U.S. FOOD & DRUG ADMINISTRATION

Perspective for Modernization of Regulatory Assessment and Submission including KASA and PQ/CMC

Bazarragchaa Damdinsuren, MD, PhD
Lead Interdisciplinary Scientist
Office of Biotechnology Products,
Office of Pharmaceutical Quality
CDER, FDA

CMC Strategy Forum North America
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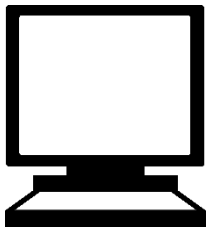
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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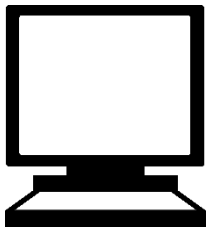



Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

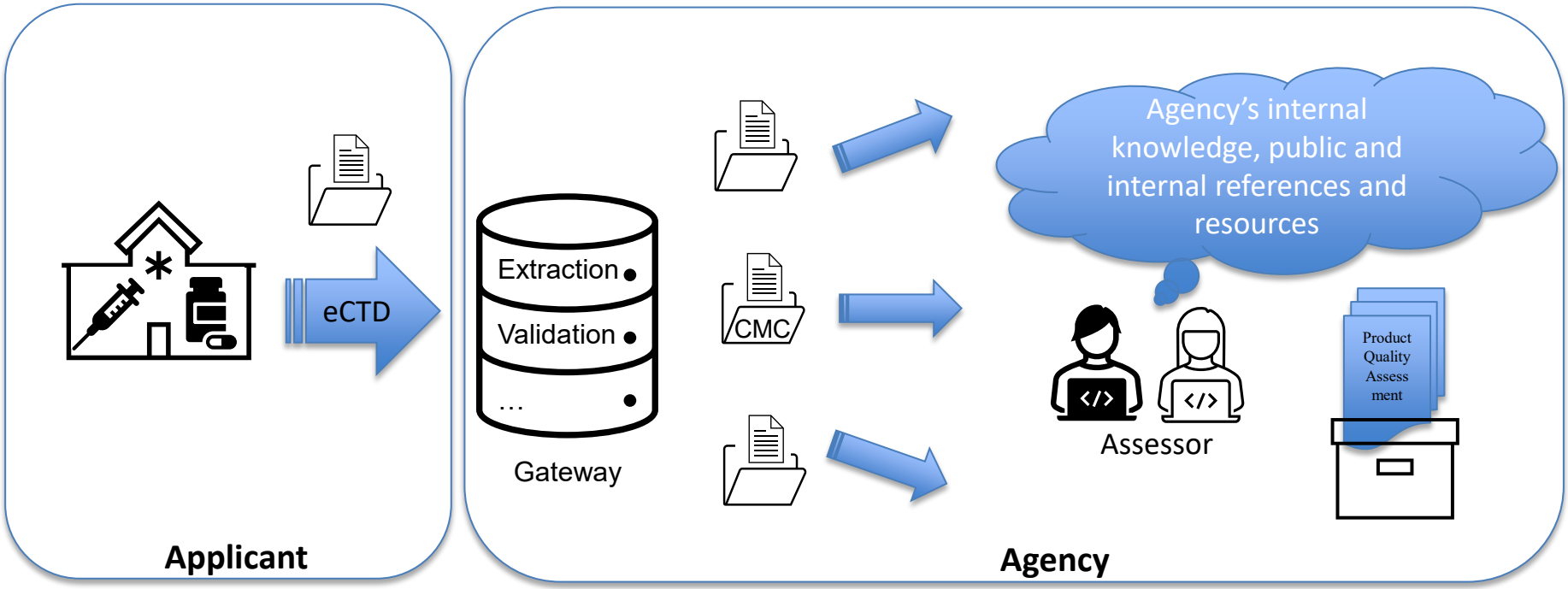

FDA
It is what gives patients confidence in their *next* dose of medicine.

Overview

- FDA's initiatives to support present-day submissions and assessments
  - Existing environment for CMC data submissions and assessment
  - Introduction for PQ/CMC and KASA initiatives
  - Current progress, and examples

- Development approach for KASA and PQ/CMC projects for biological products
  - Specific considerations
  - Current progress, and examples

