Co-Processed API in Early Clinical Development Stage

Workshop on Co-Processed API
University of Maryland Center for Excellence in Regulatory Science and Innovation (M-CERSI) and
US Food and Drug Administration (FDA)
July 13 -14, 2022

Llorente Bonaga, Ph.D.
Global Regulatory Affairs - CMC
Merck Sharp & Dohme, LLC

Agenda

Merits of Designating Co-Processed API a DS

Clinical Feasibility of a Co-Processed API

Regulatory CMC Considerations

- Critical Regulatory CMC Topics
- Regulatory Agency Engagement Strategy

Summary and Next Steps

Merits of Designating Co-processed API a DS

Enables rapid entry to clinical studies which then early informs on the technical feasibility of the co-processed API while providing critical in vivo data (clinical) on a clinical candidate

- Manufacture at an API site that is properly equipped for these processes
- Efficiency and improved robustness for the DS and DP manufacturing processes (e.g., continuous technologies)
- API Mix/Co-processed API can be manufactured to API GMPs and differences between DS and DP GMPs do not create risk to patient safety or quality
- Efficient expiry dating strategy ensuring DS and DP quality

Page, S. Recent Advances in API Mixtures, May 3, 2022, EFPIA Presentation

Clinical Feasibility of a Co-Processed API

Goal: To fully assess the viability of cPAD as an enabling technology for human studies

Validate use of the cPAD technology as a new option for generating ASDs for future development compounds in ED by establishing comparable PK profiles of DP manufactured using cPAD and other ASDs.

General Considerations for the Clinical Candidate

Technical

- A poorly soluble NCE
- Need for enabled formulation
- cPAD is best option to produce amorphous solid dispersions (vs SD and HME)
- Formulated into an ASD used in a DP currently in clinical development

