Knowledge-Aided Assessment and Structured Application (KASA): Part 1

Modernizing FDA's Regulatory Assessment

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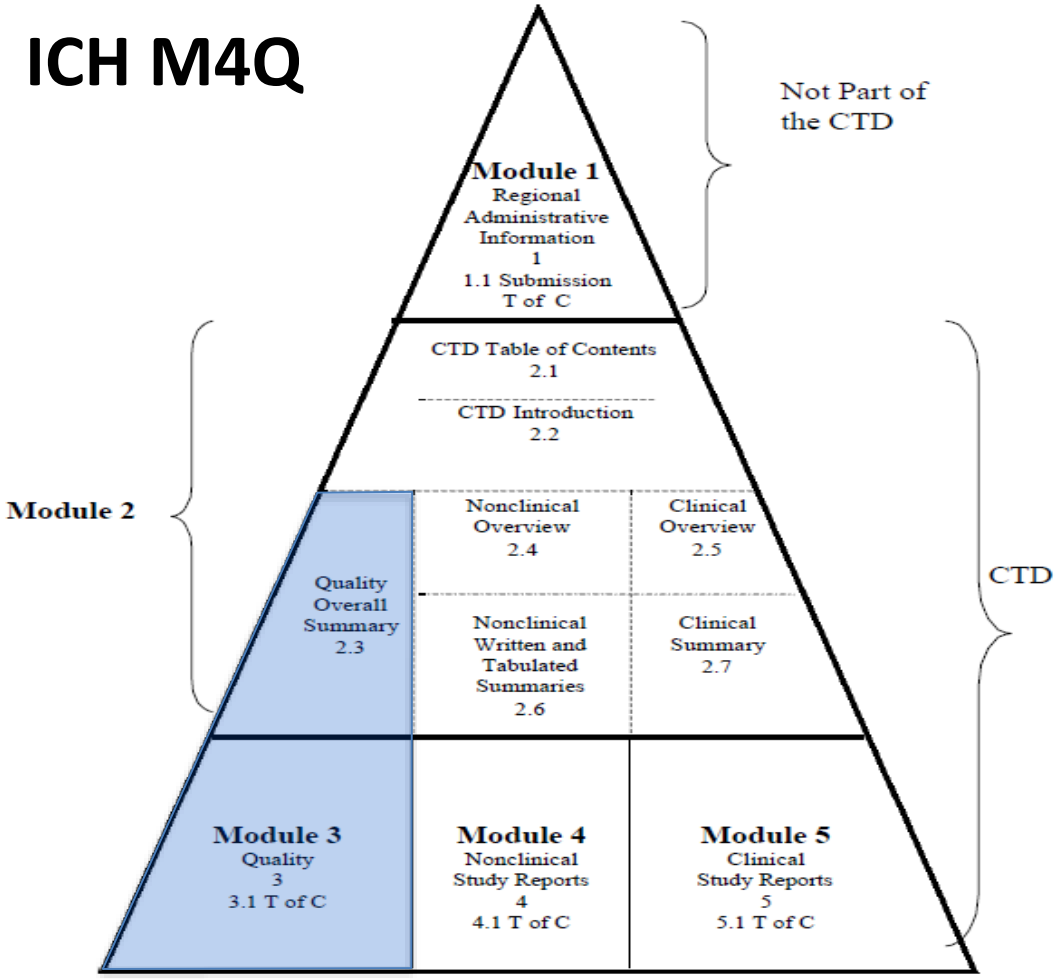
Pharmaceutical Quality Symposium 2021
October 26, 2021

FDA'S Pharm. Product Quality Journey

- Process Analytical Technology/Emerging Technology Program (PAT/ETP)
- Quality by Design (QbD)
- Integrated Quality Assessment (IQA)
- Concept of Operations for Facility Evaluation and Inspection For Human Drugs (ConOps)
- **FDA Quality Oversight New Initiative: Knowledge-aided Assessment and Structured Application (KASA)**

Regulatory Assessment

ICH M4Q



ICH The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality M4Q(R1) Quality overall Summary of Module 2; Module 3: Quality, September 2002

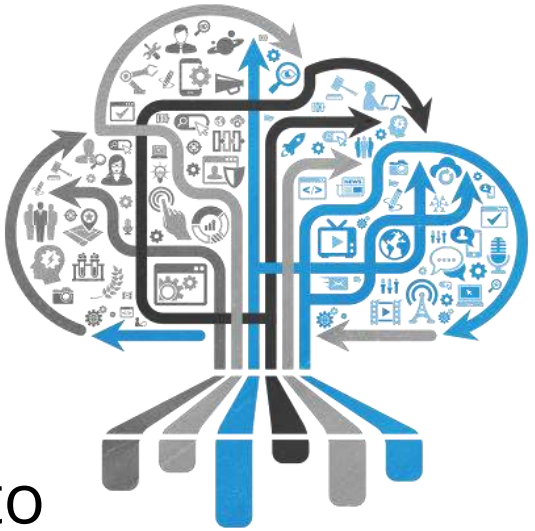
Read-Summarize Evaluate Approach

- Follow ICH M4Q(R1) Structure
  - US FDA Question-based Review
- Document assessment in MS Word; Archive in PDF
- Lengthy documents which are not searchable and difficult for knowledge management
- Industry voice “consistency”