Current CMC Data Submissions and Assessment



CDER Application- and Assessment-related Challenges

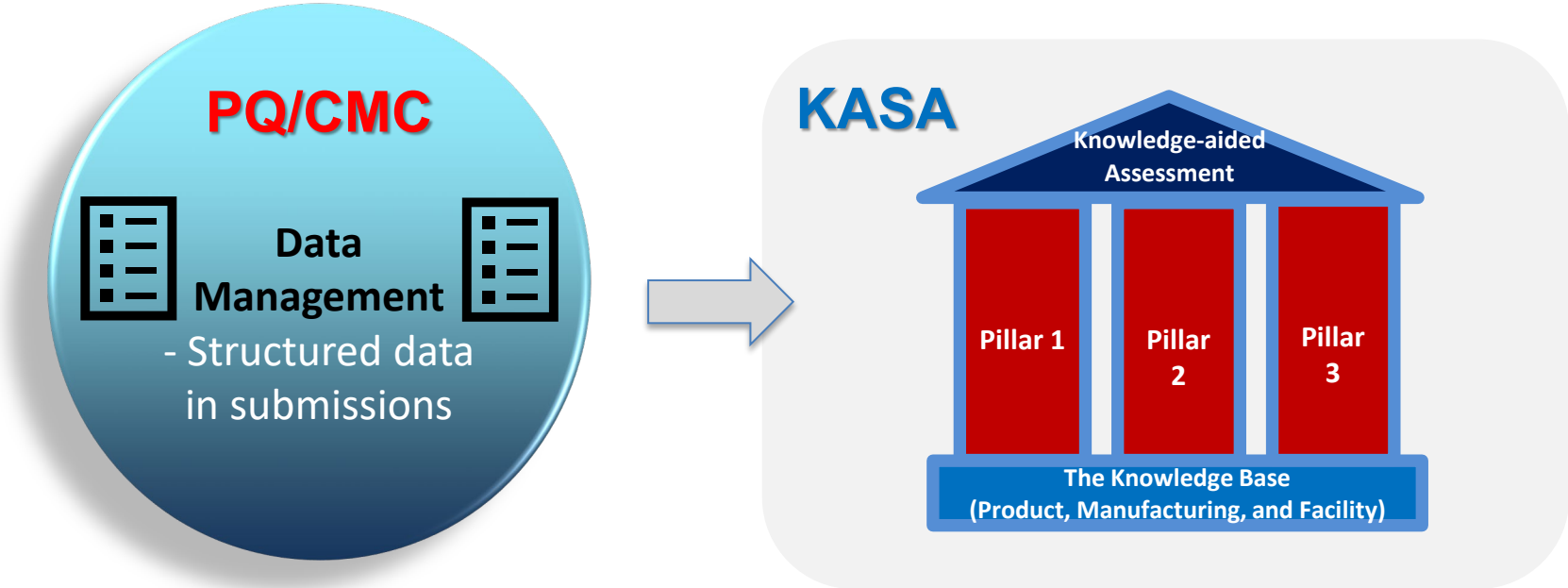
Application Challenges

- Module 3 content and data submitted in PDF format with unstructured quality data and information. This hinders the efficiency of data exchange, and lifecycle knowledge management.
- Alignment with regulatory expectations changes and technological advancement
- Complexity of biological products, and relevant terminologies (*specific for OBP*)

Assessment Challenges (internal)

- Freestyle narrative assessment:
  - Unstructured text
  - Summarization of application information
  - "Copy and paste" data/tables
- Cumbersome knowledge sharing and knowledge management
- Potential for subjective assessment based on the assessor's expertise and knowledge at hand
- Volume of new applications

FDA's Initiatives to Support the New Era of Submission and Assessment



Other projects include Modernize the Common Technical Document (CTD) Quality section (ICH M4Q(R2)), Quality Surveillance Dashboard (Agency's internal tool), etc.

What is PQ/CMC?

Pharmaceutical Quality/Chemistry, Manufacturing and Controls

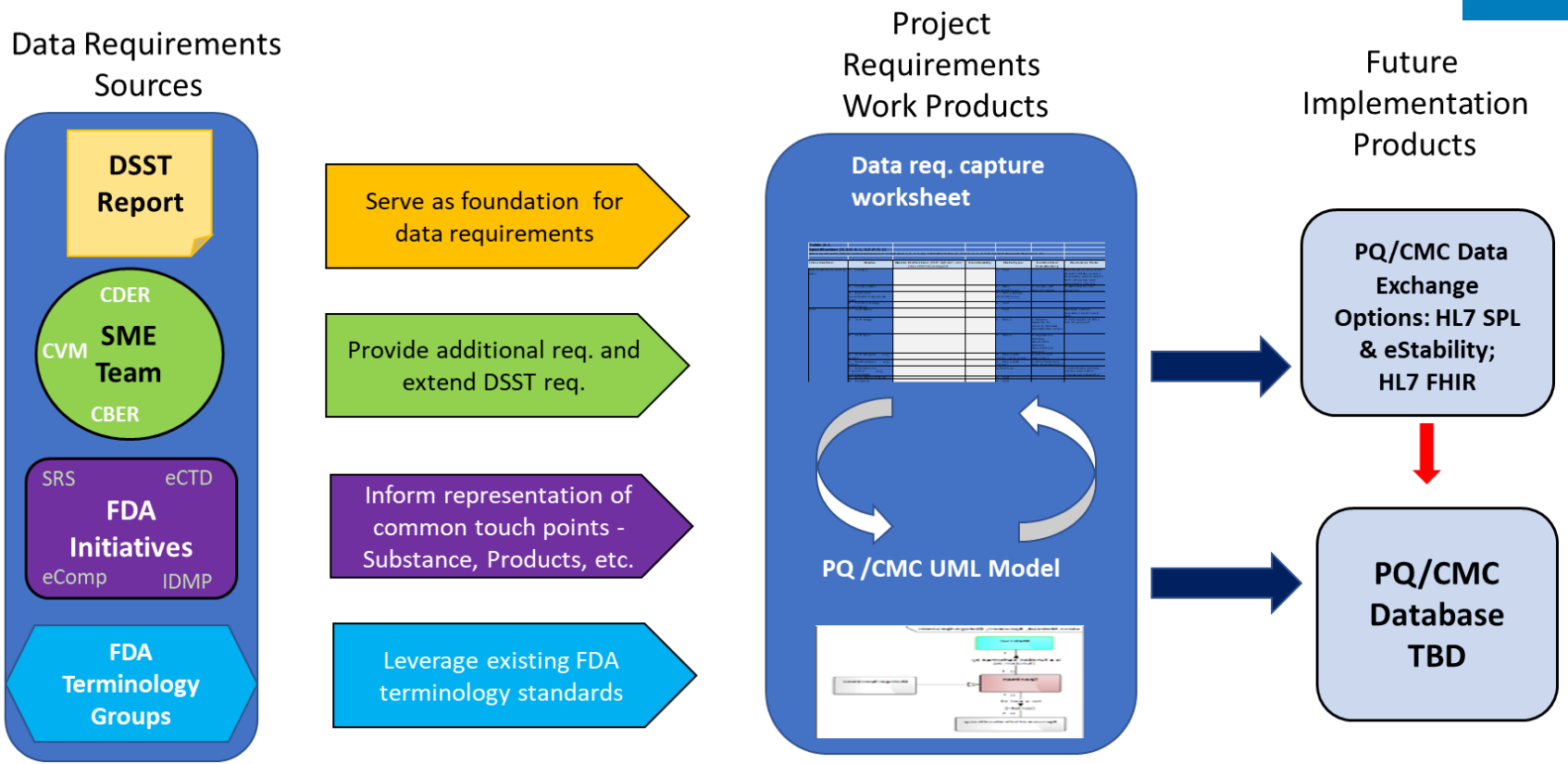
Electronic standards for CMC data submission

