FDA's KASA and PQ/CMC Initiatives: Perspectives for Biotechnology Products

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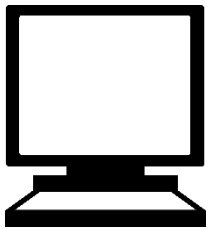
Pharmaceutical Quality

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




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.


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

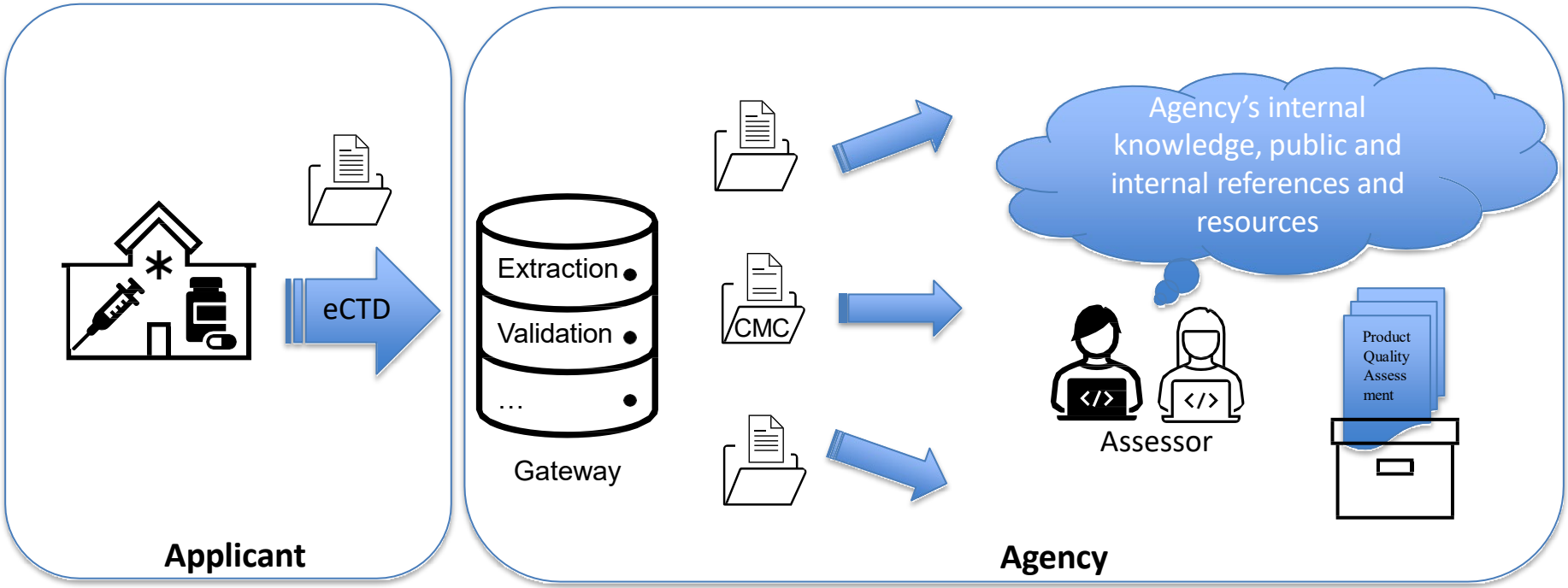
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