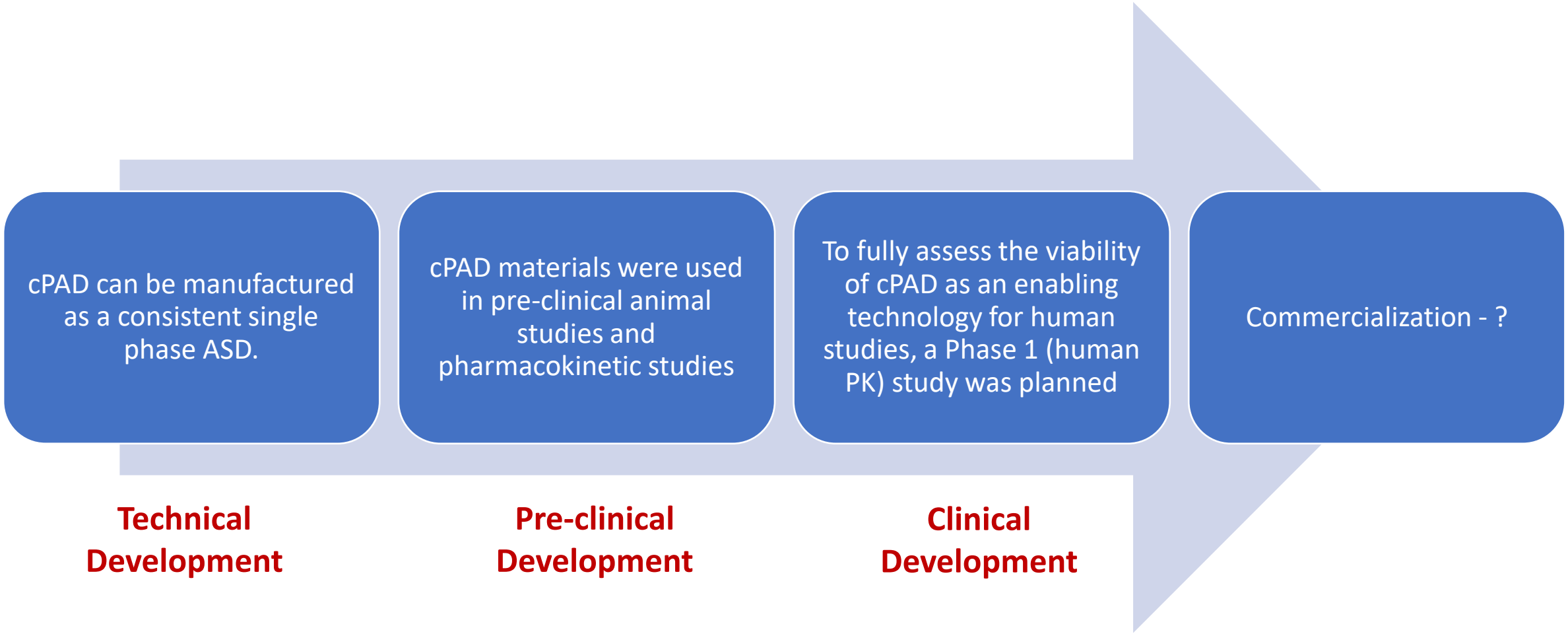
Regulatory

- Low risk of program disruption
- Allows for HA pre-engagement prior to regulatory filings