- Develop structured data* standards for CMC information
- Implement a data exchange standard for submitting CMC data as an HL7 FHIR message

[implemented as a required submission format under Section 745A(a) of FD&C Act]

* Structured data is highly specific information and is stored in a predefined format, *vs.* Unstructured data is a conglomeration of many varied types of data that are stored in their native formats.

Data Standards Development Strategy



Adopted from Geoffrey Wu: FDA's Current Effort in Structured Product Quality Submission (aka PQ/CMC) At WCBP 2023, Washington DC

PQ/CMC Scope & Phases

Phase 1 – *draft completed*

1. Specification
2. Batch Information (Drug substance/Drug product)
3. Batch Analysis
4. Stability Study
5. Stability Analysis
6. Nomenclature of Drug Substance
7. Composition of Drug Product
8. Batch Formula
9. Drug Substance – Control of Materials
10. Drug Product – Control of Excipients
11. Drug Substance Impurities
12. Drug Product Impurities

Phase 2

FRN Chapter 1:
The text of the Document "Pharmaceutical Quality/Chemistry Manufacturing and Controls (PQ/CMC) Data Exchange" published on March 18, 2022

Covers 194 elements in 12 sections

PQ/CMC Scope & Phases

Phase 1 – *draft completed*

FRN Chapter 2:
- Enhancements to support solid oral dosage form component and composition: multi-layer tablets and capsules.
- Support for drug product manufacturing of solid oral dosage forms.

Published on May 1, 2022

Covers 389 data elements

Phase 2 – *in progress: 2021~*

1. **Manufacturing Process**:
   - Manufacturer info
   - Equipment
   - Manufacturing process
   - Unit operations
   - Process parameters
   - In-process controls/tests

A. Solid oral drug product - Done
B. Solid drug substance – in progress
C. Liquid drug product – in planning …

A Demonstrative Example

Test	Limit
Description	White or almost white, crystalline powder.
Identification . *Test A:* . *Test B:*	The I.R. spectrum is concordant with the *reference spectrum* [redacted] It meets the requirements of the test for [redacted]
(+)-*trans*-paroxetine (corresponding to RC C of USP)	Not more than 0.1%
Related substances: . **Impurity I** (corresponding to RC B of USP) . **Impurity** . **Impurity** (corresp USP) . **Any othe** . **Total im**	Not more than 0.30%
Heavy metals	Not more than 20 ppm (Pb)
Water	2.2 – 2.7%
Residue on ignition	Not more than 0.1%
Assay	98.5 – 102.0% *(on anhydrous and solvent-free substance)*
Residual solvents: . **Isopropanol**	Not more than 0.2%
Additional test	
Particle size (laser)	D(v,0.1): NMT 10 μm D(v,0.5): NMT 30 μm D(v,0.9): NMT 60 μm
Polymorphic Form	The x-Ray powder diffractogram is consistent with the reference diffractogram of [redacted] Characteristic XRD peak positions are: 7.1, 10.8, 14.2, 16.7, 17.2, 18.5, 21.4, 21.8, 22.6, 23.2, 23.5, 24.0, 24.2, 28.5, 32.5 within ±0.3 degrees.

Currently unstructured Specification Table

Adopted from Geoffrey Wu: FDA's Current Effort in Structured Product Quality Submission (aka PQ/CMC) At WCBP 2023, Washington DC