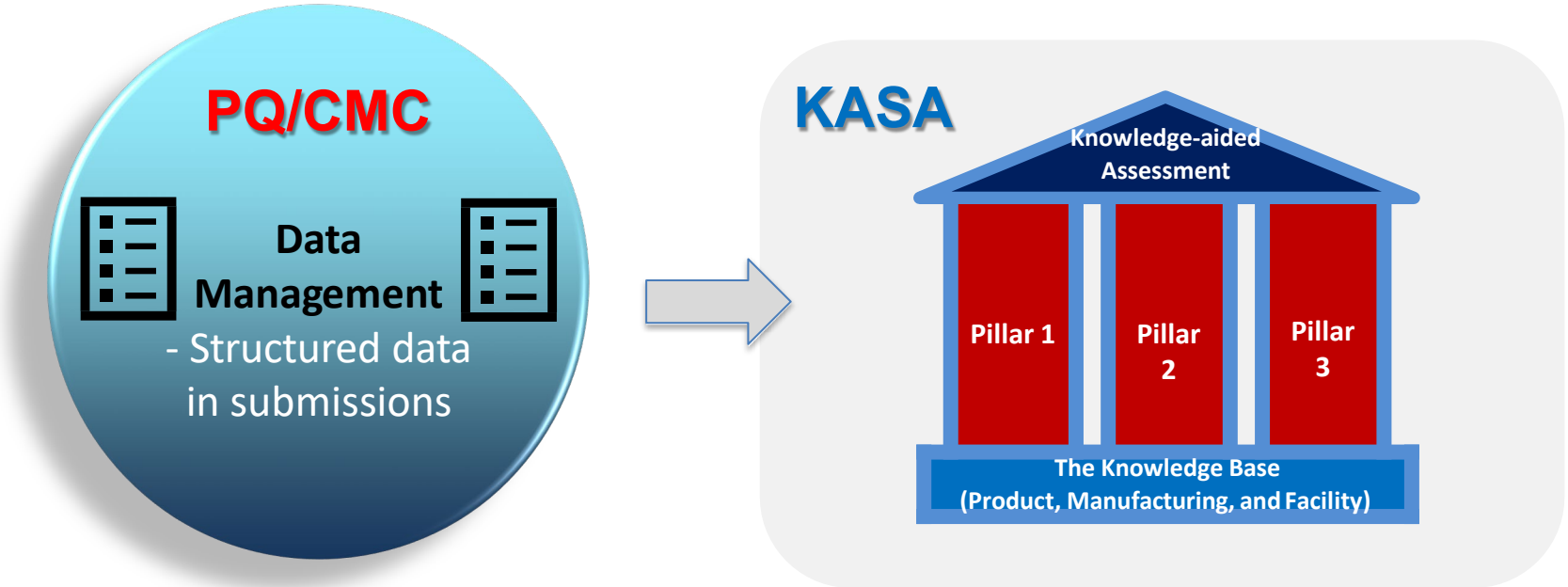
Overview

- Introduction to FDA's initiatives to support the new era of the submission and assessment
  - ✓ KASA
  - ✓ PQ/CMC
- Opportunities and challenges in KASA and PQ/CMC projects for biological products
- General development approach for KASA modules for biotechnology products

Current CMC Data Submissions and Review



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



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

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

What is PQ/CMC?

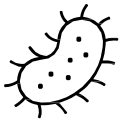
Pharmaceutical Quality/Chemistry, Manufacturing and Controls

- Establish electronic standards for submitting CMC data
- Develop structured data* standards for CMC information
- Implement a data exchange standard for submitting PQ/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.

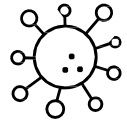
Modified from Sau Larry Lee: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022



Unique Opportunities and Challenges for Biological Products

- 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, however some modules will have a common structure



KASA System for Biological Products

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

Key Objectives of KASA System for Biological Products

1. Capture and **manage knowledge** during the lifecycle of a drug product

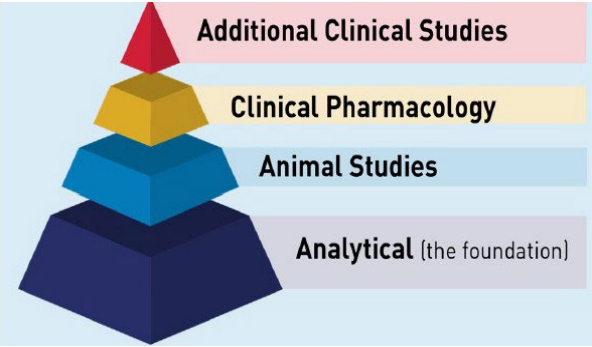
2. Establish **rules and algorithms to facilitate** risk identification, mitigation, and communication for the drug product, manufacturing process, and facilities