Advancing Forward

We recognize the need to modernize

(20th → 21st century technology)

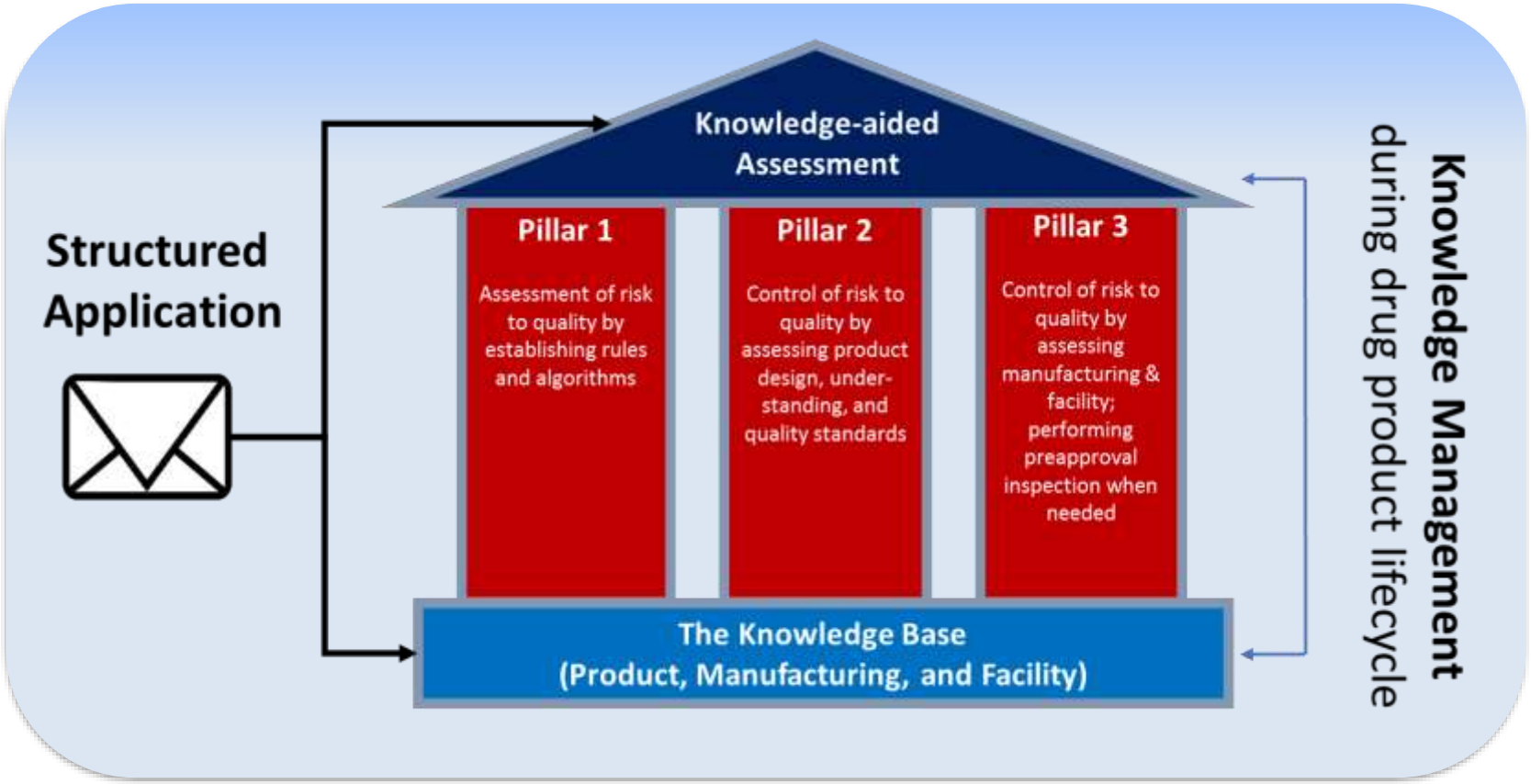


Move from narrative/unstructured data to **structured data*** in order to best capture/manage knowledge

Structured data is highly-organized and formatted so that it's easily searchable in relational databases. Unstructured data has no predefined format or organization, making it much more difficult to collect, process, and analyze.

