U.S. FOOD & DRUG ADMINISTRATION

Modernizing Drug Substance Assessment through KASA

Larisa C. Wu, PhD
Acting Associate Director for Science and Communications,
Office of New Drug Products
CDER | US FDA

SBIA API-Workshop – March 4, 2021

Learning Objectives

- Provide a brief overview of KASA
- Discuss factors that prompted development of KASA for DS
- Illustrate the major milestones of the initiative and their implication on DS assessment
- Highlight the critical components of the KASA for DS
  - framework for quantitative risk assessment
  - structured manufacturing process evaluation

Quality Assessment Challenges

External Challenges

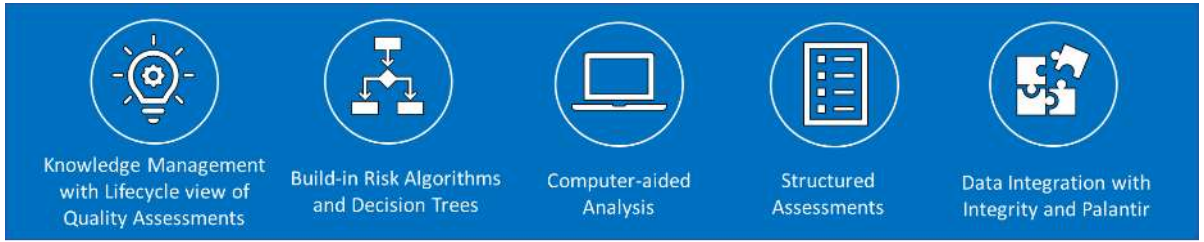
- Volume of new applications
- User fee program expectations (e.g., shorter assessment timelines for certain ANDAs under GDUFA II)
- Commissioner, Congress, the pharma industry, and the public expectations
- Technology advancements

Internal Challenges

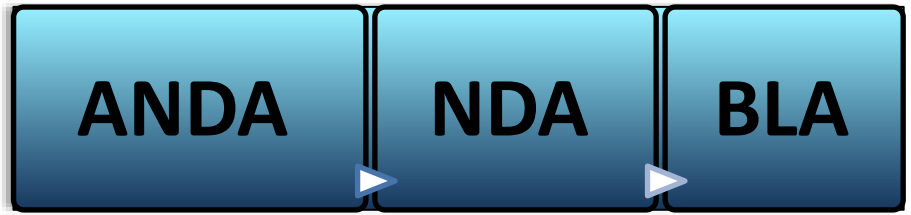
- Freestyle narrative assessment:
  - Unstructured text
  - Summarization of application information
  - “Copy and paste” data tables
- Cumbersome knowledge sharing and knowledge management
- Subjective assessment based on the assessor’s expertise and knowledge at hand

The Case for Change

OPQ is creating Knowledge-Aided Assessment and Structured Application (KASA) as part of the larger CDER effort to modernize regulatory assessment