A Demonstrative Example

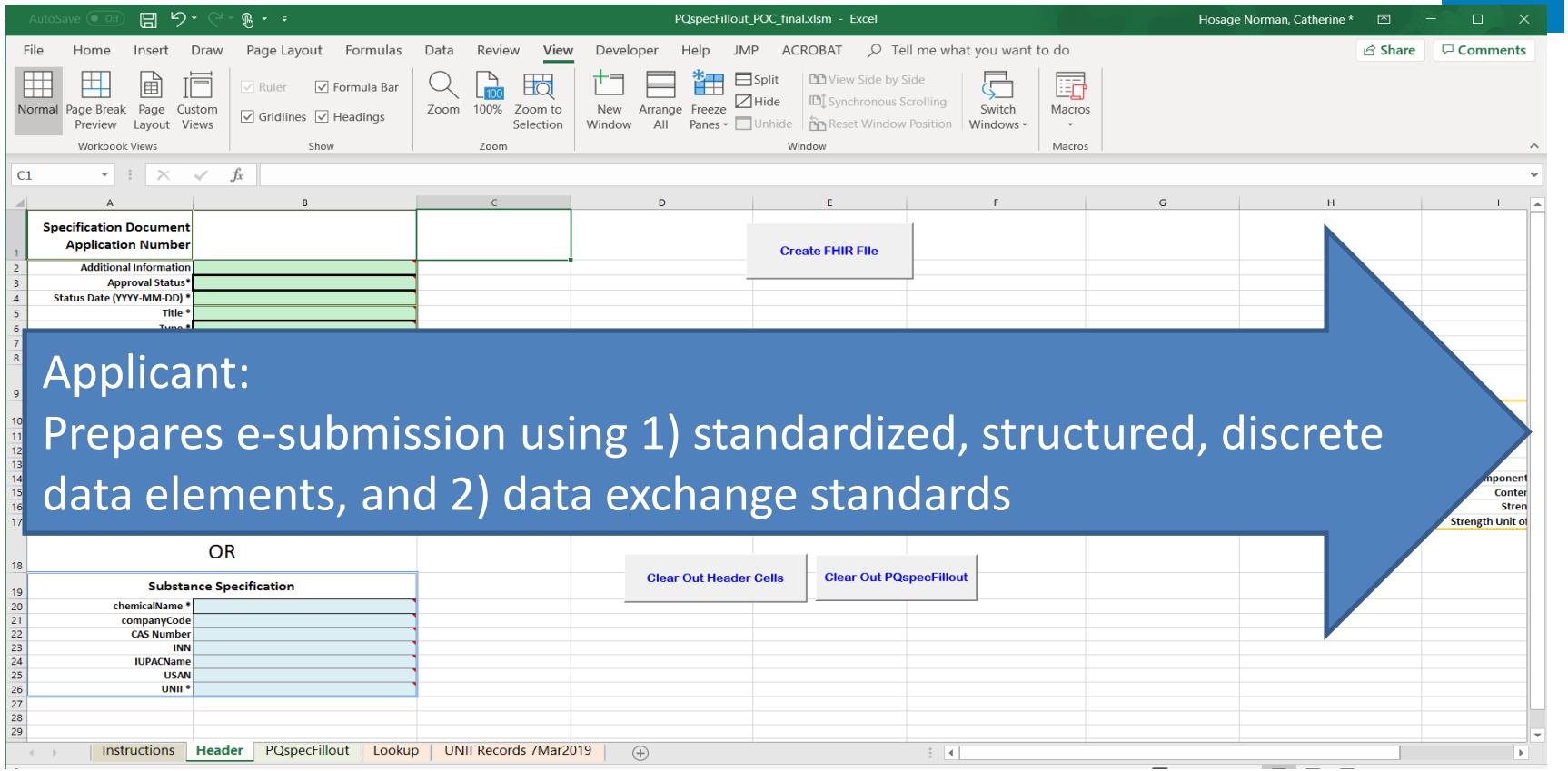
Reference: Federal Register Notice Draft PQ/CMC Data Elements and Terminologies; Request for Comments (07/11/2017)

Table	Data Element Name	Data Element Name Definition	Data type	Terminology	Controlled Vocabulary	Conformance
01-Specification	**Specification Title**	The textual identification for the specification.	Text		0	M
01-Specification	**Specification Subtitle**	An additional textual identification for the spe	Text		0	O
01-Specification	**Specification Type**	A classification of specification related to the	Code	Drug ProductDrug Su	See Controlled Terminology sheet	M
01-Specification	**Specification Version**	The alphanumeric text assigned by the spons	Text		0	M
01-Specification	**Specification Version Date**	The date when the sponsor assigned a date to	Date		0	M
01-Specification	**Specification Status**	The current FDA regulatory status of the spec	Code	ApprovedTentatively A	See Controlled Terminol heet	M
01-Specification	**Specification Status Date**	The date on which the FDA approval status fo	Date		0	M
01-Specifica						O
02-Test						M
02-Test						M
02-Test						M
02-Test						M
02-Test						M
02-Test	**Relative Retention Time**	The ratio of the retention time of a componer	Text		0	O
02-Test	**Test Additional Information**	Placeholder for providing any comments that	Text		0	O
02-Test	**Test Order**	The sequential number assigned to each Test	Numeric		0	M
02-Test	**Stage Name**	A textual description and/or a number that id	Text		0	M
02-Test	**Stage Sequence Order**	The order of the stages in regular succession.	Numeric		0	M
02-Test	Stage Additional Information	Placeholder for providing any comments that	Text		0	O
03-Acceptance Criteria	**Value**	The acceptable qualitative or text value of the	Text		0	O
03-Acceptance Criteria	**ValueNumeric**	The acceptable quantitative or numeric value	Numeric		0	O
03-Acceptance Criteria	**ValueNumeric UOM**	A named quantity in terms of which other qu	Code	http://www.fda.gov/	See Controlled Terminology sheet	O
03-Acceptance Criteria	**Original Text**	The text of the acceptance criteria as provide	Text		0	M
03-Acceptance Criteria	**Acceptance Criteria Usage**	A coded value specifying when a particular an	Code	ReleaseStability	See Controlled Terminology sheet	M
03-Acceptance Criteria	**Interpretation Code**	A code that describes how to relate the given	Code	NMT (not more than)	See Controlled Terminology sheet	M
03-Acceptance Criteria	**Additional Information**	A textual field to provide any additional infor	Text		0	O

PQ/CMC effort:
Transform into standardized and structured, discrete data elements

Adopted from Geoffrey Wu: FDA's Current Effort in Structured Product Quality Submission (aka PQ/CMC) At WCBP 2023, Washington DC

A Demonstrative Example



Adopted from Geoffrey Wu: FDA's Current Effort in Structured Product Quality Submission (aka PQ/CMC) At WCBP 2023, Washington DC

What is KASA?

Knowledge-Aided Assessment and Structured Application

A data-based platform for structured quality assessments of applications that supports knowledge management.

