug substance having undergone at least one processing step in the presence of any other substance (used in the manufacture of the drug product whether it appears in the finished dosage form or not) which must undergo further processing step(s) to become the finished dosage form.

- That first processing step of the drug substance in the presence of any other substance would be considered a drug product manufacturing activity, subject to Part C, Division 2 of the Food and Drug Regulations, and would define the date from which the expiry date for the drug product would be established…**Sponsors having situations that might be an alternative to the above interpretation (e.g. inability to isolate the drug substance in a pure and stable form or mixing with excipients for safety or stability purposes…) should discuss their case and scientific justification in advance with the pre-market approval bureau/office.**

Japan PMDA

No specific PMDA regulations or guidance documents – a ‘pre-mixed API’ may be accepted on a **case-by-case basis for exceptional circumstances e.g. safety reasons, materials that require technically challenging or unique processing.**

Regulatory Landscape Overview
Co-crystal analogies

FDA Guidance for Industry Regulatory Classification of Pharmaceutical Co-Crystals (2018)

- 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] can be tailored to enhance drug product **bioavailability and stability** and to enhance the **processability of APIs during the drug product manufacture**.
- A co-crystal with a pharmaceutically acceptable coformer that meets the above conditions can be considered to be a pharmaceutical co-crystal and has a **regulatory classification similar to that of a polymorph of the API. Specifically, it is not regarded as a new API.**

EMA Reflection Paper for Co-crystals (2015)

- By making cocrystals of active substances, their **solid state properties such as solubility, hygroscopicity and stability may be improved as well as their manufacturing behaviour (compaction, flowability, filterability etc.),** which may be of great interest to the pharmaceutical industry.
- Cocrystals, hydrates and solvates are held together by weak interactions that are in most cases broken upon dissolution. This is the same situation as with salts…**Cocrystals, hydrates and solvates will therefore be considered eligible for generic applications in the same way as salts are The formation of cocrystals**(Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC) unless they differ with respect to safety and/or efficacy.
- **Just like salts is normally subject to compliance with part II of the EU GMP Guide (active substances) and ICH Q7.** If however, in more rare cases where a cocrystal is formed in a step during the drug product manufacturing process such as a wet granulation or hot melt extrusion the formation falls under part I of the EU GMP Guide (finished product), while the part II applies to active component(s) forming the cocrystal.

Justification related to improving physical properties, processability is currently accepted for co-crystals.

Proposed regulatory classification of a co-processed API as an API polymorph is analogous to what is accepted for co-crystals. Non-active component does not alter the chemical identity/structure of the active component. Therefore, the API could meet the definition of "sameness" described in FDA ANDA regulations (21 CFR 314.92(a)(1)).

Examples of Co-processed API Regulatory Designations

Cobicistat on Silicon Dioxide (Tybost Tablets; Gilead)

- Approved as DS by FDA, EMA
- From 2013 European Public Assessment Report: “Cobicistat is an amorphous solid with a low glass transition temperature of 35 °C. Because of the low glass transition temperature, cobicistat under ambient conditions undergoes moisture and temperature induced phase transition from a foam into a rubber-like material. To **increase physical stability** of cobicistat it is adsorbed on silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow amorphous powder and, as cobicistat, it is also hygroscopic…Importantly however and contrary to cobicistat itself, moisture uptake of cobicistat on silicon dioxide is reversible and therefore **cobicistat is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture**.”
- While the carrier particles were designated as the drug substance in the NDA, the package insert lists cobicistat as the active ingredient/active moiety and includes silicon dioxide in the list of inactive ingredients.

Vemurafenib HPMC-AS (Zelboraf Tablets; Roche)

- Approved as **DS in majority of markets** including by EMA, Swissmedic, ANVISA, CFDA, TGA**, but not FDA, Health Canada, PMDA**
- From 2011 European Public Assessment Report: “Vemurafenib is a compound with low permeability and very low solubility and this has been taken into account in the development. The **difficulties with crystalline vemurafenib as regards solubility and bioavailability** have been acceptably discussed, and the development towards a **film-coated tablet comprising the amorphous substance in co-precipitation with HPMC-AS** [hydroxypropyl methylcellulose acetate succinate], has been well described and justified.”