3. Perform **computer-aided analyses of applications** for a comparison of regulatory standards and quality risk across the repository of approved drug products and facilities

4. Provide a structured assessment that **radically eliminates text-based narratives** and summarization of information from the applications

Biological Products Offer Unique Opportunities

Biosimilars and role of analytics



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

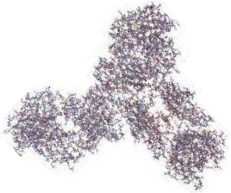
Unique submission elements (e.g., completed Process validation) are particularly suitable to KASA

Informatics power in identifying molecules of same target/pathway

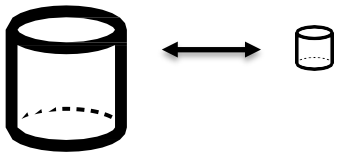
From Joel Welch: Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting. 11/3/2022

Specific Considerations for Biological Products KASA

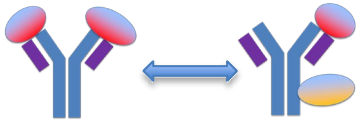
Biological Products can be highly complex



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

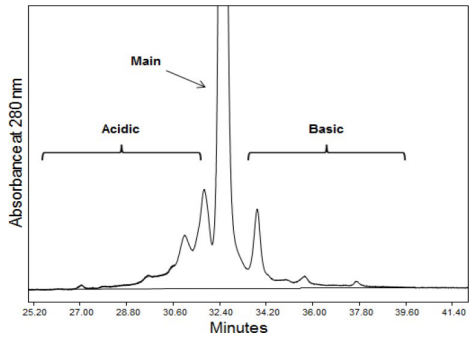


Molecules may have indication specific CQAs



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



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

Current Progress of KASA and PQ/CMC Projects

- PQ/CMC
  - On March 18, 2022, FDA published a second* FRN (FDA-2022-N-0297-000) "Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls Data Exchange; Request for Comments"
  - Covers 194 elements in 12 sections

- KASA (Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, 11/3/2022)
  - OPQ developed KASA platforms for solid oral dosage forms ANDA and in progress for other product types
  - OBP is leading a development of a KASA prototype for biological products

* Initial FRN (FDA-2017-N-2166-0001), September 11, 2017

PQ/CMC Scope & Phases

Phase 1 – *draft completed*

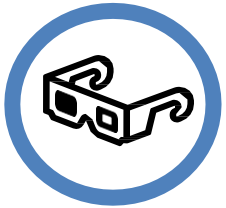
1. Specification
2. Batch Information (Drug substance/Drug product)
3. Batch Analysis
4. Stability Study
5. Stability Analysis
6. Nomenclature of Drug Substance
7. Composition of Drug Product
8. Batch Formula
9. Drug Substance – Control of Materials
10. Drug Product – Control of Excipients
11. Drug Substance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

Phase 2 – *in progress*

FRN (#2022-05790) "Draft Pharmaceutical Quality/Chemistry Manufacturing and Controls Data Exchange; Request for Comments" was published on March 18, 2022

