Knowledge-Aided and Structured Application (KASA) and Pharmaceutical Quality/CMC (PQ/CMC) Update:

KASA for Biologics

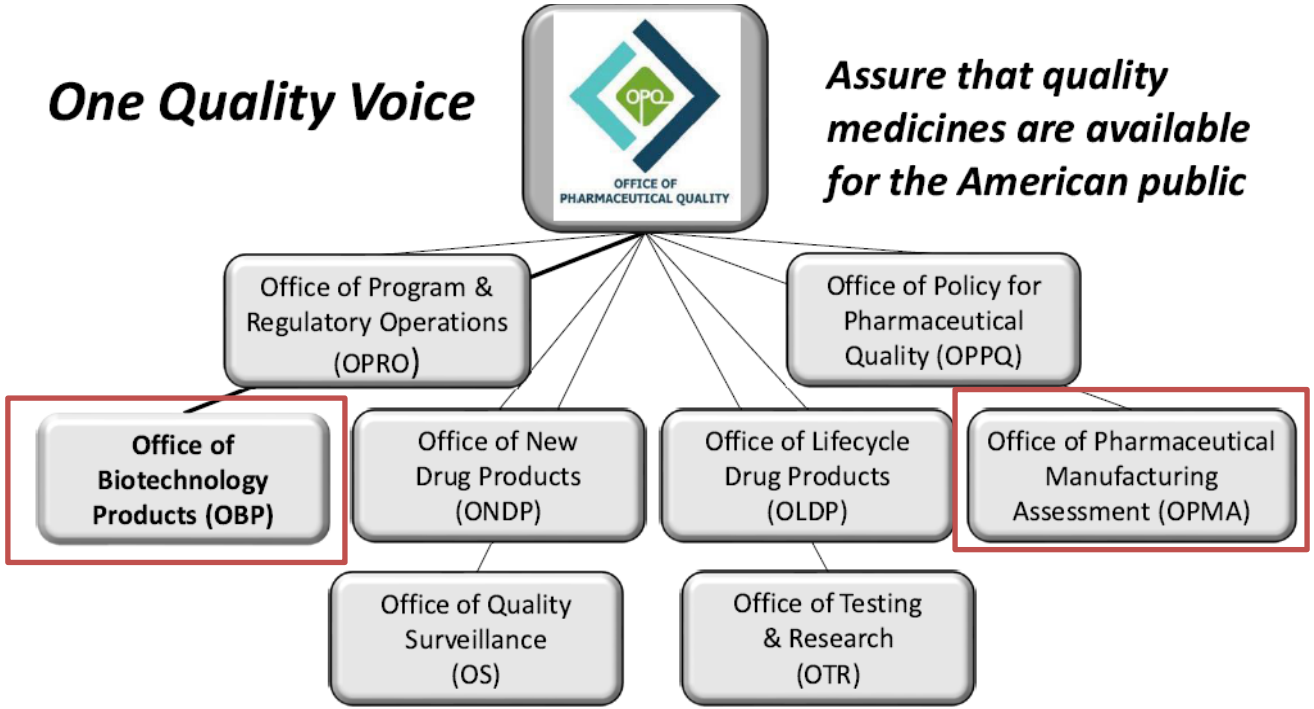
Steven Kozlowski, M.D.
Director, Office of Biotechnology Products,
Office of Pharmaceutical Quality, CDER, US FDA

5th FDA/PQRI Conference on Advancing Product Quality:
Advancing Quality & Technology of Future Pharmaceuticals
Virtual Event | December 1-3, 2021

Learning Objectives

- Understand the Key Benefits of the KASA System
- Identify the Unique Opportunities and Challenges for Biologics and KASA
- Explain the General Development approach for KASA modules for Biological Products in CDER

Offices involved in KASA for Biologics



OPMA responsible for microbiology and facility assessment

CDER Application Assessment Challenges

External Challenges

- Volume of new applications
- User fee program expectations
- Commissioner, Congress, the pharma industry, and the public expectations
- Technology advancements

Internal Challenges

- Freestyle narrative assessment:
  - Unstructured text
  - Summarization of application information
  - "Copy and paste" data tables
- Cumbersome knowledge sharing and knowledge management
- Subjective assessment based on the assessor's expertise and knowledge at hand

Key Objectives of KASA System

1. Capture and **manage knowledge** during the lifecycle of a drug product
   (Applicable for biological products)
2. **Establish rules and algorithms to facilitate** risk identification, mitigation, and communication for the drug product, manufacturing process, and facilities
   (Applicable for biological products)
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;
   (Applicable for biological products)
4. Provide a structured assessment that **radically eliminates text-based narratives** and summarization of information from the applications.
   (Applicable for biological products)

What's Different with Biological Products?