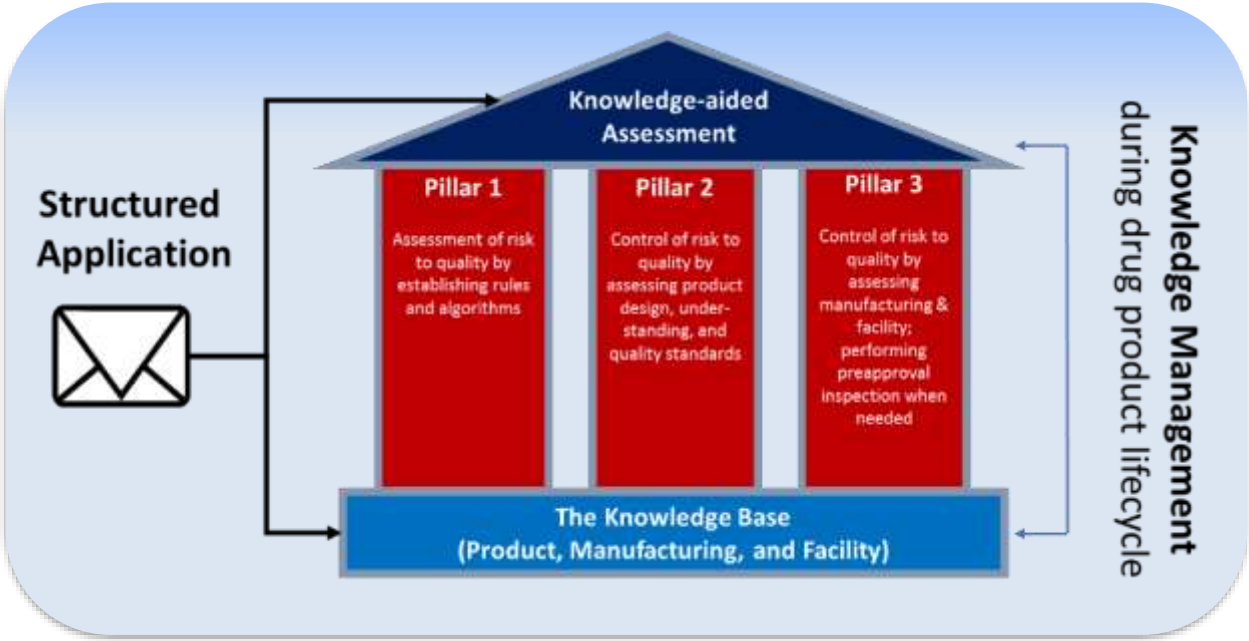


GOAL: Move from narrative information to structured data and capture and manage *KNOWLEDGE*



KASA System

KASA – Knowledge-aided Assessment and Structured Application



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

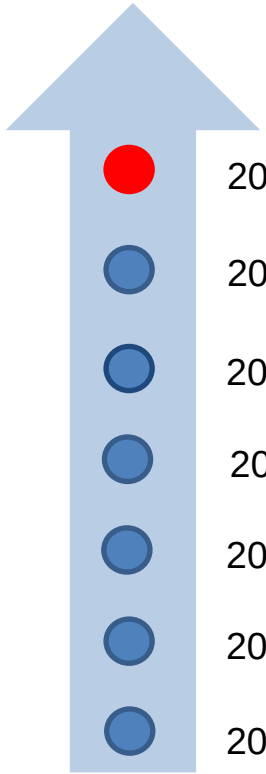
Lawrence X. Yu, Andre Raw, Larisa Wu, Christina Capacci-Daniel, Ying Zhang, and Susan Rosencrance "FDA's New Pharmaceutical Quality Initiative: Knowledge-aided Assessment and Structured Applications" *International Journal of Pharmaceutics* (2019) https://www.sciencedirect.com/science/article/pii/S2590156719300246