KASA for Biologics Roadmap

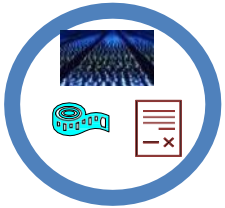
Development of Early Prototype Approach



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

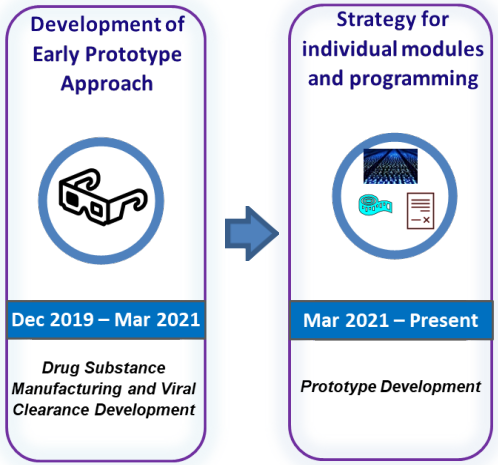
OPQ Internal development and evaluation

Implementation

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

Biologics KASA First Prototype Modules

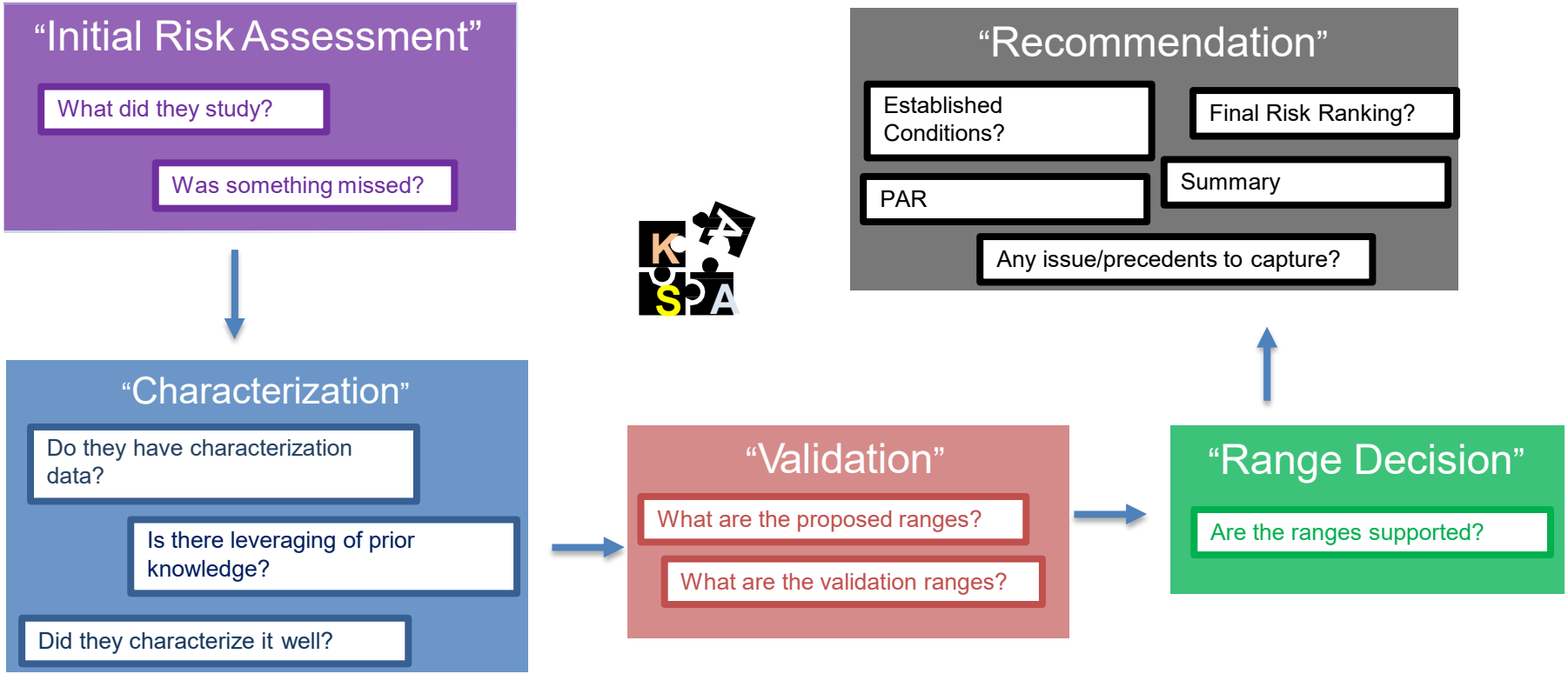
- Designed for fed-batch monoclonal antibodies BLAs that represent the majority of BLA submissions
- Prototypes apply to new BLAs (though framework can be adapted for supplements)
- Two prototype modules created:
  1. DS Manufacturing
     - Designed to capture description for manufacturing steps
     - Process parameter risk-based assessment and range evaluation
     - Key elements that aren't characterized, but need to be described
  2. Viral Clearance/Adventitious Agents Testing