Nature of Process

Viral Safety, Aggregation, etc

Few "low risk" unit operations

DNA, HCP Clearance

Resin Lifetime

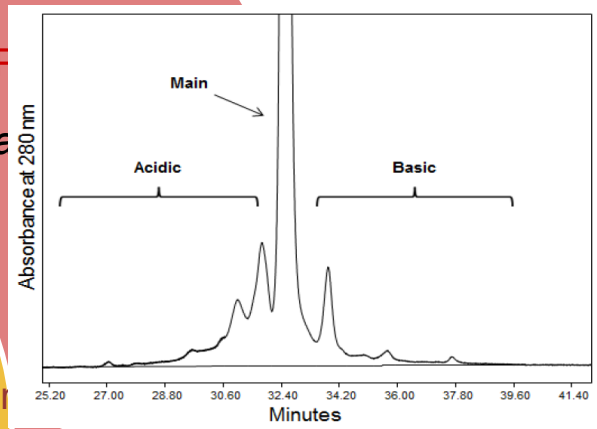
Small Scale Models

Spiking Studies

"Platform" Validation

Viral Clea

Data Submitted



Unique safety concerns

Retain Activity?

Product Related Substances vs. Impurities

COMPLEXITY

Adventitious Agents, Viral Clearance

Methods monitor multiple CQAs

Understanding of target and distribution

Mor[illegible]?

MOA

Molecular Function and Context

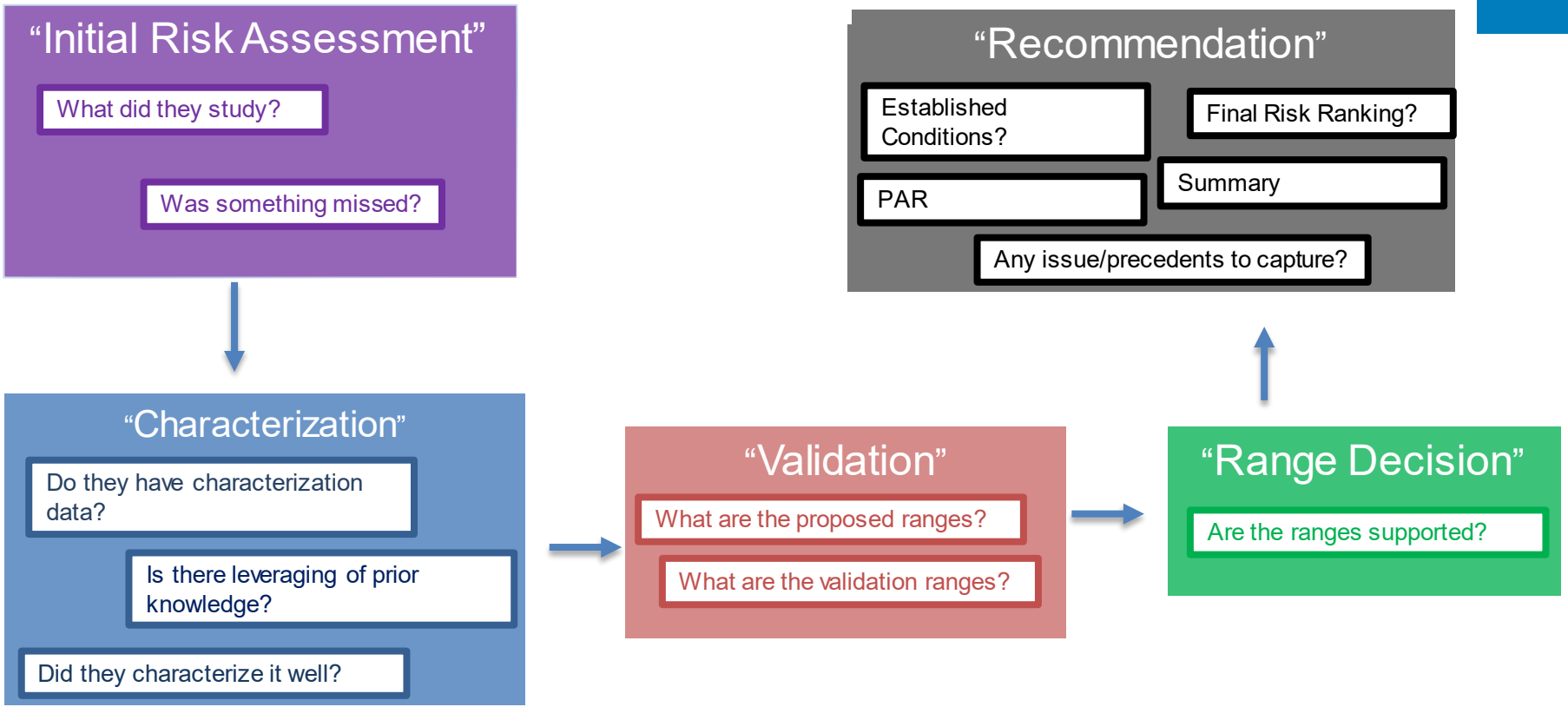
Biotechnology KASA First Prototype Module:

- A risk-based assessment module for drug substance manufacturing
- Applies only to fed batch monoclonal antibodies
  - The majority of BLA submissions
- Prototype applies to new BLAs (though framework can be adapted for supplements)
- Does not include microbiology and facility portion yet
- Designed to capture description for manufacturing steps, including:
  - Process parameter Criticality assessment
  - Process parameter Range evaluation
  - Key elements that aren't characterized, but need to be described

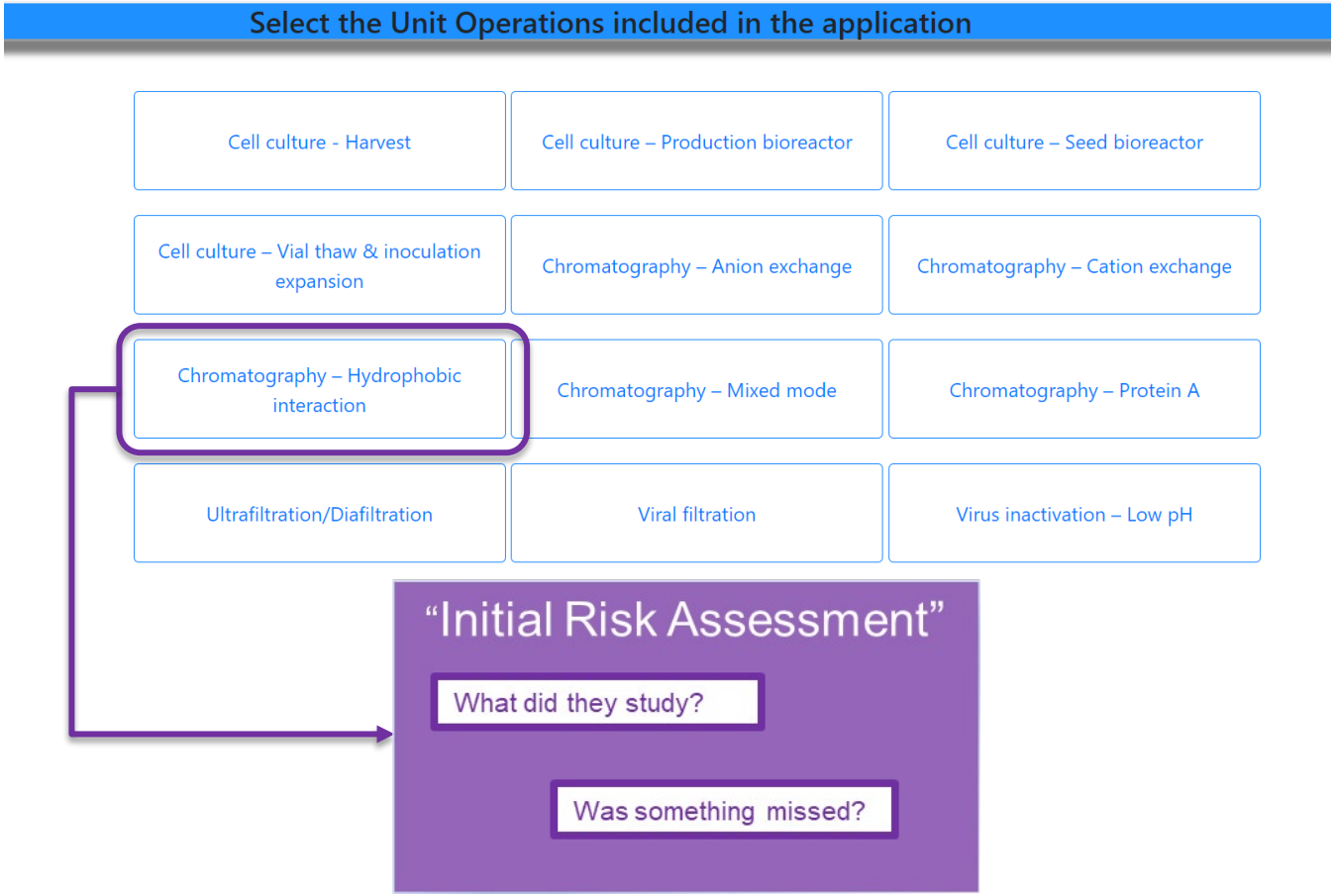
OBP KASA 1.x prototype: Key Features

- Data submitted by the sponsor can drive risk ranking up or down
- Initial risk ranking based on assessor expertise and scientific consensus
- Flags for assessment issues and IRs (to facilitate discussion between primary and secondary assessors)
- Able to capture revisions during assessment cycle
- Generates a summary output to be integrated in assessment document