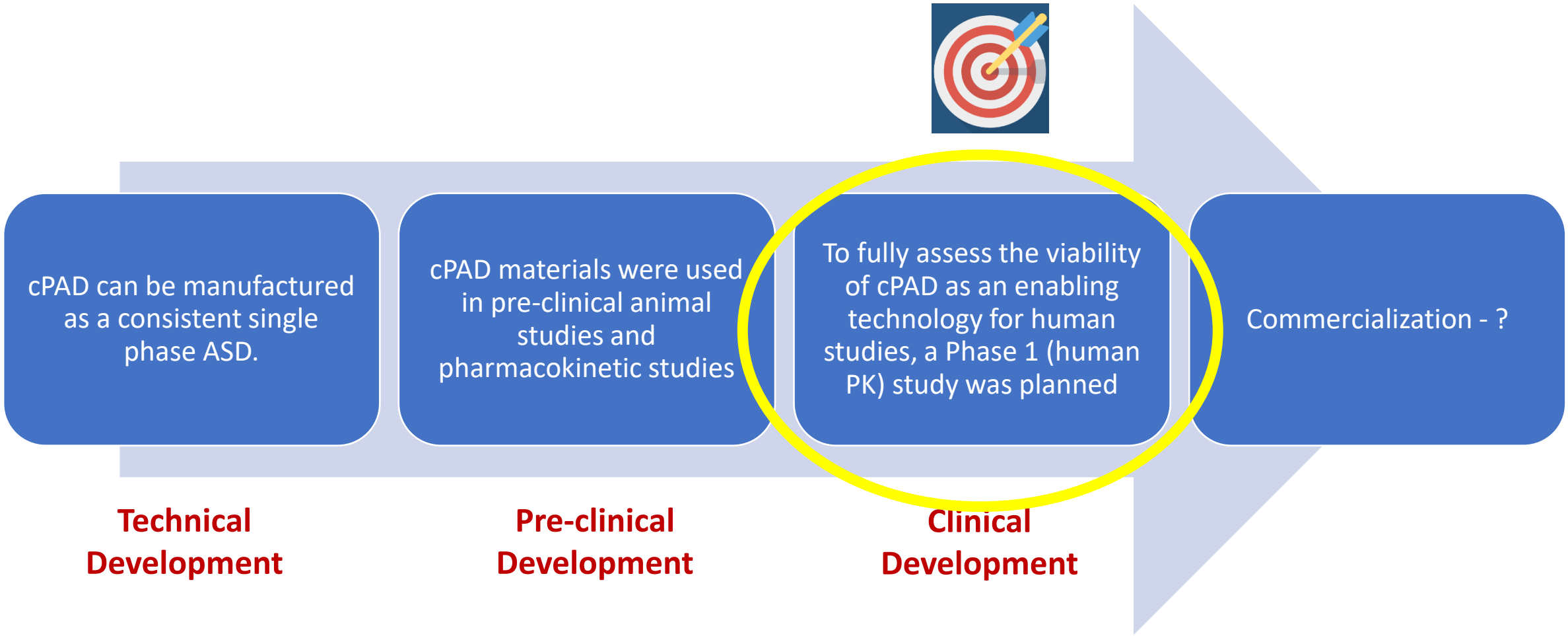
Clinical

- Straightforward clinical study, PK studies, Phase 1

Co-Processed API in Development



Co-Processed API in Development



Considerations for Co-Processed API

- DS designation: Quality/Manufacturing implications?
- Chem and physical characterization, testing of CQAs
- Impurity characterizations
- Control strategies (specifications), CQAs, CPPs, CMAs
- Stability expectations: ICH FSS vs Bulk-hold time studies
- Expiry dating: How is it assigned?
- DP in vitro equivalence with DP using another ASD
- Bioequivalence of DP from other ASDs: Need for in vivo comparison?
- Regulatory documentation strategy in INDs, CTAs
- GMP expectations

Regulatory Agency Engagements Strategy

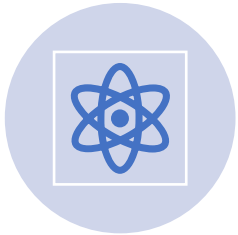
Overall Goal: To collect regulatory intelligence via HA consultations on the co-processed API technology to determine regulatory CMC expectations when applied in various stages of the product lifecycle; initially as applied to a clinical candidate in ED

BELGIUM FAHMP SCIENTIFIC TECHNICAL ADVICE

FDA TYPE C MEETING

EMERGING TECHNOLOGY TEAM (ETT)

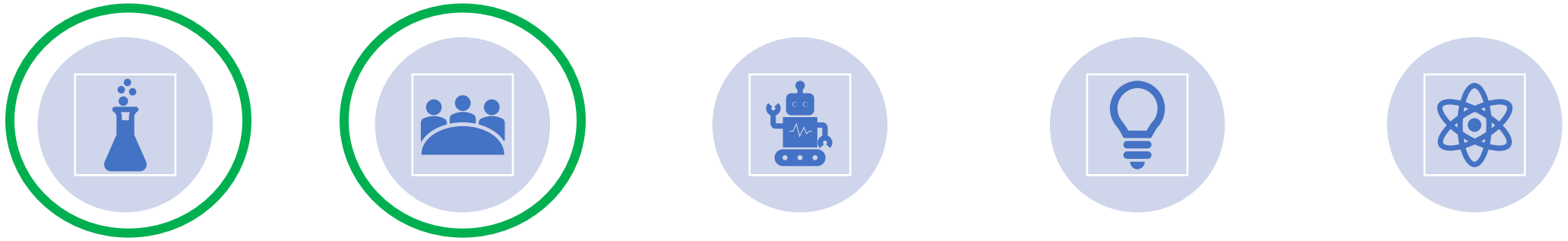
INNOVATION TASK FORCE (ITF)



PARALLEL SCIENTIFIC ADVICE (EMA/FDA)

Regulatory Agency Engagements Strategy

Overall Goal: To collect regulatory intelligence via HA consultations on the co-processed API technology to determine regulatory CMC expectations when applied in various stages of the product lifecycle; initially as applied to a clinical candidate in ED



BELGIUM FAHMP SCIENTIFIC TECHNICAL ADVICE

FDA TYPE C MEETING

EMERGING TECHNOLOGY TEAM (ETT)

INNOVATION TASK FORCE (ITF)

PARALLEL SCIENTIFIC ADVICE (EMA/FDA)

Product Specific: Early Development

Expectations on Critical Regulatory CMC Topics?