KASA System

KASA – **K**nowledge-aided **A**ssessment and **S**tructured **A**pplication



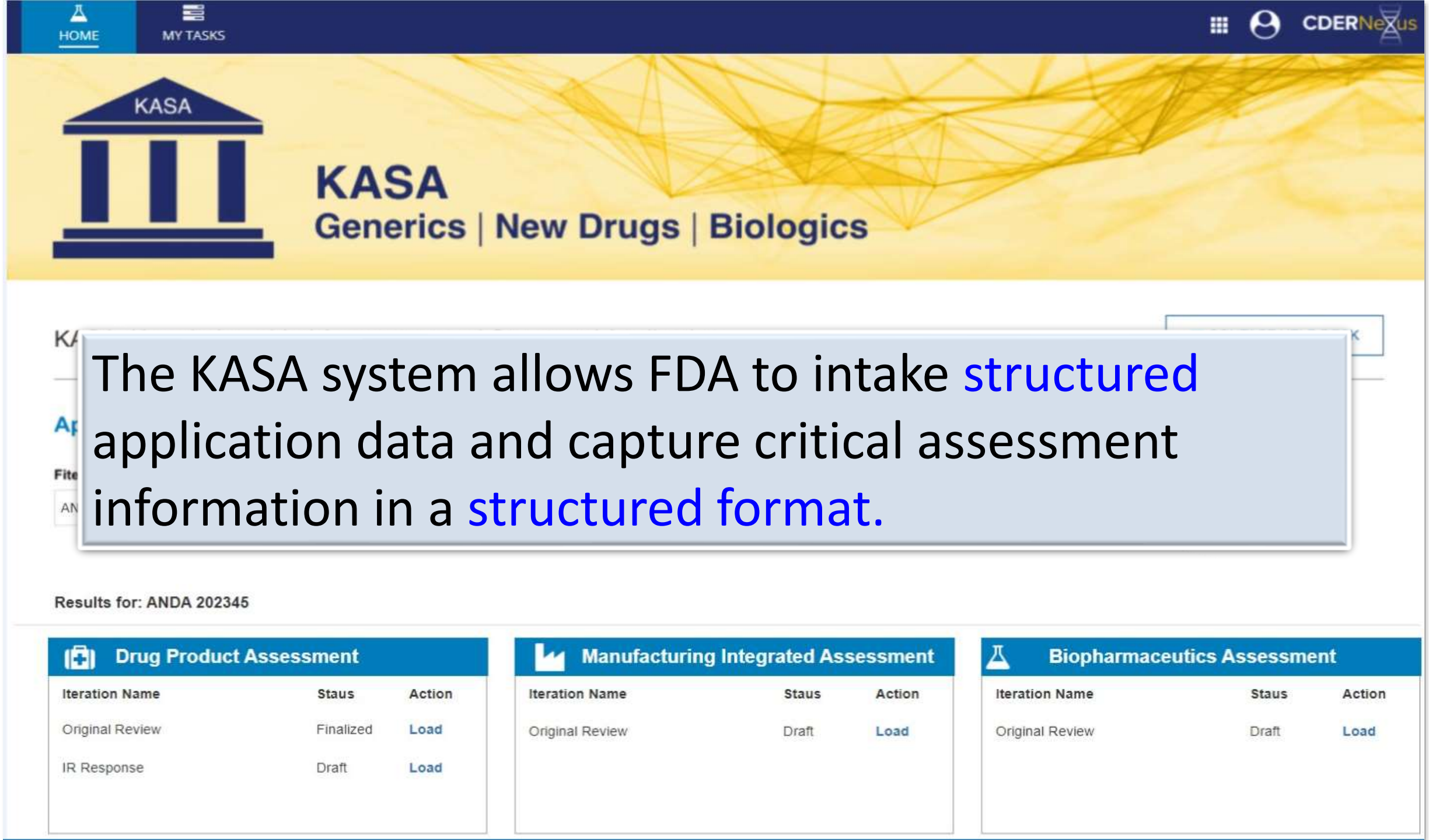
An advanced IT system for regulatory review and knowledge management using structured submission data.

Lawrence X. Yu, Andre Raw, Larisa Wu, Christina Capacci-Daniel, Ying Zhang, and Susan Rosencrance "FDA's New Pharmaceutical Quality Initiative: Knowledge-aided Assessment and Structured Applications" *International Journal of Pharmaceutics* (2019) https://www.sciencedirect.com/science/article/pii/S2590156719300246

Objectives

The KASA system is being designed to:

- Deliver a structured regulatory assessment and submission
- Institute rules and algorithms for risk management and decision-making
- Perform intelligent data analysis to establish regulatory standards
- Capture and manage knowledge during the lifecycle of a drug product


