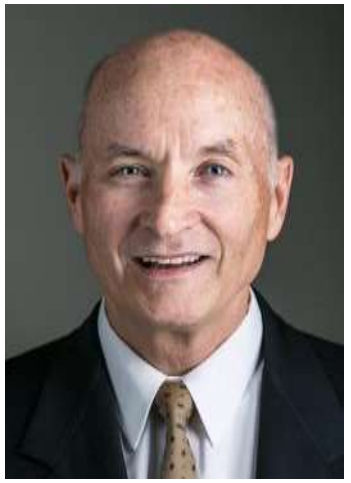
Standardizing Quality Submissions and Assessments: PQ/CMC and KASA



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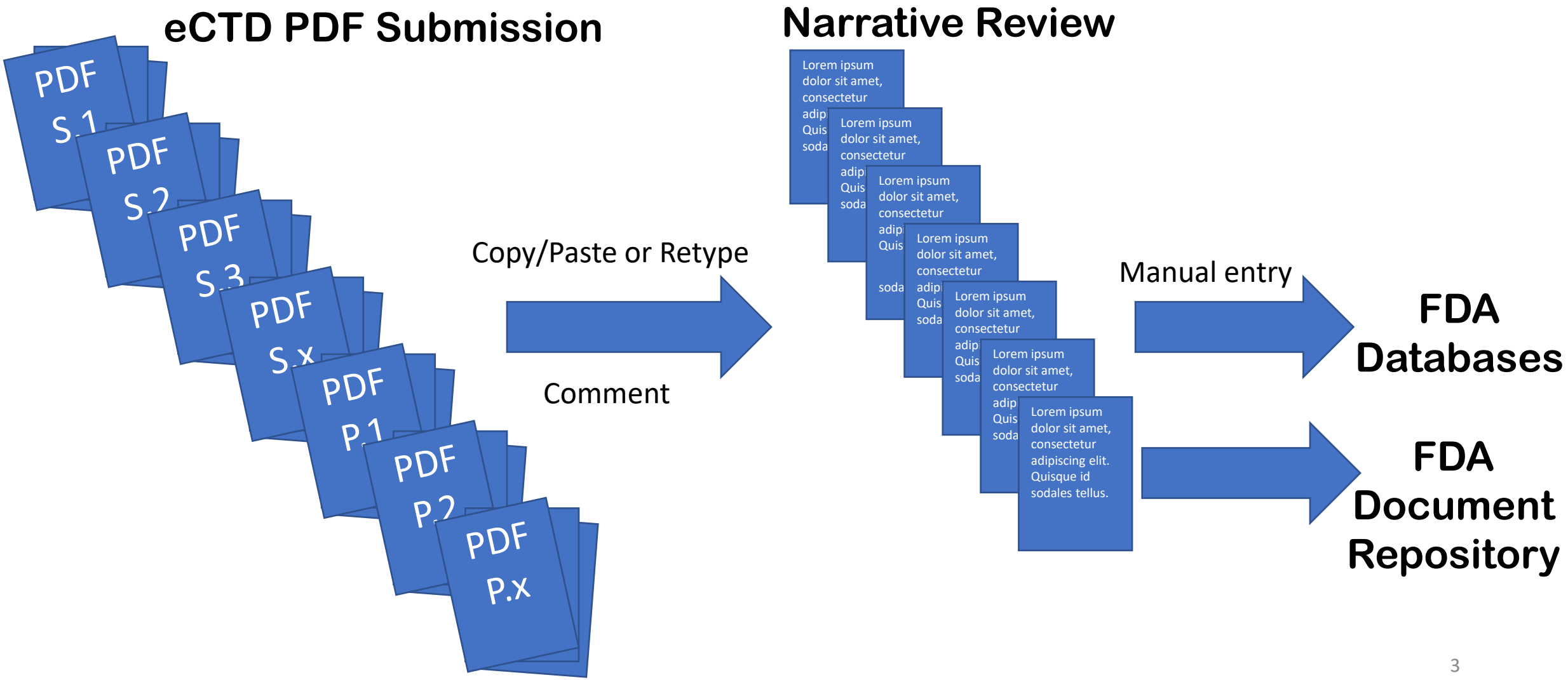
Learning Objectives