1. Approach for the use of Co-precipitated amorphous dispersion (CPAD) to support early phase clinical trials – Technical regulatory considerations, e.g., **control strategy**, specification, characterization, stability
2. Regulate a co-processed API as a drug substance
3. Filing strategy for the CMC information provided in CTAs and INDs

1 - Control Strategy for cPAD

- Regulatory feedback on cPAD technology for a Phase 1 clinical study from the Belgian Federal Agency for Medicines and Health Product (FAMHP) via Scientific-Technical Advice (STA) request

Does the Agency concur with the CMC approach for “co-precipitated amorphous dispersion (cPAD)” technology to support early phase clinical trials? Does the Agency concur with the planned control strategy of cPAD?

1 - Control Strategy for cPAD

- Regulatory feedback on cPAD technology for a Phase 1 clinical study from the Belgian Federal Agency for Medicines and Health Product (FAMHP) via Scientific-Technical Advice (STA) request

Does the Agency concur with the CMC approach for “co-precipitated amorphous dispersion (cPAD)” technology to support early phase clinical trials? Does the Agency concur with the planned control strategy of cPAD?

The control strategy of cPAD as proposed is generally acceptable.

Plus other typical Agency comments on impurity limits, CQAs and testing, stability expectations, retest assignment, etc.

Considerations for cPAD Control Strategy

- Controls of input materials - incoming DS and non-active components
- Manufacture and in-process controls
- Specifications and justifications including potential CQAs (ID, assay, impurities, residual solvents, polymorphic form, surface area, particle size, etc.)
- Solid state characterization by TGA, XRPD, DSC and DVS
- Verification of the amorphous nature of the cPAD (at release and on stability)
- Container closure and storage conditions
- Stability studies & testing

2 - cPAD as Drug Substance

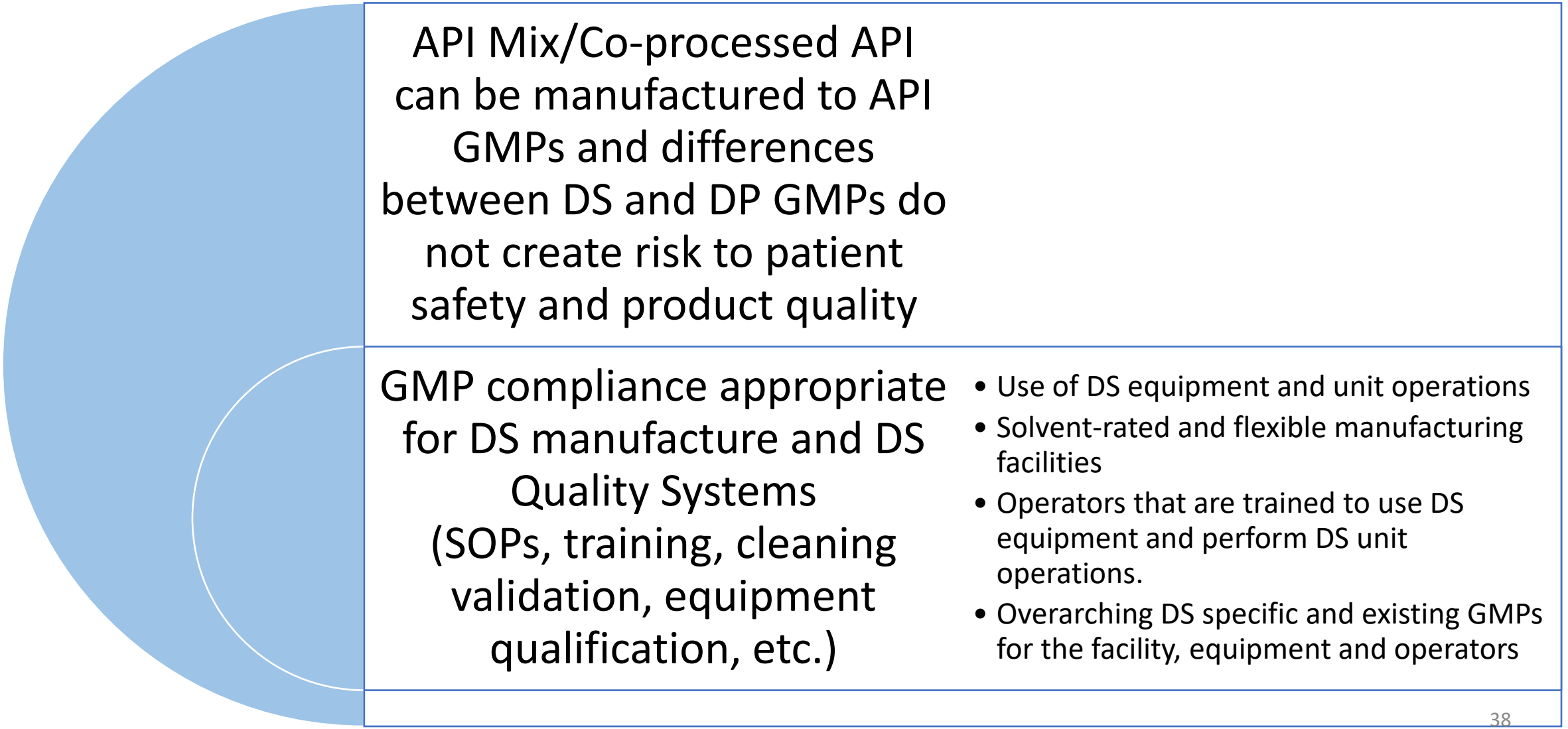
Does the Agency concur with the proposal to consider cPAD as a drug substance?