HOME
MY TASKS
CDERNexus
KASA
KASA
Generics | New Drugs | Biologics
The KASA system allows FDA to intake structured application data and capture critical assessment information in a structured format.
Results for: ANDA 202345
Drug Product Assessment
Iteration Name
Staus
Action
Original Review
Finalized
Load
IR Response
Draft
Load
Manufacturing Integrated Assessment
Iteration Name
Staus
Action
Original Review
Draft
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Biopharmaceutics Assessment
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OPQ Integrated Quality Assessment (IQA)

***Integrated Quality Assessment** = A team of experts performing a quality assessment of an application (**NDA, BLA, ANDA**) based on risk and knowledge management

KASA Development

FDA

Drug Product	Biopharmaceutics	Manufacturing	Drug Substance
Initial inherent DP risk based on DP characteristics	Biopharmaceutics risk based on risk assessment decision tree	Manufacturing risks from facilities and specific unit operations	Algorithm to calculate overall risk for predefined DS risk categories and impact on DS CQAs
Product risk control focuses on the drug substance characteristics, and drug product design, understanding, and control	Drug product risk control and mitigation focus from a Biopharmaceutics perspective	Manufacturing risk control and mitigation includes controls for specific unit operation and facilities/site capability and CGMP history	DS risk control and mitigation focuses on proposed synthetic pathway, DS manufacturing process and controls

KASA promotes consistency and objectivity of assessment

KASA for DS: Enhanced DS Risk Management

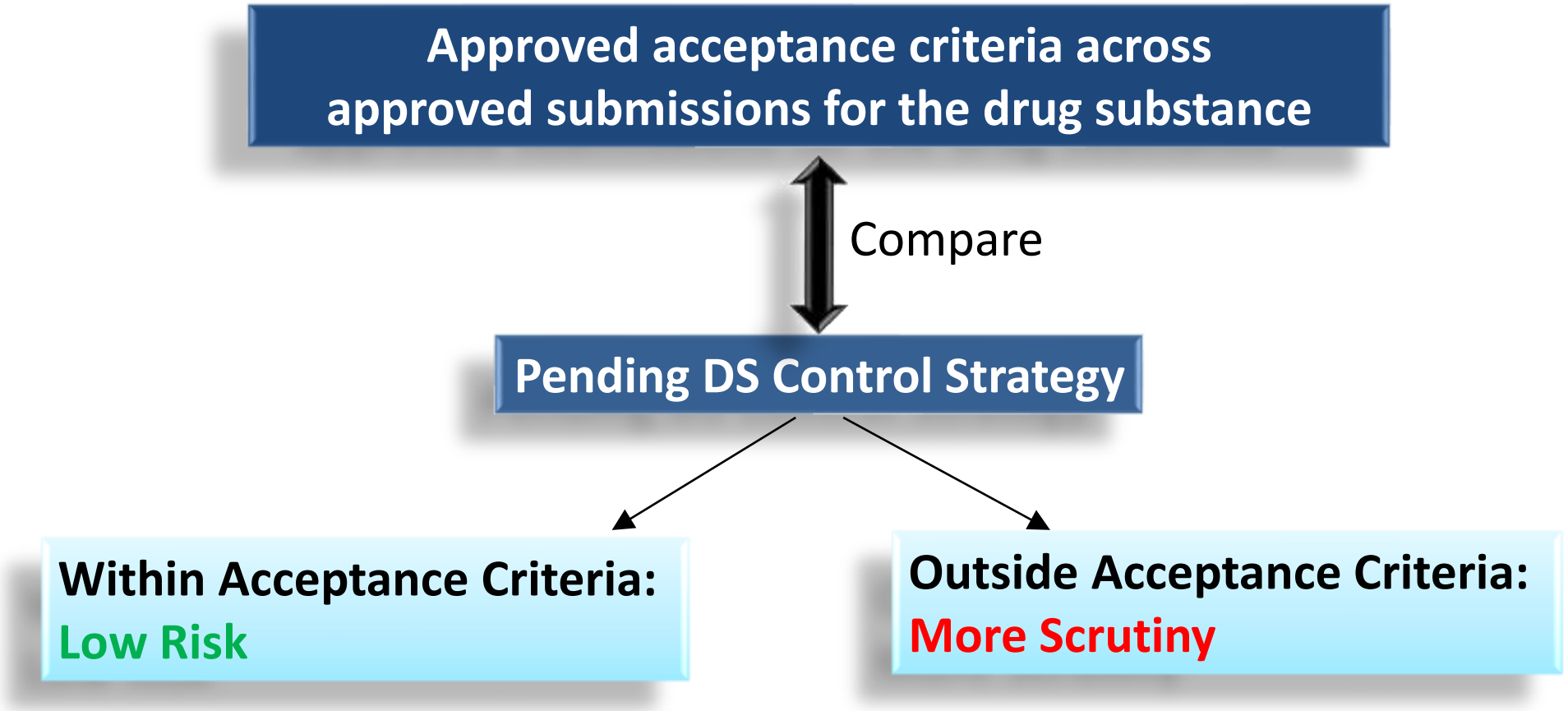
Risk Category	Impacted CQAs	Calculated Risk Level	Assessment Comment	Updated Risk Level	Deficiencies
Starting material	impurities	**Low**	Adequate.	**Low**	-
ID/ Characterization	assay	**Low**	Inadequate. Justification A	**Medium**	**Deficiency #1**
Stability	assay, impurities	**High**	Inadequate. Justification B	**Medium**	**Deficiency #2**

Consistent, objective, and quantitative risk assessment

Assessor can override final risk ranking, but must provide justification in the review assessment box.