Objectives of KASA System

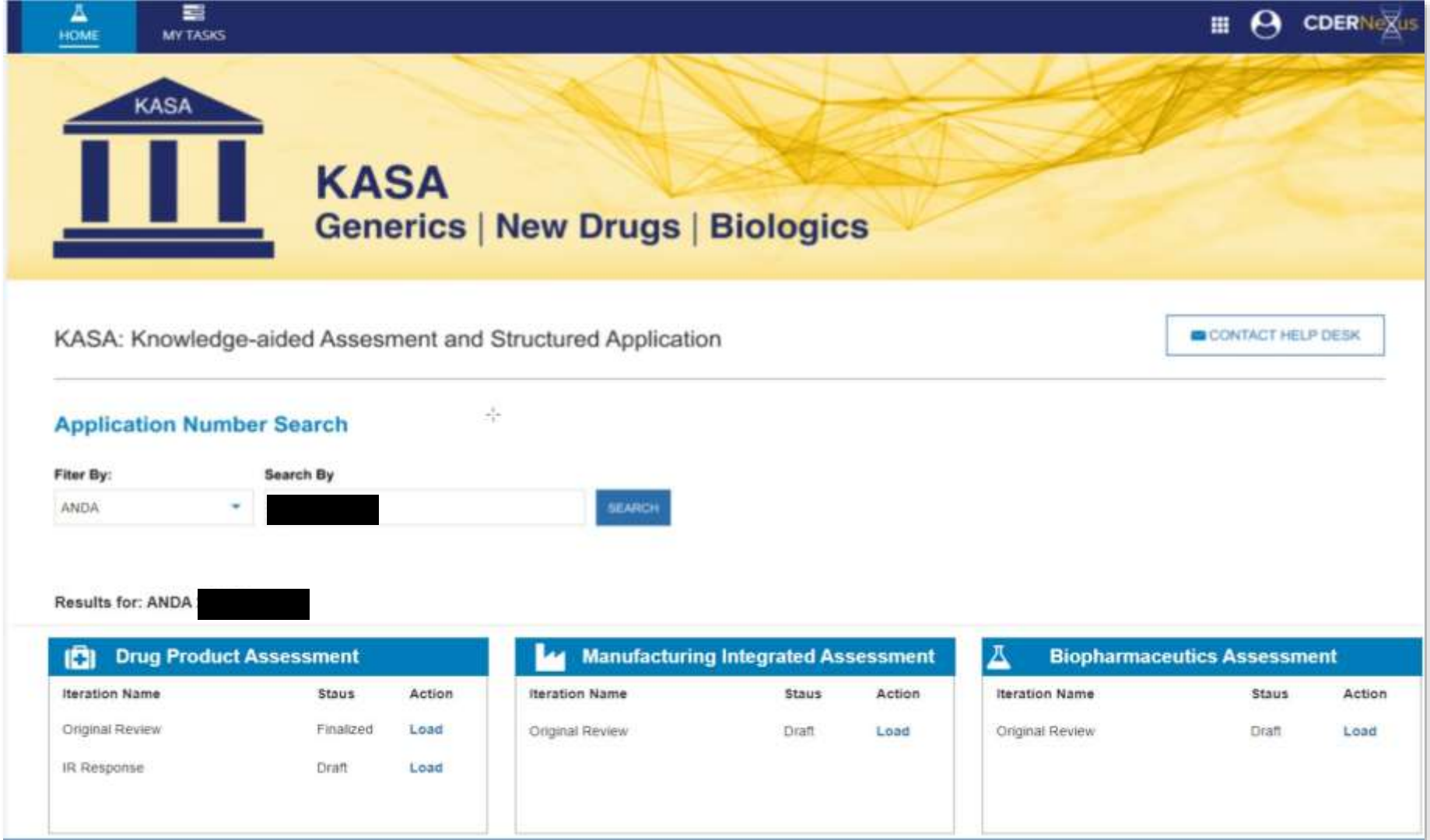
KASA is designed to:

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

KASA Road Map

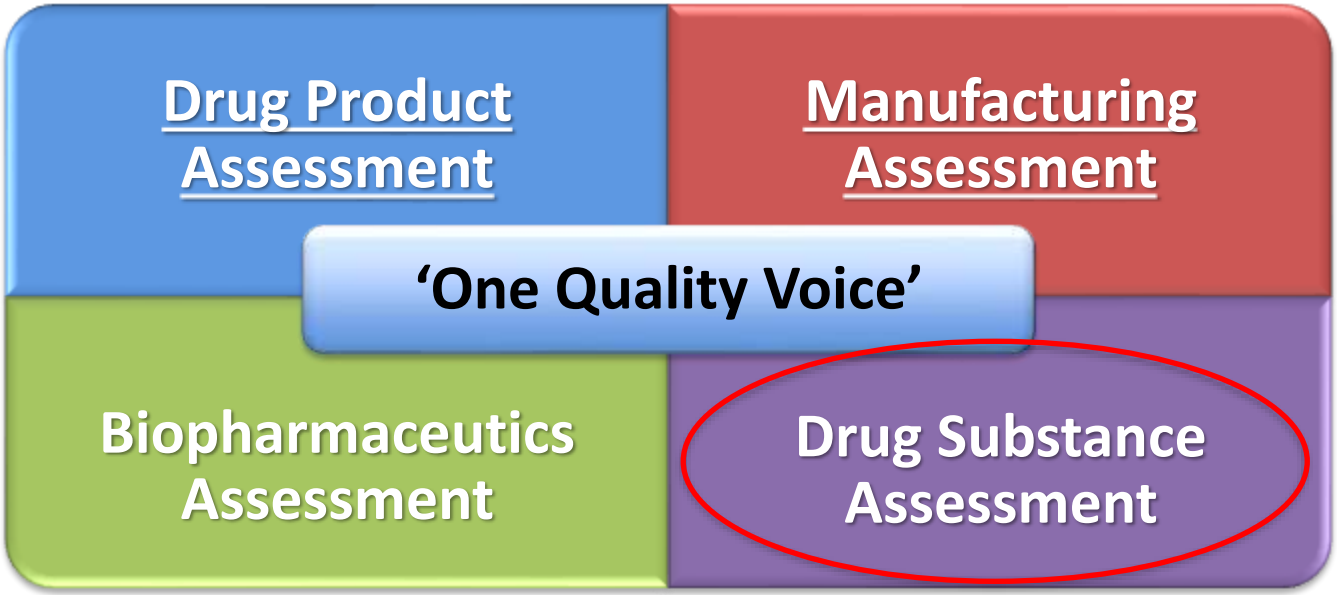


2021	KASA for DS applicable to DMFs, ANDAs, and NDAs in CDER IT platform
2020	Drug product, Biopharm, and Manufacturing KASA in CDER IT platform; KASA for DMF CA and KASA for DS prototypes
2019	Manufacturing KASA prototype
2018	Biopharm KASA prototype
2017	Multiple reiterations of the Drug Product KASA
2016	First homegrown KASA prototype for solid oral dosage forms drug product
2015	OPS/OPQ Quality Risk Management rules and algorithms