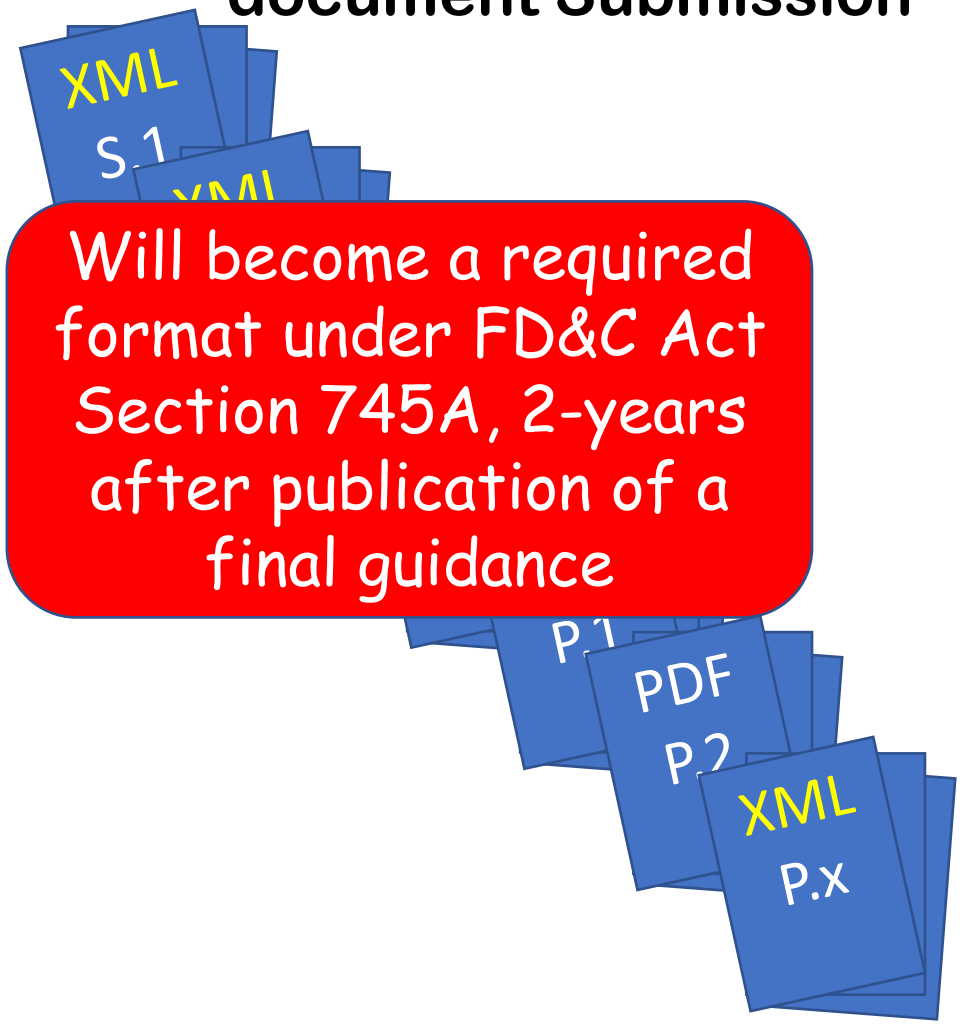
- Describe the PQ/CMC vision
- Explain what's been done so far
- Describe the role of ICH and the ISO IDMP standards
- Explain the ongoing work & its challenges
- Describe what applicants might do to prepare for the future of structured applications

Current Module 3 Submission Model



Possible Future Module 3 Submission Model

eCTD "M3 structured data & document Submission"



Will become a required format under FD&C Act Section 745A, 2-years after publication of a final guidance

FDA Document Repository

Auto-populate FDA Databases & Systems
(e.g., KASA, Facilities, Unit Operations)