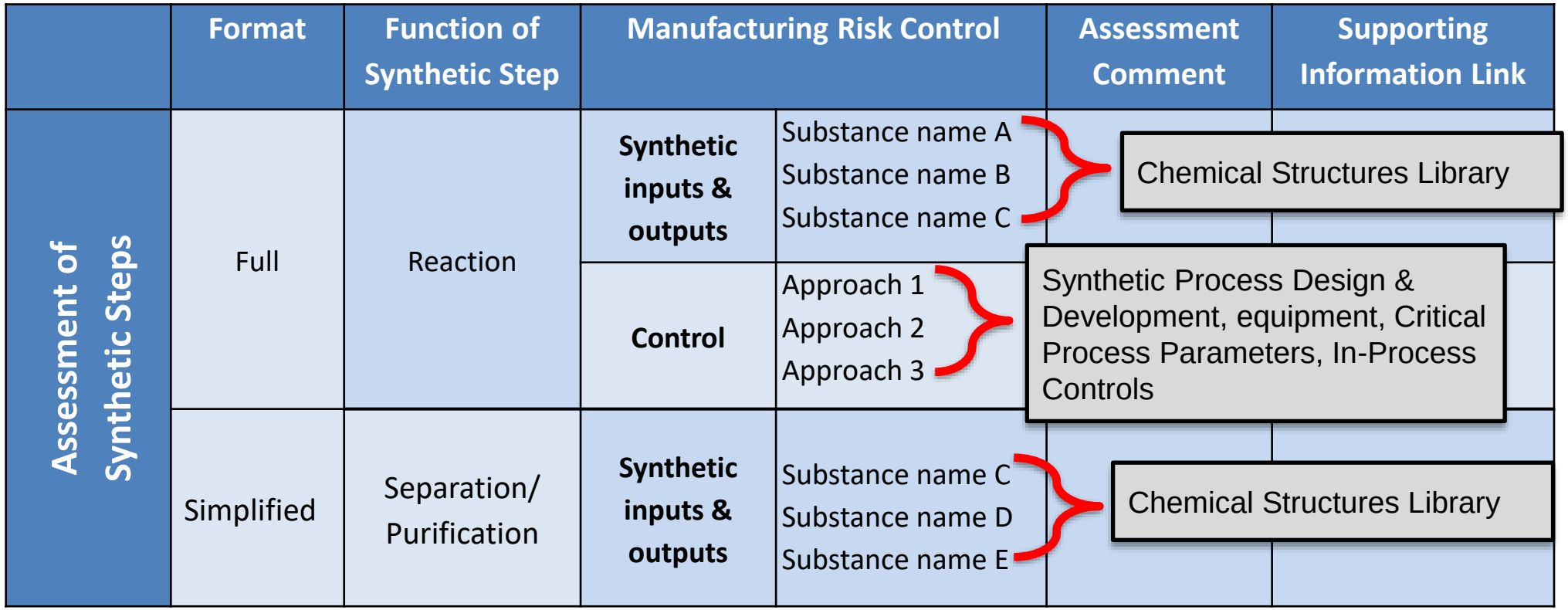
Assessment and deficiencies are aligned with the level of risk

KASA Analytics: Drug Substance (1)