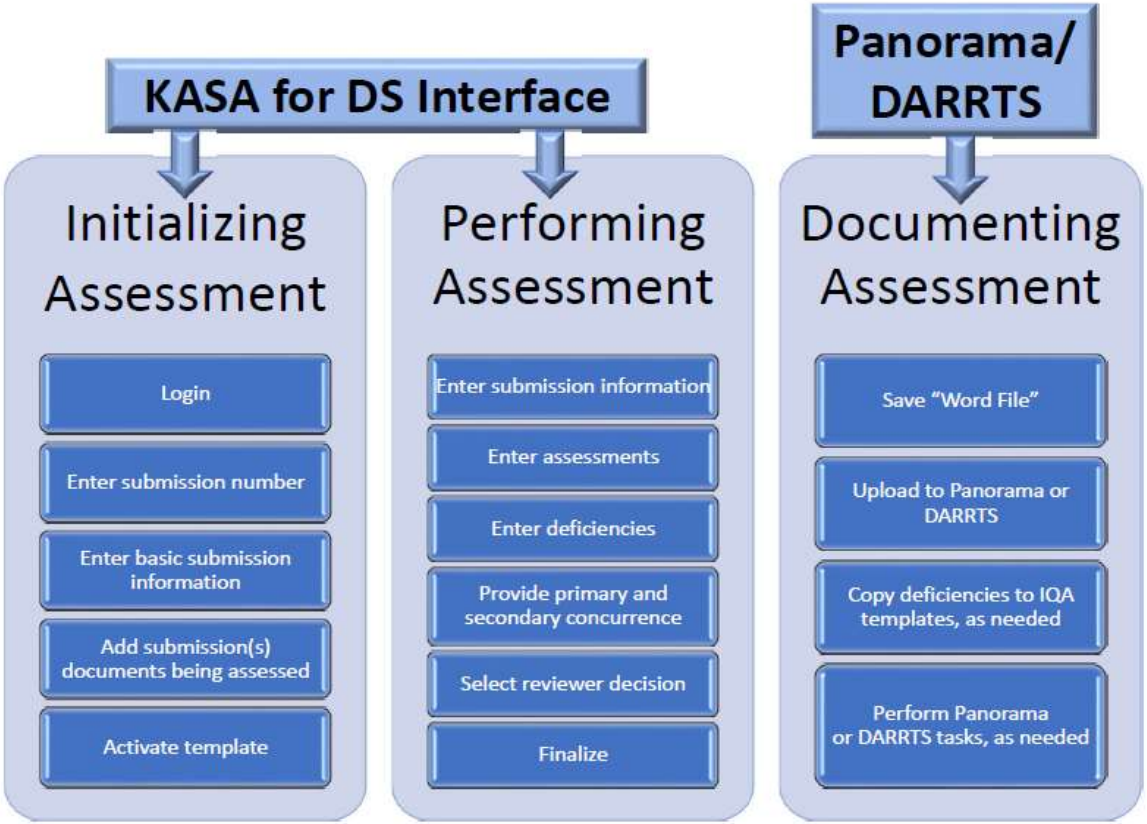

HOME
MY TASKS
CDERNexus
KASA
KASA
Generics | New Drugs | Biologics
KASA: Knowledge-aided Assesment and Structured Application
CONTACT HELP DESK
Application Number Search
Filter By:
ANDA
Search By
[redacted]
SEARCH
Results for: ANDA [redacted]
Drug Product Assessment
Iteration Name
Staus
Action
Original Review
Finalized
Load
IR Response
Draft
Load
Manufacturing Integrated Assessment
Iteration Name
Staus
Action
Original Review
Draft
Load
Biopharmaceutics Assessment
Iteration Name
Staus
Action
Original Review
Draft
Load