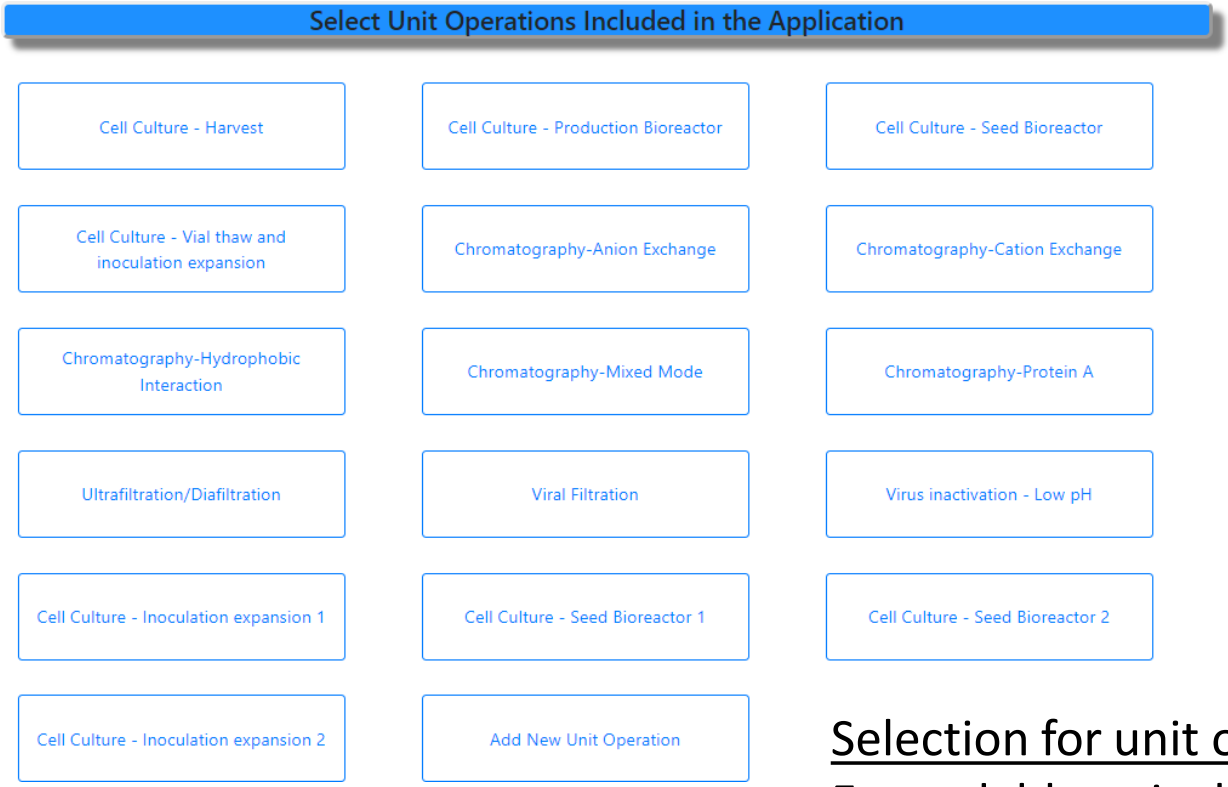
Key Features of Biologics KASA Prototypes

- For risk-based assessment for DS manufacturing
  - Data submitted by the applicant can drive risk ranking up or down. Initial risk ranking based on assessor expertise and scientific consensus
  - Provides a clear connection between available development data, validation results, and the proposed acceptable ranges for critical process parameters
- For both DS manufacturing and Viral clearance/Adventitious agents modules:
  - Flags for assessment issues and IRs (to facilitate discussion between primary and secondary assessors)
  - Able to capture revisions during assessment cycle
  - Designed to be consistent with ICH Q12 concepts
  - Does not include microbiology and facility portion yet