- Captures and manages knowledge during lifecycle
- Establishes rules and algorithms for risk assessment, control and communication for product, manufacturing, and facilities
- Performs computer-aided analyses
- Provides framework for a structured quality assessment

Modified from Sau Larry Lee: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022

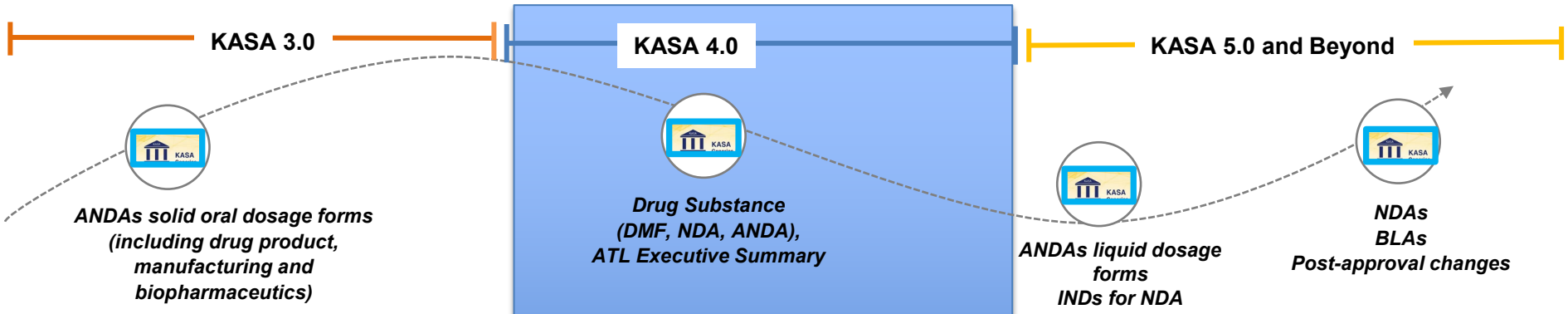
Agency's KASA system

- In 2016 CDER/OPQ's KASA system was envisioned as a means of modernizing FDA's assessment by taking advantage of Structured data, Advanced analytics and Knowledge management.

- KASA is an internal assessment tool intended to streamline practices already in place for assessments, increasing efficiency and consistency.

- KASA will support:
  - Efficiency gains through focused assessment of risk parameters
  - Streamlined assessment using concise dropdown menus to replace long written text, generation of direct links to a content in submission
  - Consistent assessment across product lifecycle
  - Standardized knowledge management/analytics

Roadmap for KASA IT Production



KASA 3.0	
2021	KASA 3.0 Release (Feb. 2021): Drug product, Biopharm, and Manufacturing KASA modules for generic solid oral drug products
2022	KASA 3.2 Release (Feb. 2022): Updates to the interface and data analytics

Completed Targets

KASA 4.0	
2023	KASA 4.0 Release: Drug substance (DMF, NDA, ANDA) modules KASA 4.1 Release: ATL Executive summary

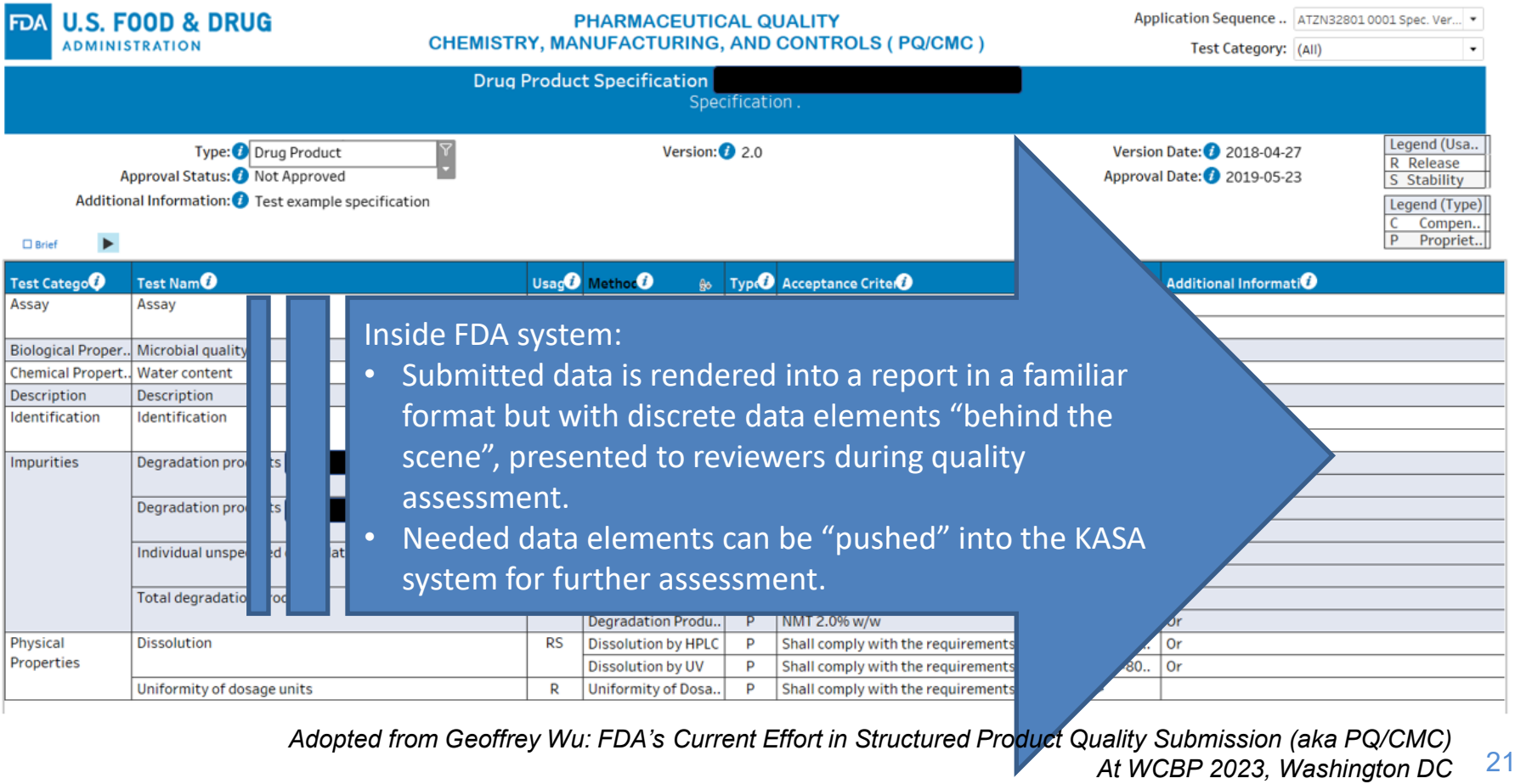
KASA 4.0 deployed in March of 2023

KASA 5.0 and beyond	
2024 - 2027	ANDA liquids dosage forms INDs for NDA NDA Drug product BLA • INDs for BLA • DS/DP/viral safety • Analytics/Biosimilars ANDA, NDA, BLA Supplements