Team-based Integrated Quality Assessment (IQA) at OPQ

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



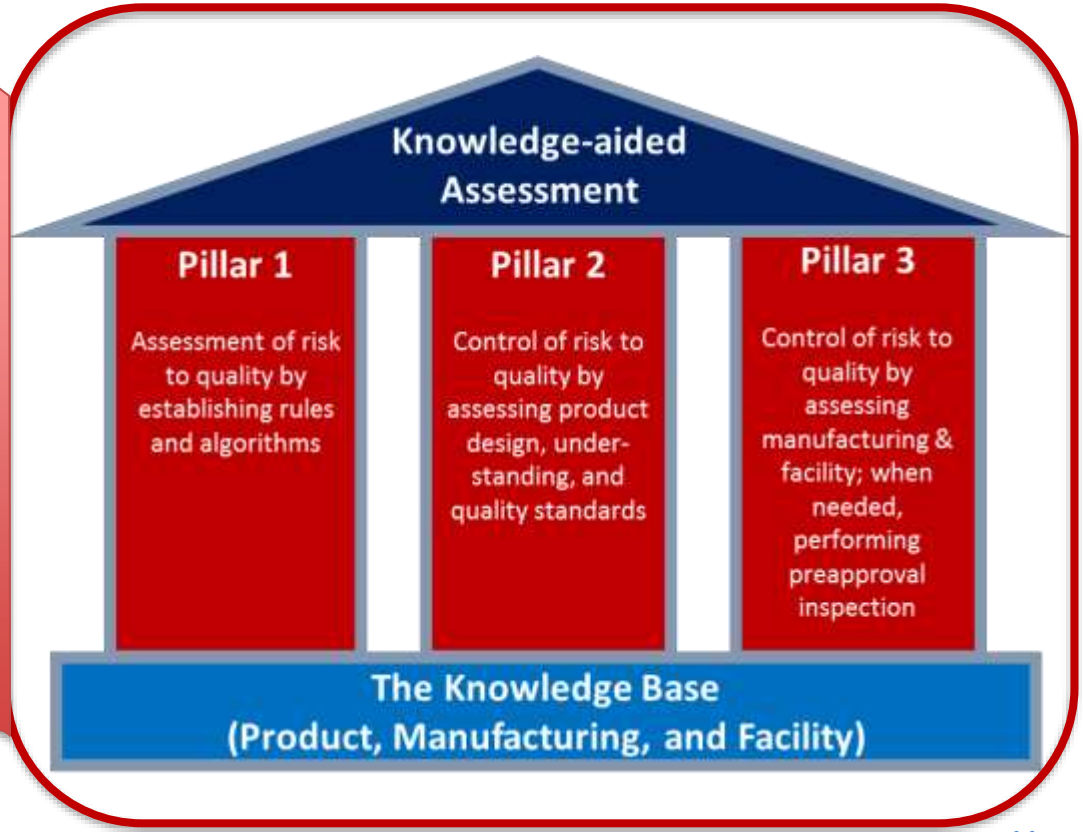
Functions Associated with KASA



KASA for DS Interface

- One stop shop for reviewers to assess DS information

- *Module 1*: **DS Overview**
- *Module 2*: **DS Risk Assessment**
- *Module 3*: **DS Manufacturing**
- *Module 4*: **DS Characterization**
- *Module 5*: **DS Control**
- *Module 6*: **DS Stability**



DS Risk Assessment

- Algorithm calculates overall risk of *predefined* DS risk categories
- *Predefined* questions with option answers have associated FMECA scores of Probability of Occurrence, Severity, and Detectability to assess the impact of a risk category on the DS critical quality attributes (CQAs)
- Overall risk is considered **low**, **medium**, or **high** based on *predefined* ranges

KASA promotes consistency and objectivity of assessment

Enhanced DS Risk Management

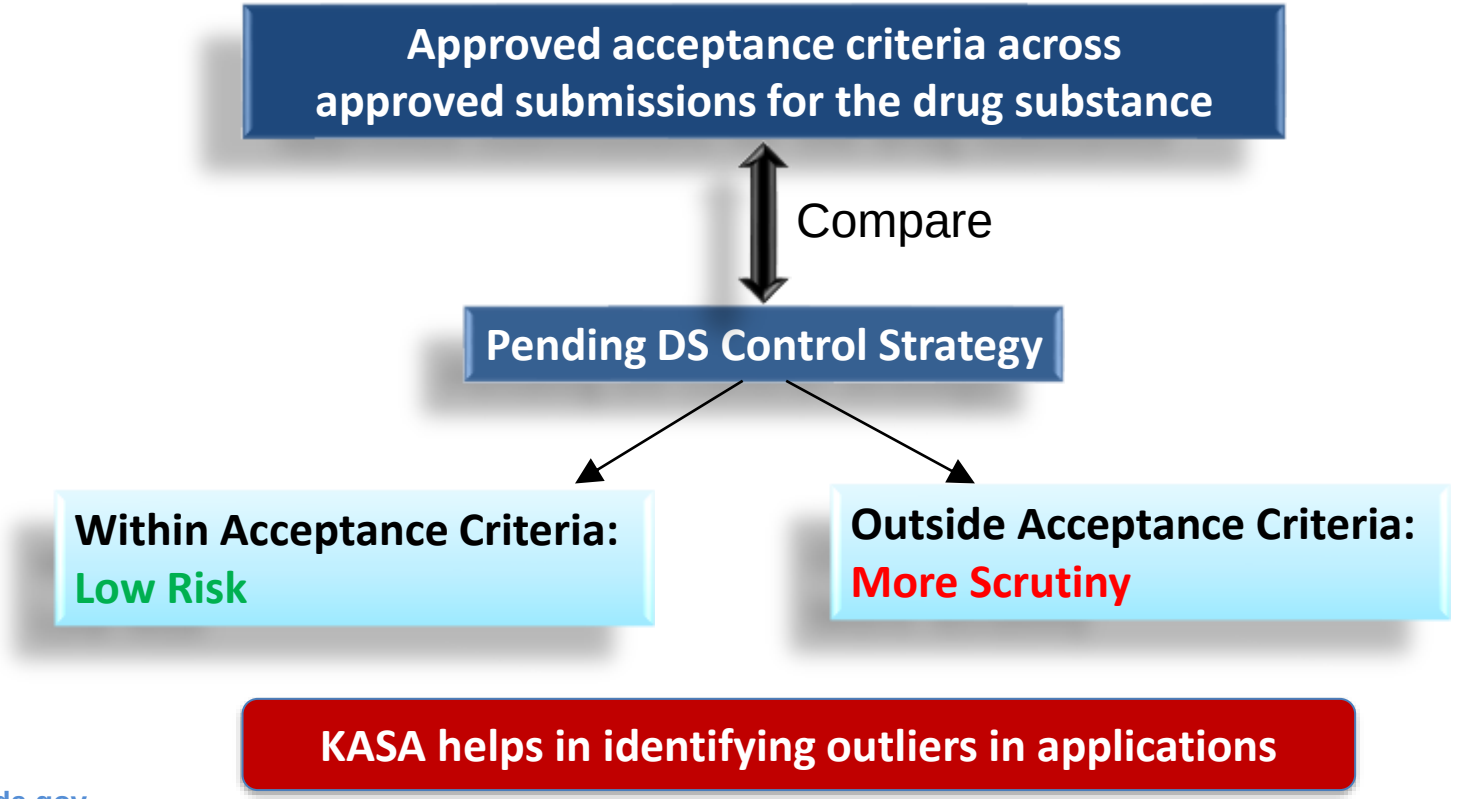
Risk Category	Impacted CQAs	Calculated Risk Level	Assessment Comment	Updated Risk Level	Deficiencies
Starting material	impurities	**Low**	Adequate.	**Low**	-
ID/ Characterization	assay	**Low**	Inadequate. Justification A	**Medium**	**Deficiency #1**
Stability	assay, impurities	**High**	Inadequate. Justification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