Decision Making Overview for KASA prototype on DS Manufacturing



KASA at a Glimpse – DS Manufacturing



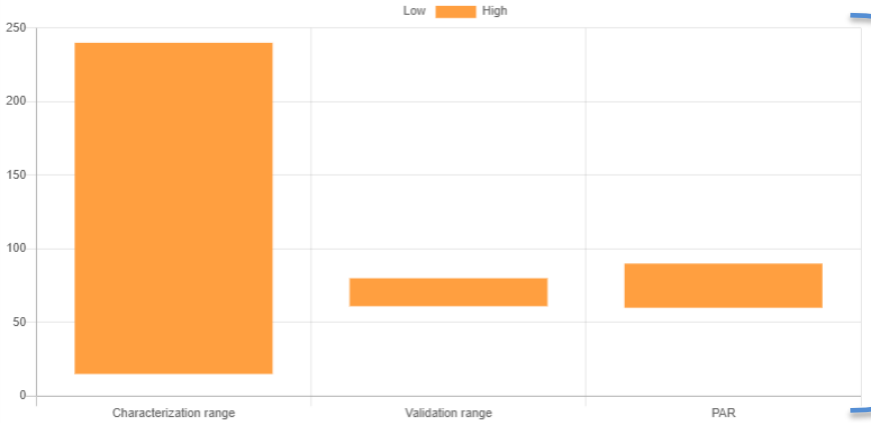
Selection for unit operations
Expandable to include additional unit operations

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

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

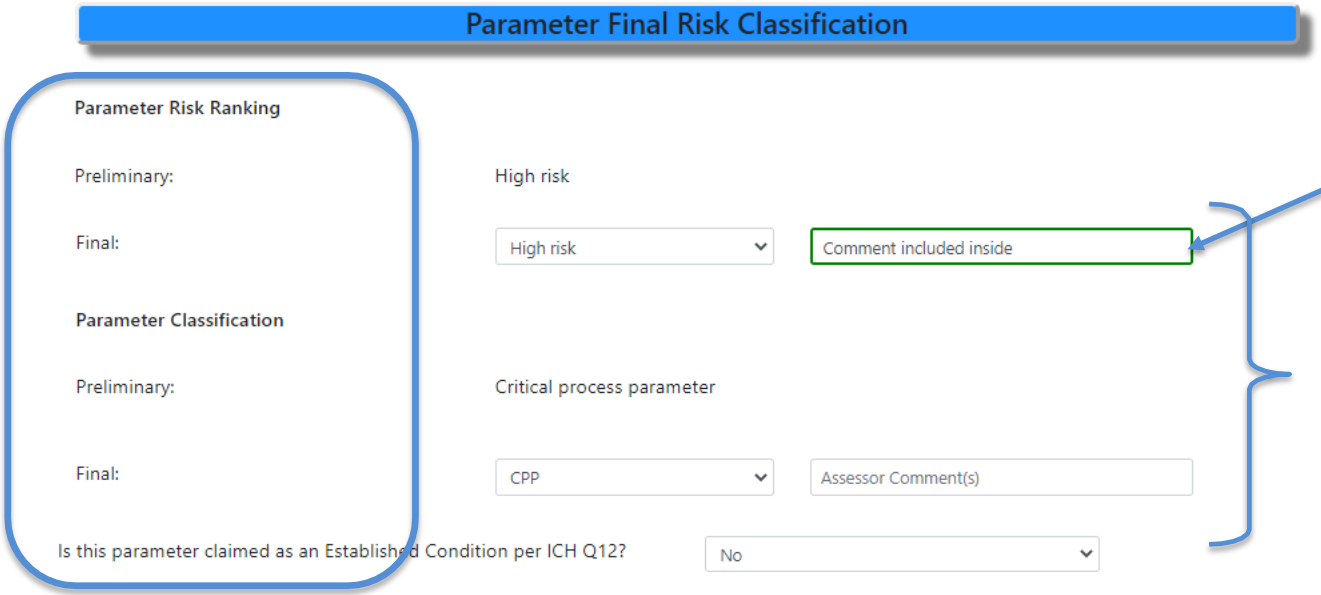
Link to Assessor's comment

Link to IR comment (resolved)