Future Targets

Updated from Andre Raw: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022

A Demonstrative Example



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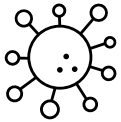
Development approach for KASA and PQ/CMC projects for biological products



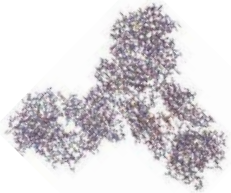
Biological Products vs Small Molecule Drugs

- PQ/CMC
  - Requirements for each CMC element are being developed accounting for applicability to product (biological vs small molecule drugs), dosage form (injectable, oral solid, etc.)

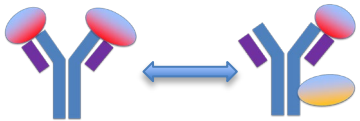
- KASA
  - Platforms are being developed specific for biological or for small molecule products, while some modules will have a common structure

Specific Considerations for Biological Products

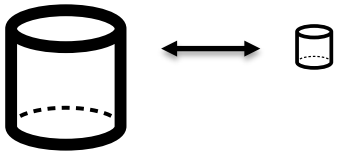
Biological Products can be highly complex



Molecules may have indication specific CQAs

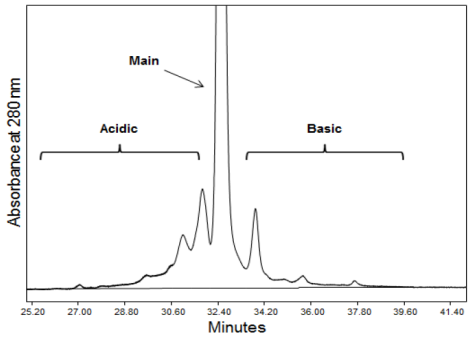


Many controls/parameters must be established based on small scale models (e.g., viral clearance)



Biological products may contain product-related substances (retaining activity) as well as product-related impurities

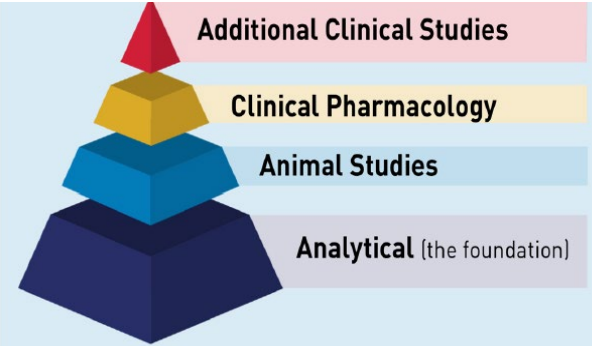
CQAs may not always be fully resolved by a given method



Modified from Joel Welch: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022

Biological Products Offer Unique Opportunities

Biosimilars and role of analytics



Explosion in use of “Platform” and “Modular” manufacturing approaches

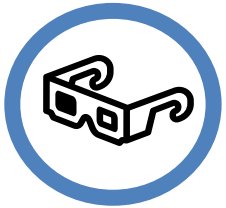
Informatics power in identifying molecules of same target/pathway

Unique submission elements (e.g., completed Process validation) are needed for PQ/CMC and suitable to KASA

Modified from Joel Welch: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022

KASA for Biologics Roadmap

Development of Early Prototype Approach



Dec 2019 – Mar 2021

Drug Substance Manufacturing and Viral Clearance Development

Strategy for individual modules and programming

Mar 2021 – Present

Prototype Development

Pilot Evaluation and Continued Development

Present – FY 2024

Collaboration and Refinement

KASA 8.0

(8.1, 8.2, 8.3)

FY 2025+

Phased Integration

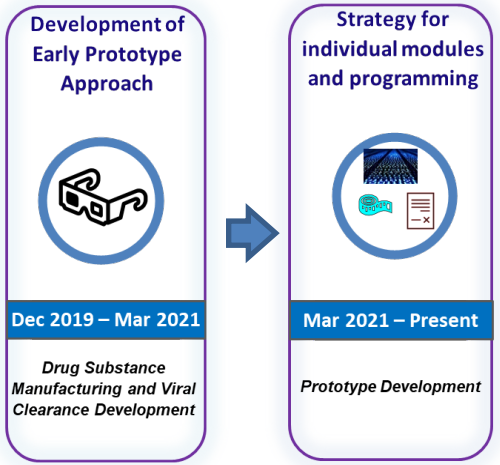
OPQ Internal development and evaluation

Implementation

Adopted from Joel Welch: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022

Biologics KASA Prototype Modules & Key Features

- Modules developed and in roll out:
  - DS manufacturing - *risk-based assessment* based on OBP expertise and scientific consensus
  - Viral clearance/Adventitious agents testing
  - Comparative analytical assessment – in development
- Designed for fed-batch monoclonal antibody BLAs that represent the majority of BLA submissions
- Able to capture revisions during assessment cycle
- Designed to be consistent with ICH concepts



- Modules apply to new BLAs (though framework can be adapted for supplements)