PQ/CMC and KASA

- PQ/CMC (Pharmaceutical Quality/Chemistry, Manufacturing, and Controls
  - Standardize & structured eCTD **submissions**
  - XML, JSON and HL7 FHIR
  - Controlled vocabularies for drop-down lists
- KASA (Knowledge-Aided Assessment and Structured Application System:
  - Pre-populated structured **assessments**
  - Risk-ranking algorithms
  - Pre-analyzed data, e.g., linear regression of stability data
  - Data analytics
  - Comparison to historical data
  - Lifecycle knowledge management
- Implementation of PQ/CMC will significantly enhance the KASA system, by removing manual data entry

What we've done

- Assembled SMEs across CDER, CBER & CVM
- Modeled Specification, Components and Composition, Impurities, Batch Analysis and Stability
- Standardized terminology and definitions
- Tested proof of Concept with 5 PhRMA firms
- Harmonized data elements with the KASA system
- Collaborated with stakeholders and other interested parties

What we've Published

- Federal Register
  - 2017 FR Notice*: Phase 1 PQ/CMC Terms and Definitions
    - Main comments: Our Response
      - Effort should be international: Response (next slide)
      - Terminology should conform to ISO IDMP**: Response
        - Completed a 157-page mapping document
        - Held a collaborative mapping webinar with PhRMA
  - 2022 FR Notice***: PQ/CMC to HL7 FHIR Mapping
    - Comments period closed May 17
    - Received comments from 8 parties

Visit FDA PQ/CMC webpage

https://www.fda.gov/industry/fda-data-standards-advisory-board/pharmaceutical-qualitychemistry-manufacturing-controls-pqcmc

* http://go.usa.gov/xNe8S
** Identification of Medicinal Products (5 ISO standards) http://go.usa.gov/xzuxc
*** http://go.usa.gov/xzVdc

PQ/CMC and ICH

- “Structured Product Quality Submissions” (SPQS) accepted as a topic by the ICH Assembly
- Prioritized as follows:
  - After Q13 completes Step1/Step 2 (Step 2b completed:27 July 2021)
  - New M4-Q (CTD-Q) Expert Working Group in progress with FDA’s Lawrence Yu as Rapporteur
  - SPQS group formation to be determined by new M4-Q EWG
- FDA’s PQ/CMC will continue

Identification of Medicinal Products (IDMP)

- Goal: Define data elements and structures for the unique identification and exchange of medicinal product information
- Five standards:
  - Substances (ISO 11238)
  - Pharmaceutical dose forms, units of presentation, routes of administration and packaging (ISO 11239)
  - Units of measurement (ISO 11240)
  - Regulated pharmaceutical product information (ISO 11616)
  - Regulated medicinal product information (ISO 11615)