Metformin premix (Metformin HCl + 0.5% MgSt) (Merck KGaA)

- Approved as DS in 1999 by ANSM for Glucophage® to **improve powder flowability**. Then approved as **DS in most countries.**
- In 2010 EMA requested that new DP combination with metformin premix comply with DP GMP. Following EMA Q&A from 2016, **HA challenged the status of Metformin premix as DS during renewals** (in 2017 for Czech republic) **& variations** in UK
- Since 2020, metformin premix removed by ANSM from the GMP Certificate of DS.

Clinical candidate co-precipitated amorphous dispersion (Merck)

- Federal Agency for Medicines and Health Product (FAMHP) of Belgium agreed with DS designation for Phase 1 clinical study. Rationale that the **co-precipitate was regarded as essential for the physical stability of amorphous form**, needed for bioavailability and clinical performance.
- N. Strotman, L. Schenck; Co-Precipitated Amorphous Dispersions as Drug Substance: Opportunities and Challenges, *Org Process Res Dev.* 2022, 26, 10.

Proposal to extend/clarify current regulatory framework

To encompass new technologies, support continuous manufacture, supply chain flexibility and manufacturability of pharmaceuticals.

- Need regulatory harmonization.
- Alignment that co-processed APIs can be defined as a DS and manufactured at a DS facility per ICH Q7 is critical to industry progressing these new technologies.
- Regulatory alignment on the definition of a co-processed API would provide clarity and expand the acceptable justification to include Quality aspects, for when a DS can include the active and non-active component(s).
- The importance of quality in addition to safety is reflected in the updated EU IMPDQ guidance for evaluation of changes.
  - Extending the safety category
    - e.g. to safely manufacture these co-processed materials at a drug substance manufacturing site with equipment and controls required for processes that typically use organic solvents or unit operations from API plants. To address industrial hygiene safety concerns by eliminating fines for potent compounds.
  - Extending the stability category
    - e.g. co-processed APIs can improve the physical stability of an API or stabilize a particular polymorph which can enable the isolation and/or manufacturability of the drug which otherwise may not be possible, and therefore would be unavailable to patients.
  - Extend/clarify additional justification
    - e.g. enhance the processability/manufacturability of APIs during the drug product manufacture (already accepted for co-crystals).

Bigger picture – moving towards end-to-end CM

With DS/DP continuous manufacturing more common in the pharmaceutical industry, and interest in integrated DS and DP CM processes (refer to ICH Q13 Annex IV) the distinction between DS and DP will continue to be blurred.

Need to remove non-value added barriers to bringing forward new technology that can improve manufacturing process robustness/efficiency/quality. The right science, control strategy, and GMPs that ensure product quality are most important.

Conclusions

Ability to designate a co-processed API a drug substance enables:

- Manufacture at an API site that is properly equipped for these processes.
- Efficiency and improved robustness for the drug substance and drug product manufacturing processes. Possibility to isolate and scale up synthesis of APIs which may otherwise not be possible.
- Efficient expiry dating strategy that ensures quality of the drug substance and drug product.

Co-processed API can be manufactured to API GMPs and does not risk patient safety or product quality.

Current regulatory landscape does not prevent use of co-processed APIs or their designation as a drug substance if there is acceptable justification for the inclusion of the non-active components; However, acceptable justification generally limited to safety and chemical stability.

- Industry/academic position that acceptable justification should be extended/clarified to include physical stability, polymorphic form stability, and processability/manufacturability.

Next Steps
Regulatory engagement

Feedback from regulators on the topics and proposals presented herein is key next step for industry to be able to translate promising technologies from proof of concept studies into commercial applications.

- Global regulatory harmonization on expectations is important.

- Waiting for project specific advice may be challenging/lead to delays in development given the implications on manufacturing.

Recent regulatory engagement includes:

- FDA ONDP Education Committee Seminar held in October 2021.
- Today's M-CERSI workshop.
- EMA topic raised by EFPIA at EMA Interested Parties meeting held on 3 May 2022.
  - EFPIA plan to follow up with the Quality Working Party and the IQ Co-processed API working group also plans to address the EMA Innovative Task Force by year end 2022.

Acknowledgements

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Thank You