2 - cPAD as Drug Substance

Does the Agency concur with the proposal to consider cPAD as a drug substance?

The Agency concurs with the proposal to consider cPAD as a drug substance, from regulatory point of view, since it is regarded essential for the (physical) stabilization of the amorphous form of the drug substance and, therefore, its bioavailability and clinical performance.

cPAD Manufacture as a DS Manufacture



3 - Regulatory Documentation for cPAD

On CMC documentation supporting a CTA, does the Agency concur with the proposal to provide an independent IMPD-Quality (CMC) sections for the cPAD?

3 - Regulatory Documentation for cPAD

On CMC documentation supporting a CTA, does the Agency concur with the proposal to provide an independent IMPD-Quality (CMC) sections for the cPAD?

Considering the Agency's position with regards to DS designation and the EMA CHMP Guideline on the requirements for the chem and pharm quality documentation concerning investigational medicinal products in clinical trials, the proposal as well as the IMPD content outline for the CMC information on cPAD is considered acceptable.

Filing Strategy for the CMC information

- Per the ICH M4Q
- Content outline and location for CMC information: Mod 3.2.S – cPAD

THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY

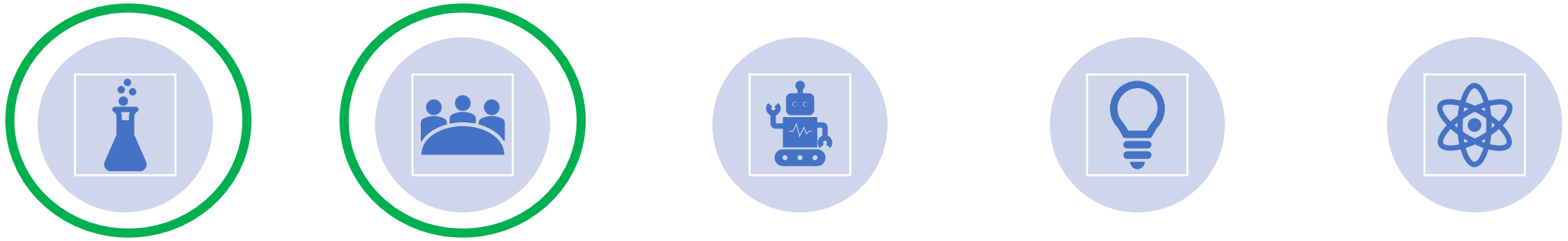
QUALITY OVERALL SUMMARY OF MODULE 2
MODULE 3 : QUALITY