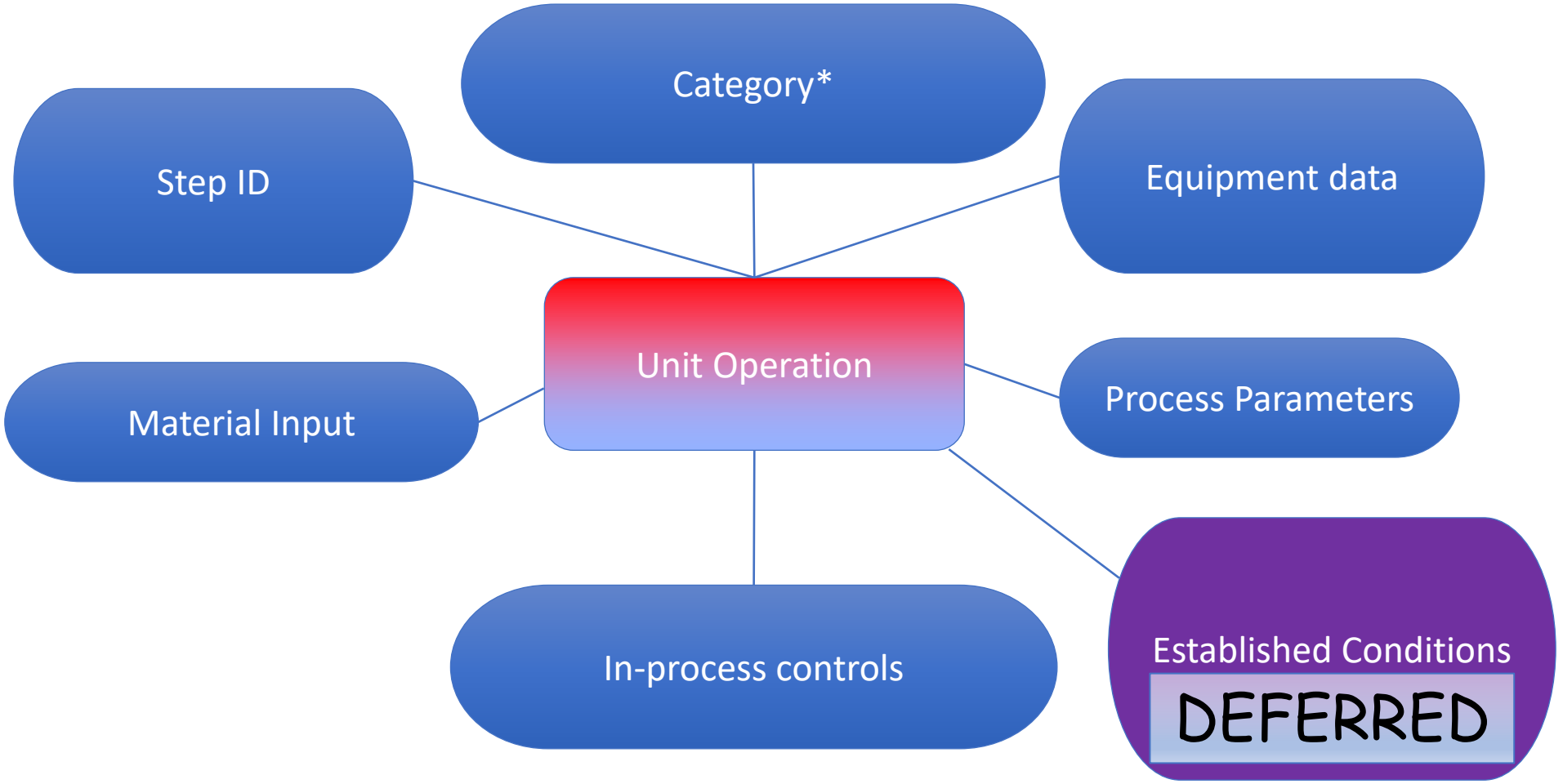
“Terminology should conform to ISO IDMP”

- Mapping is problematic, e.g., different granularity
- Many code lists are deferred to regional implementation (e.g., MPID)
- Some terms are regionally mandated (e.g., US FD&C statute requires USP, EU mandates EDQM)
- Some regions have multiple code lists used in different contexts, e.g., FDA has four dosage form lists in use
  - USP terminology is required by FD&C Act in labeling
  - SPL uses a list from the NCI Enterprise Vocabulary Service
  - Orange book uses a list for acceptable ANDA submissions
  - ICH allows for the EDQM list as an option for E2B submissions
- PQ/CMC terminology will be aligned with where possible, but conformance frequently not feasible

Standardized Terminology & Definitions

- Why
  - Eliminates confusion about synonyms, potentially synonymous terms
  - Enables an ontology (i.e., properties and the relations between them)
  - Permits data analytics
    (e.g., how many assay procedures use CZE, for what classes of drugs, is this better than HPLC for certain drug classes)
  - Facilitates risk-ranking
- Controlled vocabularies (ISO: coded concepts)
  - Enables drop-down lists & data analytics
    - E.g., “Ingredient role” for PQ/CMC (Active, Inactive, Adjuvant)

Drug Product Unit Operations



* From 2014 “SUPAC: Manufacturing Equipment Addendum Guidance for Industry”

Typical WG Meeting Activity

PQ/CMC - KASA - Trk 2 meeting - 8/6/2021 --Harmonization Notes for Excipient Function Names