KASA helps in identifying outliers in applications

KASA for DS: Structured DS Synthetic Pathway



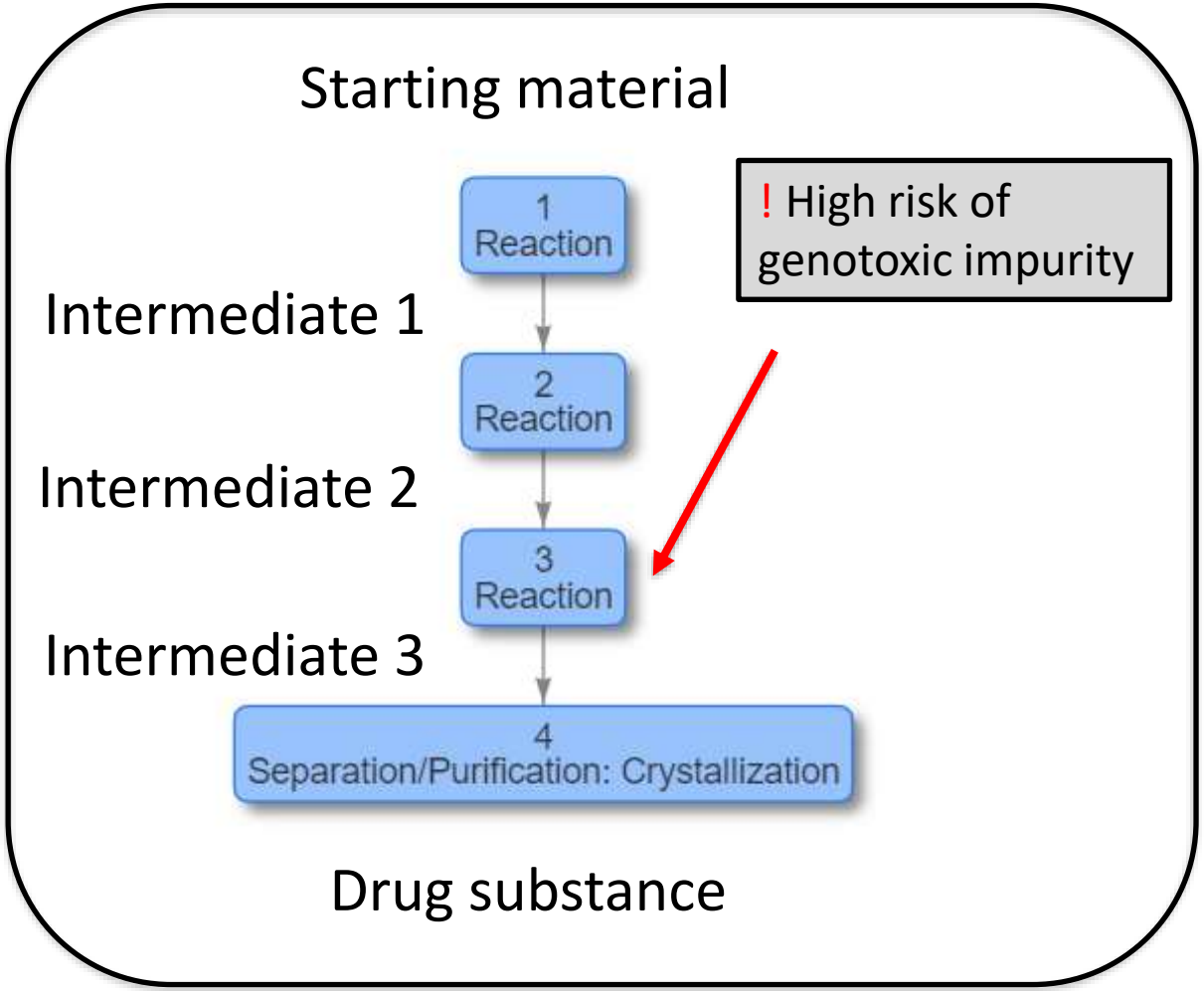
+ control of starting materials, control of intermediates, control of reagents

KASA Analytics: Drug Substance (2)

Data for each DS synthetic route captured in the KASA for DS platform is:

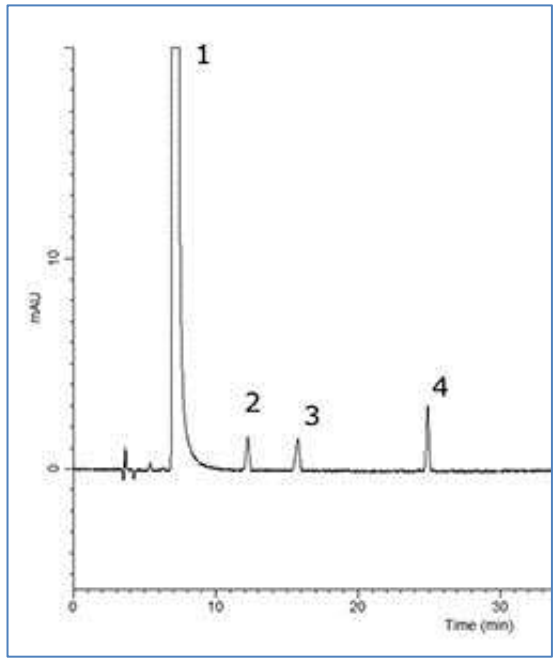
- searchable
- visualizable
- comparable