Consistent, objective, and quantitative risk assessment

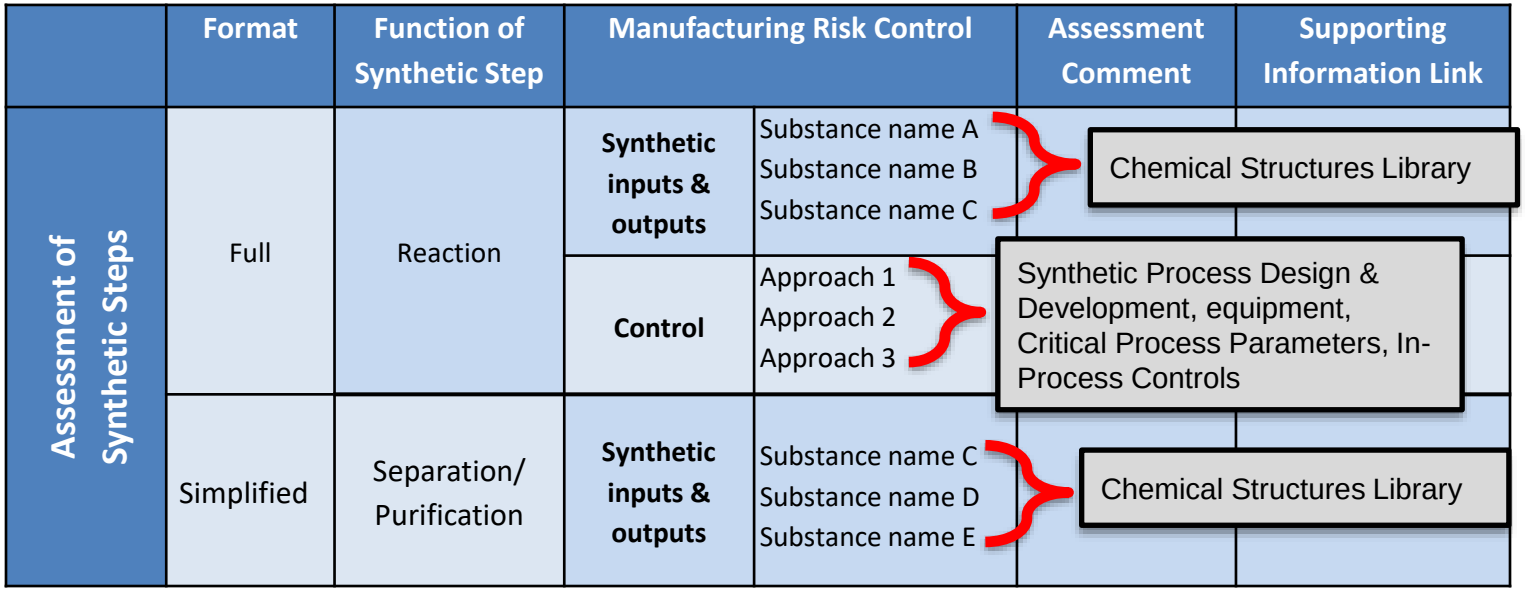
Assessor can override final risk ranking, but must provide justification in the review assessment box.