OBP KASA at a Glimpse – DS Manufacturing

Select Unit Operations Included in the Application

Cell Culture - Harvest	Cell Culture - Production Bioreactor	Cell Culture - Seed Bioreactor
Cell Culture - Vial Thaw and Inoculation Expansion	Chromatography - Anion Exchange	Chromatography - Cation Exchange
Chromatography - Hydrophobic Interaction	Chromatography - Mixed Mode	Chromatography - Protein A
Ultrafiltration/Diafiltration	Viral Filtration	Virus Inactivation - Low pH
Perfusion Production Bioreactor	Perfusion Seed/Pre-production Bioreactor	Add New Unit Operation

Selection for unit operations

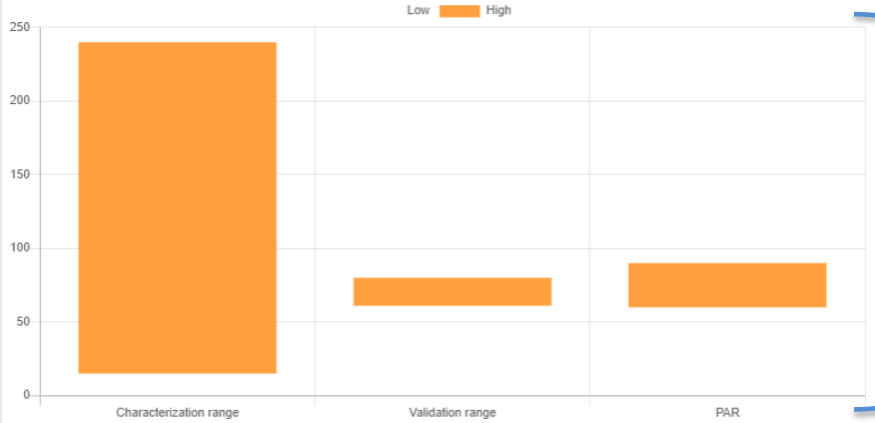
Expandable to include additional unit operations

**Data you see in the slides are mock data for presentation purpose*

OBP KASA at a Glimpse – DS Manufacturing

**Data you see in the slides are mock data for presentation purpose*

Process parameter	Duration (Low pH)	minutes	
Has the process parameter been characterized?	Yes (Characterization data)		IR
Is the characterization study appropriate?	Yes Characterization is appropriate	Comment included inside	IR
Characterization range:	15	240	IR
Has the process parameter been validated?	Yes	Assessor Comment(s)	IR
Validation range:	61	80	IR Graph
Proposed process parameter range:	60	90	IR Graph



Is the proposed PAR acceptable:	Yes	Comment included inside	IR

Key Questions

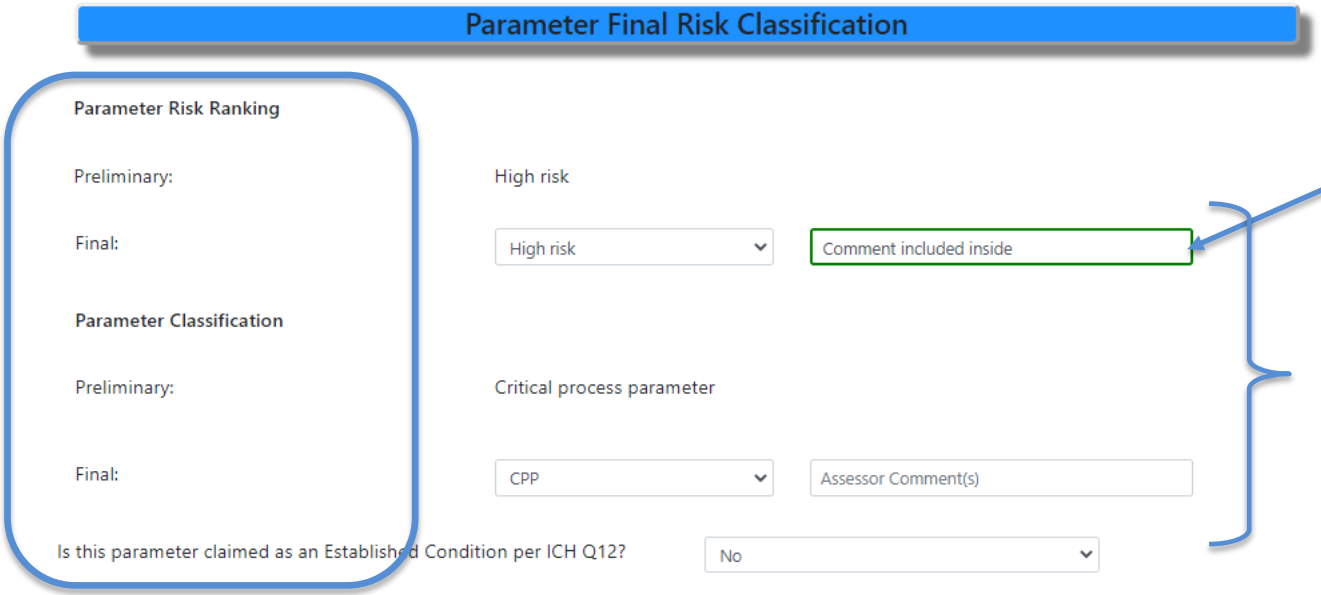
Link to Assessor's comment

Link to IR comment (resolved)