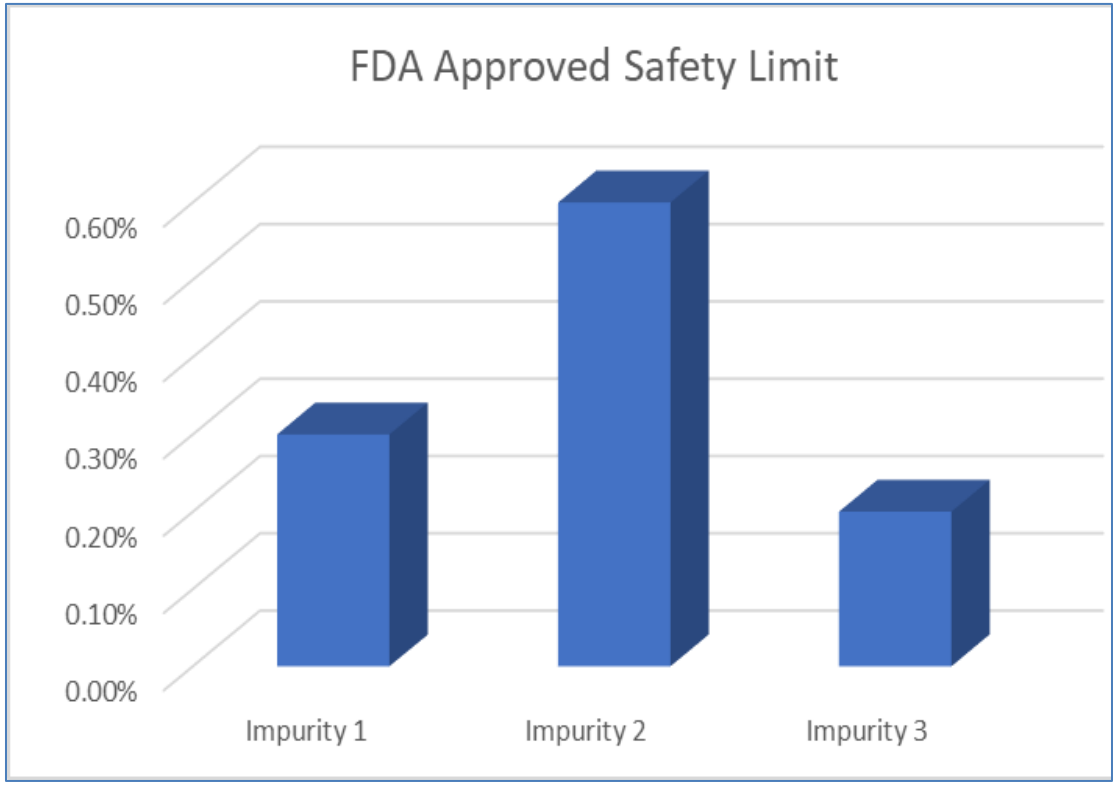
KASA improves overall efficiency and excels regulatory decision by improving the DS knowledge management



KASA Analytics: Drug Product Impurity

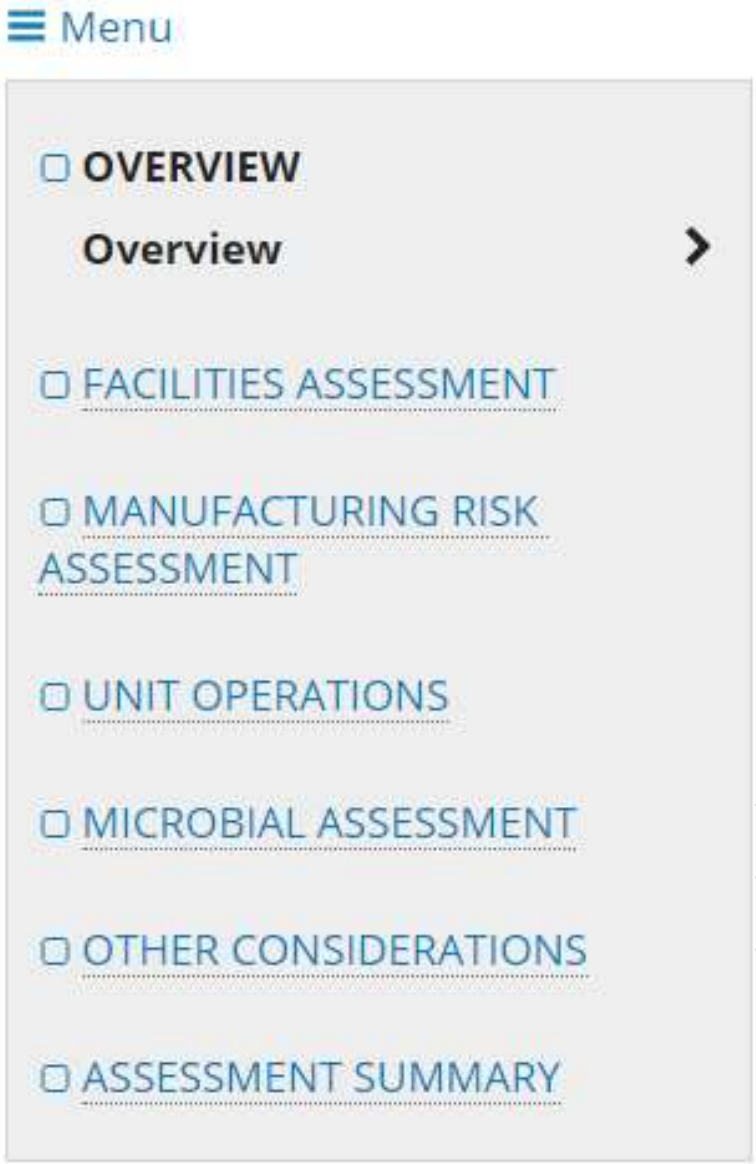
Compare impurity with the FDA approved limits