#	KASA Excipient Function List	PQ/CMC Excipient Function Names Mapping to KASA list	NEW values to be added to PQ/CMC Excipient Function Names List	Recommendations/ Notes for KASA & PQ/CMC
1	API	NA		
2	Acidfier	pH Modifier		
3	Adhesive	Adhesive		
4	Alkalizing Agent	pH Modifier		
5	Anti-Adherent	Lubricant		
6	Anti-foaming Agent	GAP	NEW - Anti-foaming Agent	
7	Antioxidant	Antioxidant		
8	Anti-static Agent	GAP	NEW- Anti-static Agent	
9	Anti-tacking Agent	Lubricant		
10	Binder	Binder		
11	Buffer	Buffering agent		
12	Chelating Agent	Chelating agent		
13	Colorant	Organoleptic agent		
14	Crystallization inhibitor	GAP	NEW- Crystallization inhibitor	
15	Cushioning agent	Filler		
16	Diluent/Filler	??		
17	Disintegrant	Disintegrant		
18	Emulsifier	Emulsifying Excipient		

Notes here on harmonization of:

- Consensus terminology
- Who will make the change

What we plan to do

- Continue external collaboration
  - International Pharmaceutical Regulators Programme
  - International Coalition of Medicines Regulatory Authorities
  - ICH M4Q
  - UNICOM
  - Global IDMP Working Group (WHO Uppsala)
  - EMA
  - HL7
  - IRISS IDMP
  - ISO TC215 WG 6 IDMP
  - CTADHL
- Continue internal collaboration
  - FDA IDMP Steering Committee
  - FDA Global Substance Registration System (GSRS)
  - FDA Data Standards Board
  - CDER Data Standards and Data Governance Board
  - CDER Product Data Control Board
- Model other Module 3 (& 2.3 CTD sections)
- Publish a Draft PQ/CMC Guidance (estimated in 2024)

PQ/CMC IDMP Challenges

- In IDMP standards
  - Spun out of ICH initially as a pharmacovigilance topic
  - 11238 SSG 4 specification use case differs from PQ/CMC
  - Not all terms are defined
  - Most controlled vocabulary code (“coded concept”) lists undefined
- PQ/CMC items not included in IDMP
  - Stability
  - Quality data for drug product,
    e.g., specification (may include test stages)
  - Quality data for excipients
  - Lifecycle model for specification
  - Batch Analysis Tables
  - Control of Excipients

Challenges

- Standards
  - Diversity e.g., IDMP, UNICOM, SPOR, ICH, CFR, EMA, MEDDRA, EDQM
  - Gaps e.g., controlled vocabulary (CV) for analytical procedures, chemical & physical attributes for characterization, specification, in-process controls; IDMP code lists
- Developing data models & ontologies
- HL7 FHIR vendor support is lagging, although well supported by Clinical vendors
- Internal FDA infrastructure

Conclusion

- PQ/CMC will
  - Substantially change the submission process
  - Necessitate new business processes and infrastructure for FDA and the Applicants
  - Enable alignment with IDMP and other Product Quality efforts
- Years in the future
  - To become a required submission under 745A(a)
  - ICH “Structured Product Quality Submissions”

Preparing for the Structured Data Future

- Follow PQ/CMC, ISO IDMP, SPOR Developments (with e.g., Google alerts)
  - For PQ/CMC, follow FDA webpage
- Collect & organize your data in line with IDMP, PQ/CMC & EMA's SPOR
  - Apply "Master Data" concepts
  - Group data according to IDMP concepts
    - Drug Substance
    - Drug Product (e.g., regional MPIDs* for all marketing regions)
    - Dosage form (e.g., consider adding an administrable dose form used in PhPID**)
  - Do data cleansing, QC, curation

* MPID: ***Regional*** Medicinal Product Identifier with three standardized segments described in ISO 11615

** PhPID: ***Global*** Unique Pharmaceutical Product Identifier, currently an MD5 algorithmically generated 32-digit hash code as described in ISO TS 20415

Challenge Question #1

Which of the following statements is true?

1. PQ/CMC is primarily about application assessments?
2. KASA is primarily about application submissions and their assessments
3. PQ/CMC & KASA are primarily about application submissions and their assessments
4. PQ/CMC will provide the structured data needed for KASA assessments

Challenge Question #2

Which of the following is not true?

- PQ/CMC submission format will become mandatory in 2025
- PQ/CMC attempts first to use existing data standards
- PQ/CMC is now an FDA only project
- PQ/CMC has published two Federal Register notices