Visual Comparisons of Ranges

Assessor's conclusion

OBP KASA at a Glimpse – DS Manufacturing



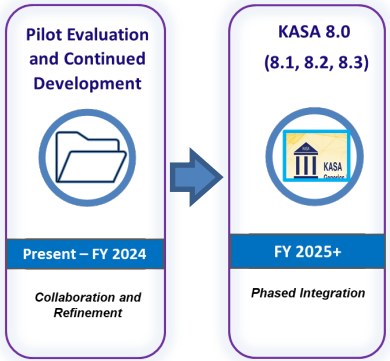
Link to Assessor's comment

Conclusion for Parameter risk

Key Questions

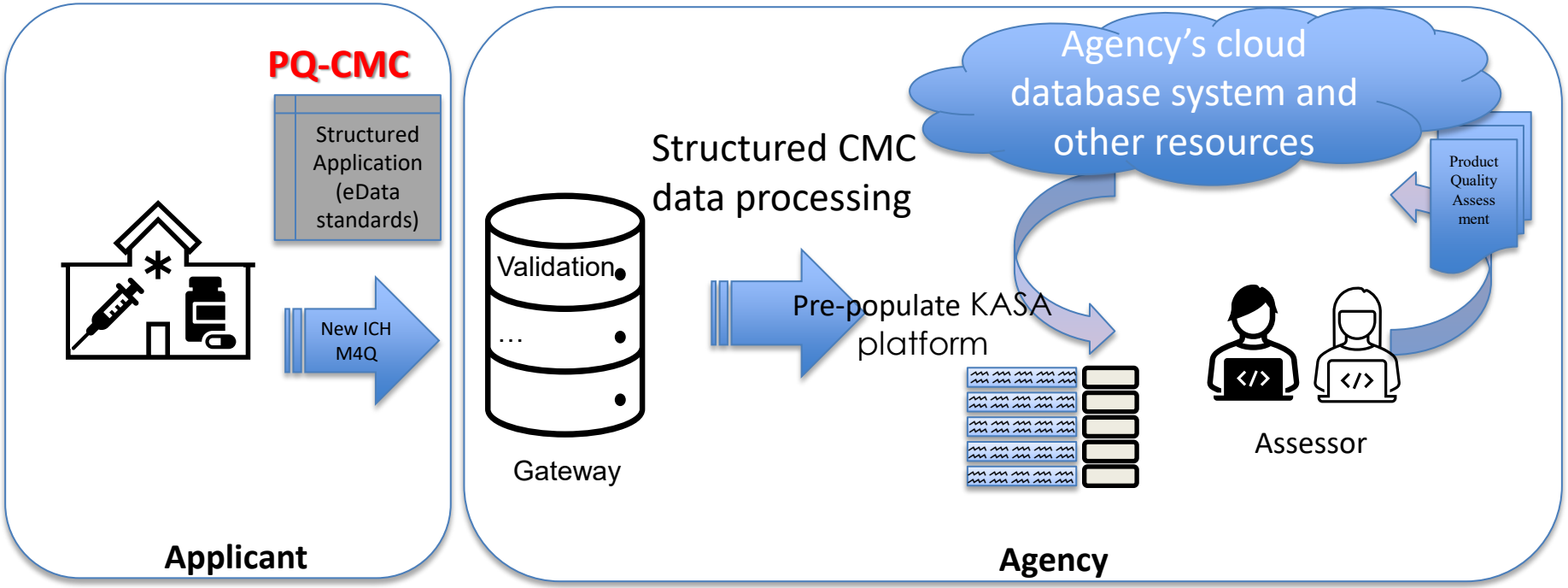
**Data you see in the slides are mock data for presentation purpose*

Biologics KASA: Ongoing Development & Integration Strategy



- Identify areas of existing KASA work from small molecules that can be leveraged
- Create additional modules and user requirements
  - Expansion of Manufacturing modules to additional cell substrates/product classes (e.g., E. coli, insulins) and additional unit operations (e.g., perfusion systems, DP manufacturing)
  - Additional modules covering Methods, Specifications, Comparative analytical assessment, etc.
- Develop a single platform with multiple modules covering manufacturing, controls and product quality for DS and DP
- Anticipate a phased implementation where inter-related topics are introduced in groups

Future CMC Data Submissions and Review



Content and organization of submission and electronic data standards

Integrated set of tools and framework to aid regulatory assessment and knowledge management

Envisioned Benefits of PQ/CMC and KASA

- Ensures Industry and FDA are using the “same data”
- For Industry
  - Could provide consistent formats for internal and external data management and storage (e.g., in LIMS), and data exchange with Contract Manufacturing Organizations
- For FDA
  - Receives consistent high-quality data that can be consumed by computer systems without data entry and interpretations
  - Operationalize submitted data to enhance the effectiveness of quality assessment – a significant enabler for KASA
- Facilitates the M4Q implementation and enhances global regulatory convergence

Modified from Geoffrey Wu: FDA’s Current Effort in Structured Product Quality Submission (aka PQ/CMC) At WCBP 2023, Washington DC

Envisioned Benefits of PQ/CMC and KASA

- KASA presents incredible opportunities for knowledge management, consistency in decision making, and improving efficiency for assessing pharmaceutical products
  - Development of KASA for biologics uses similar approaches and leverages the knowledge/systems from Small molecule drug KASA, as well as includes unique elements applicable only for protein products
- Accelerate the digitization efforts in both industry and FDA, eventually enhances lifecycle knowledge management (e.g., for crisis response)
- Accelerate the submission process by industry and assessment review by FDA, thus accelerating availability of drugs to patients

Acknowledgments

OBP KASA members:

- Joel Welch
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- Kristen Nickens
- Emine Guven-Maiorov
- Dilip Devineni
- Sireesha Vardhineedi
- Paul Xu
- Bazarragchaa Damdinsuren

Former members:

- Fabiola Gomez
- Pick-Wei Lau
- Ramesh Potla
- Christelle Yemeck

Other FDA contributors (slides):

- Steve Kozlowski
- Geoffrey Wu
- Norman Schmuff
- Andre Raw
- OPQ PQ/CMC Workgroup
- FDA PQ/CMC SME Group (Smita Hastak)
- and many others


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