ICH HARMONISED TRIPARTITE GUIDELINE

CTD Module 3.2.	Description
S.1	Nomenclature, structure, and properties/solid-state characterization (e.g., XRPD, DSC, TGA)
S.2	Manufacturing / testing site(s), manufacturing process description and scheme, in-process controls, control of materials – excipients, solvents
S.3	Characterization of appropriate quality attributes (e.g., IR and UV), impurities
S.4	Specifications (testing of cQAs), analytical methods, analytical method validation, batch analyses, justification of specification
S.5	DS working standard
S.6	Container closure system
S.7	Stability protocol, retest date assignment, stability data

Regulatory Agency Engagements Strategy

Overall Goal: To collect regulatory intelligence via HA consultations on the co-processed API technology to determine regulatory CMC expectations when applied in various stages of the product lifecycle; initially as applied to a clinical candidate in ED



BELGIUM FAHMP SCIENTIFIC TECHNICAL ADVICE

FDA TYPE C MEETING

EMERGING TECHNOLOGY TEAM (ETT)

INNOVATION TASK FORCE (ITF)

PARALLEL SCIENTIFIC ADVICE (EMA/FDA)

Product Specific: Early Development

Regulatory Agency Engagements Strategy

Overall Goal: To collect regula tations on the co-processed API technology to ectations when applied in various stages of t applied to a clini

BELGIUM FAHMP SCIENTIFIC TECHNICAL ADVICE

FDA TYPE C MEETING

EMERGING TECHNOLOGY TEAM (ETT)

INNOVATION TASK FORCE (ITF)

PARALLEL SCIENTIFIC ADVICE (EMA/FDA)

Product Specific: Early Development

Product Lifecycle

Summary and Next Steps

Shown the feasibility of cPAD technology as a new option for generating ASDs for future development compounds in early phase development.

Obtained concurrence on major regulatory CMC considerations enabling use of co-processed API in early stages of clinical development

- Designation as drug substance
- Phase- appropriate control strategy (specifications, CQAs, etc.)
- Regulatory documentation strategy

Summary and Next Steps

Needs continued Agency engagement on the regulatory framework for co-processed API as DS in the later stage in product lifecycle, i.e., registration and post-approval stages

- Via technology platform-based Agency engagements
- Via continued engagement with industry and academia
  - Acceptable rationale of co-processed API should be extended/clarified beyond safety and stability and include improvement of API physical properties and DP processibility

Acknowledgment

- Luke Schenck, Process Research and Development
- Robert Orr, Regulatory CMC
- Chad Dalton, Pre-clinical Dev. Oral Formulation Sciences
- Merck cPAD Operationalization team
- IQ Working Group on Co-Processed APIs

Questions

Primary References

Strotman, N.; Schenck, L.; Coprecipitated Amorphous Dispersions as Drug Substance: Opportunities and Challenges. Org. Process. Res. Dev. 2022, 26, 10-13. (https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.1c00380)

Schenck, L.; Mann, A. K. P. et al. Building a better particle: Leveraging physicochemical understanding of amorphous solid dispersions and a hierarchical particle approach for improved delivery at high drug loadings. Int. J. Pharm. 2019, 147–155. (https://doi.org/10.1016/j.ijpharm.2019.01.009)

Page, S. Recent Advances in API Mixtures, May 3, 2022, EFPIA (European Federation of Pharmaceutical Industries and Association)