- Designed to be consistent with ICH Q12 concepts

Basic Algorithm Module



KASA-DS Draft Glimpse



Unit Op Process Parameter

Enter unit for process parameter, if applicable

Wash Volume (CV)

"Characterization"

"Validation"

"Range Decision"

Has the process parameter been characterized? Yes (Characterization data) IR

Link to IR

Is the characterization study appropriate? Yes Characterization is appropriate | Additional comments | IR

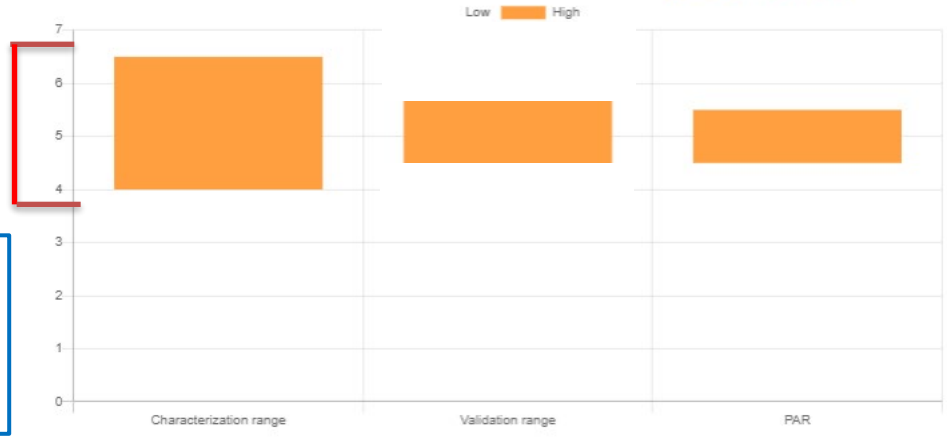
Characterization range 4 | 6.5 | IR

Is validation appropriate/acceptable? Yes | Additional comments | IR

Validation range 4.4 | 5.6 | IR | Graph

Proposed process parameter range 4.5 | 5.5 | IR | Graph

Comparisons of Ranges



KASA-DS Draft Glimpse

Is the proposed PAR acceptable Yes | Additional comments | IR

KASA Viral Clearance Module

Draft Glimpse

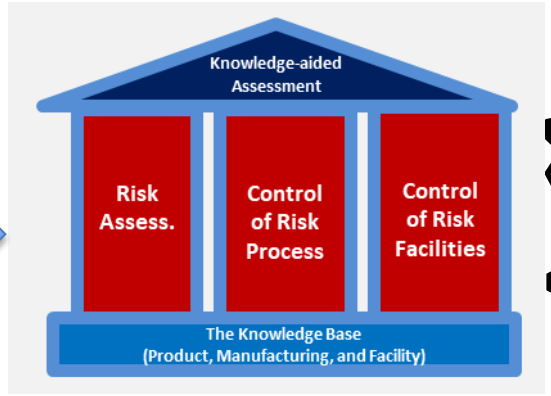
Select a Unit Operation for viral clearance study: Virus Inactivation - Low pH