A chart of the FDA approved safety limits can be generated for comparison

KASA Analytics: Manufacturing



Knowledge-Aided Assessment Summary

Application	CQA impacted	Unit Operation	Initial Risk Assessment	Process Control Approach	Facility Status (GMP, etc.)	Pre-Approval Inspection (PAI) Needed?	Risk Assessment Post PAI
A	CU	Direct compression	High	Approach A	Approach C	**YES**	**LOW**
B	CU	Direct compression	High	Approach B	Approach A	**NO**	**MEDIUM – Rec. Surveillance inspection**
C	CU	Direct compression	High	Approach C	Approach C	**YES**	**HIGH – Potential withhold**

- **Intelligent algorithm capabilities for efficient risk assessments**
- **Informed decisions with access to other relevant information**
- **Conduit to investigators enhancing risk management of facilities**

Benefits of KASA

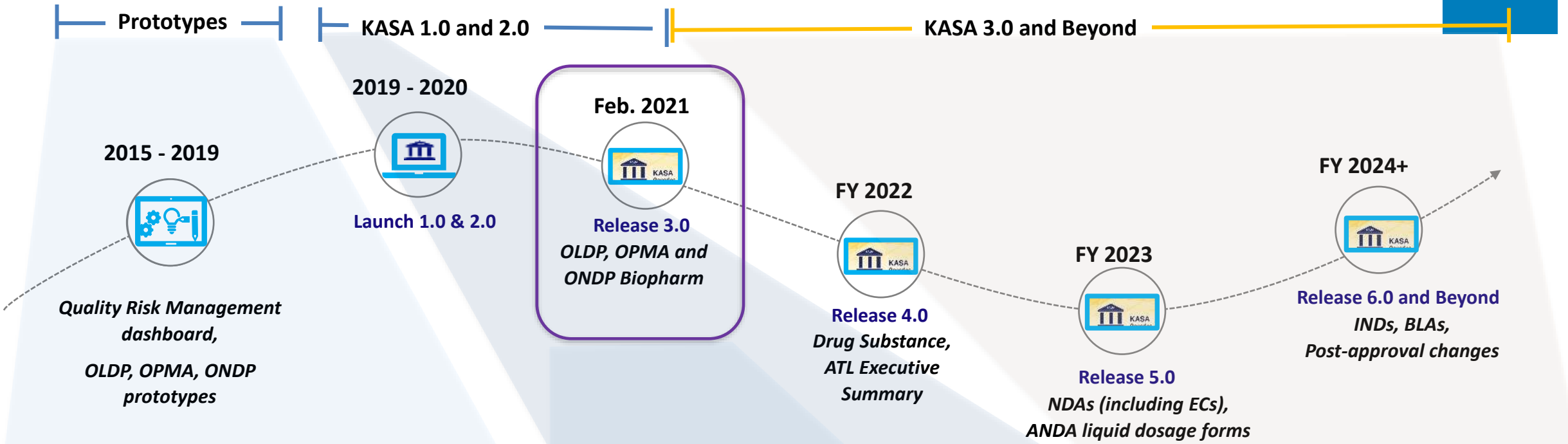
FDA

- Modernizes regulatory review
- Enhances efficiency, consistency and objectivity of regulatory assessment
- Enables knowledge management of information in **DMFs, ANDAs, NDAs, BLAs**
- Excels regulatory action and decision-making

Industry and Patients

- Clearer communication of regulatory expectations; enhanced transparency and consistency
- Increased 1st cycle approvals (esp. generics)
- More affordable and accessible medicines

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

FDA U.S. FOOD & DRUG ADMINISTRATION

Acknowledgement

- Lawrence Yu, Larisa Wu, Susan Rosencrance, Andre Raw, Scott Furness
- OPQ KASA for DS Working Group
- FDA KASA Steering Committee
- KASA Integrated Project Team
- FDA M4Q Working Group
- All developers, super-users, testers, and staff implementing KASA