Visual Comparisons of Ranges

Assessor's conclusion

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*

Piloting and Ongoing Development

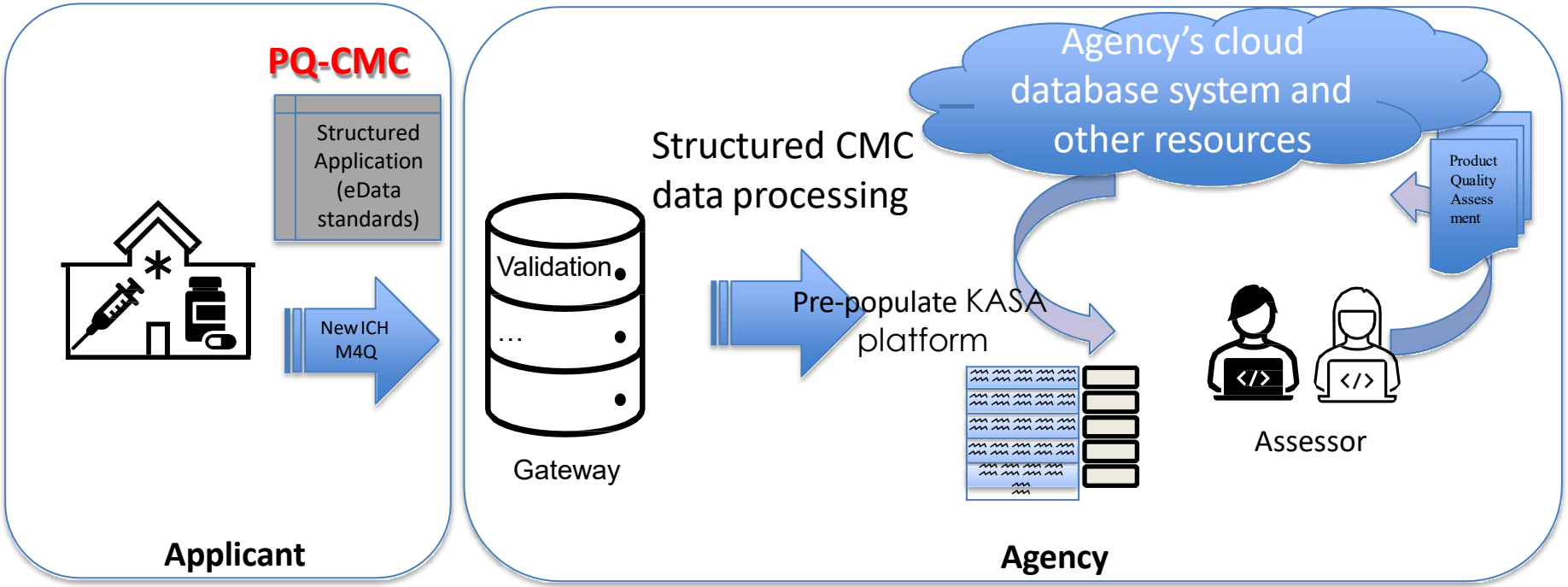
- Includes testing of system using already submitted applications as well as new applications
- Identifies gaps and outcomes from pilot experience

- Areas for the next expansion:
  - 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.

Integration Strategy

- Continue to use key learnings from pilot experience to create additional modules and user requirements
- Identify areas of existing KASA work from small molecules that can be leveraged
  - Facility and microbiological considerations
- 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

Conclusions

- KASA presents incredible opportunities for knowledge management, consistency in decision making, and improving efficiency for assessing biotechnology 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
- PQ/CMC development for structured data standards for CMC information is in progress considering specifics for biological products

Acknowledgments

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