Does VC study used a modular or platform approach? No

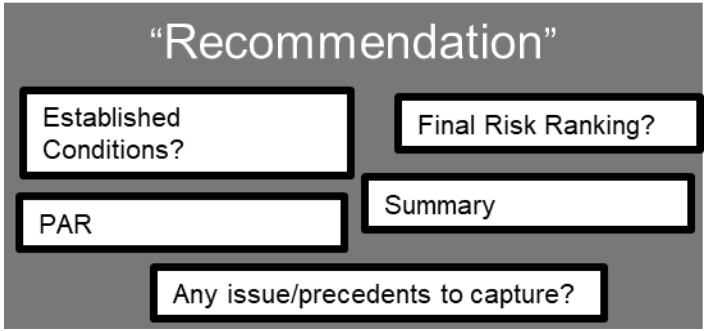
Process Parameters	Check Box (Link to Commercial Manufacturing Process)	Parameter Values
Hold Constant		
Liquid pH	☐	3.90-3.95
Liquid composition (i.e. buffer composition and molarity)	☑	
Protein concentration	☑	
Time	☐	5, 10, 20, 30, 55
Temperature	☐	14.5-15.4
Scaled Down		
Liquid Volume	☑	

Are Unitoperations for Viral Clearance study done? Yes

Structured Modules

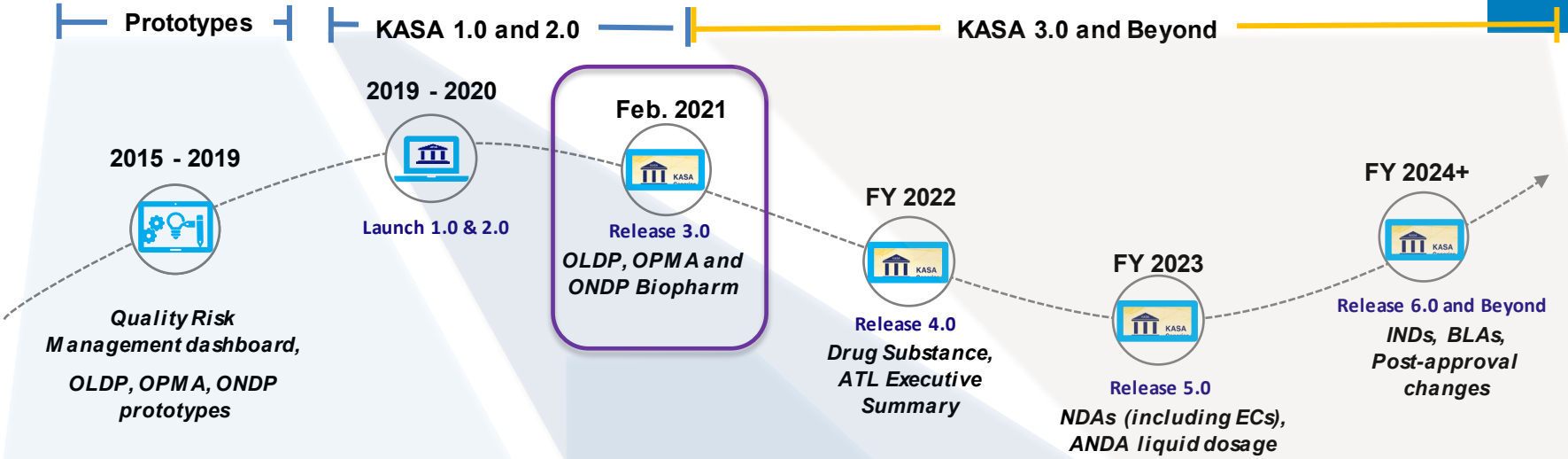


KASA



Knowledge Management

FDA KA(SA) Roadmap



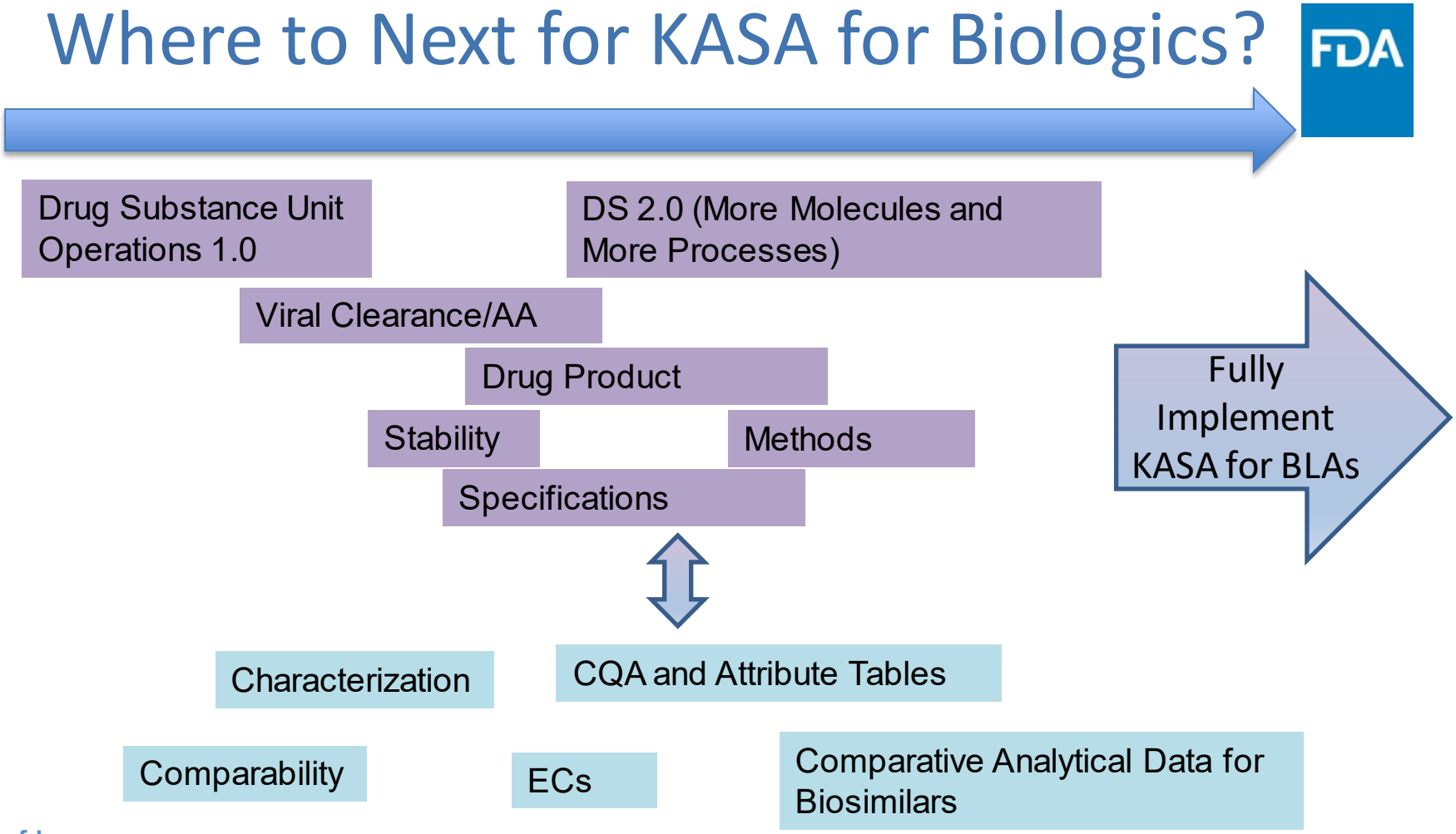
KASA Prototypes	
2015	Quality Risk Management dashboard
2016	Small team develops homegrown KASA prototype for solid oral dosage forms drug product assessment
2017	Multiple reiterations of the KASA for solid oral dosage forms drug product assessment are developed and tested
2018	Biopharm KASA prototype is developed and tested
2019	Manufacturing KASA prototype is developed and tested

KASA Release 1.0 & 2.0	
2019	KASA 1.0 for assessment of generic solid oral drug products is released
2020	KASA 2.0 for assessment of generic solid oral drug products is released

KASA Release 3.0	
FY 2021	Drug product, Biopharm, and Manufacturing KASA for generic solid oral drug products are rolled out

KASA Release 4.0 and Future Releases	
FY 2022	Develop Drug Substance Modules, ATL Executive summary
FY 2023	Develop KASA for New Drug Products including modules for ECs, and KASA for ANDAs liquid dosage forms
FY 2024	Develop IND Modules, Post Approval changes modules, and start work on BLA modules
FY 2025	Continue to develop BLA Modules

Where to Next for KASA for Biologics?



Conclusions

- KASA presents incredible opportunity for knowledge management, consistency in decision making, and improving efficiency
- KASA for biologics is beginning a pilot to assess its prototype modules
- The biologic KASA module builds on the same approach as others but includes unique elements based on nature of biotechnology products

Acknowledgments

- Larisa Wu
- Andre Raw
- Bazarragchaa Damdinsuren
- Pick-Wei Lau
- Kristen Nickens
- Ramesh Potla
- Brian Roelofs
- Fabiola Gomez
- Sireesha Vardhineedi
- Christelle Yemeck

Joel Welch


FDA
U.S. FOOD & DRUG
ADMINISTRATION