Assessment and deficiencies are aligned with the level of risk

KASA for DS Analytics (1)



Structured DS Synthetic Pathway



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

Chemical Structures Library

- To capture synthetic inputs, synthetic outputs, impurities from synthetic steps
- Structures will receive a tag for immediate and future use in the reviews

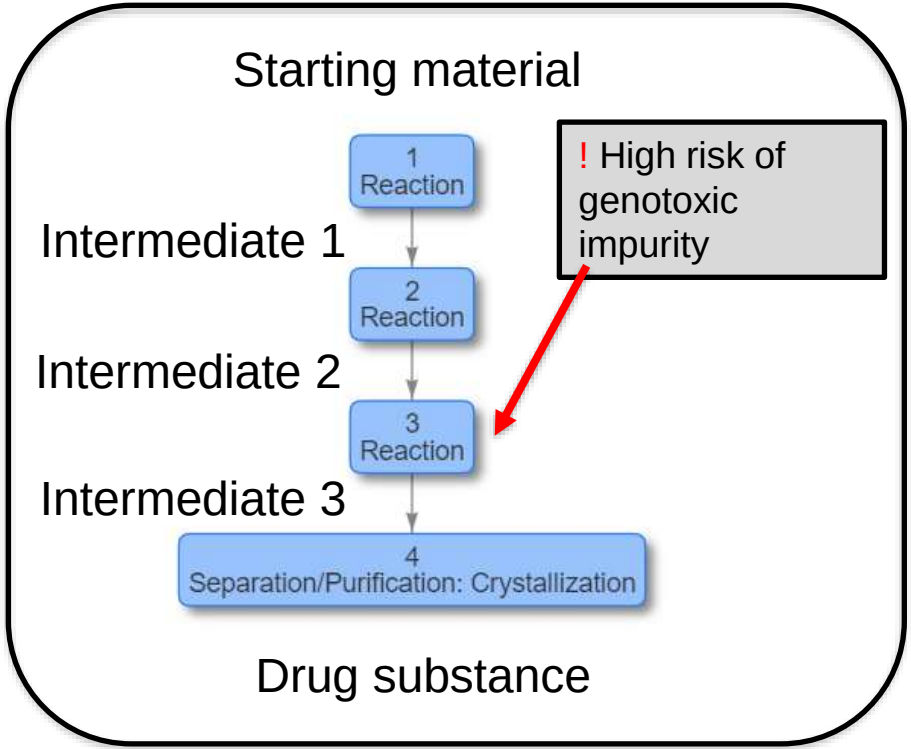
Chemical name	Structure	Role	Identifiers	Additional note	Edit
ID: Chemical Name: aspirin		Drug Substance	CID: 2244 UNII: Smile: CC(=O)OC1=CC=CC=C1C(=O)O	N/A	Edit + x

KASA for DS Analytics (2)

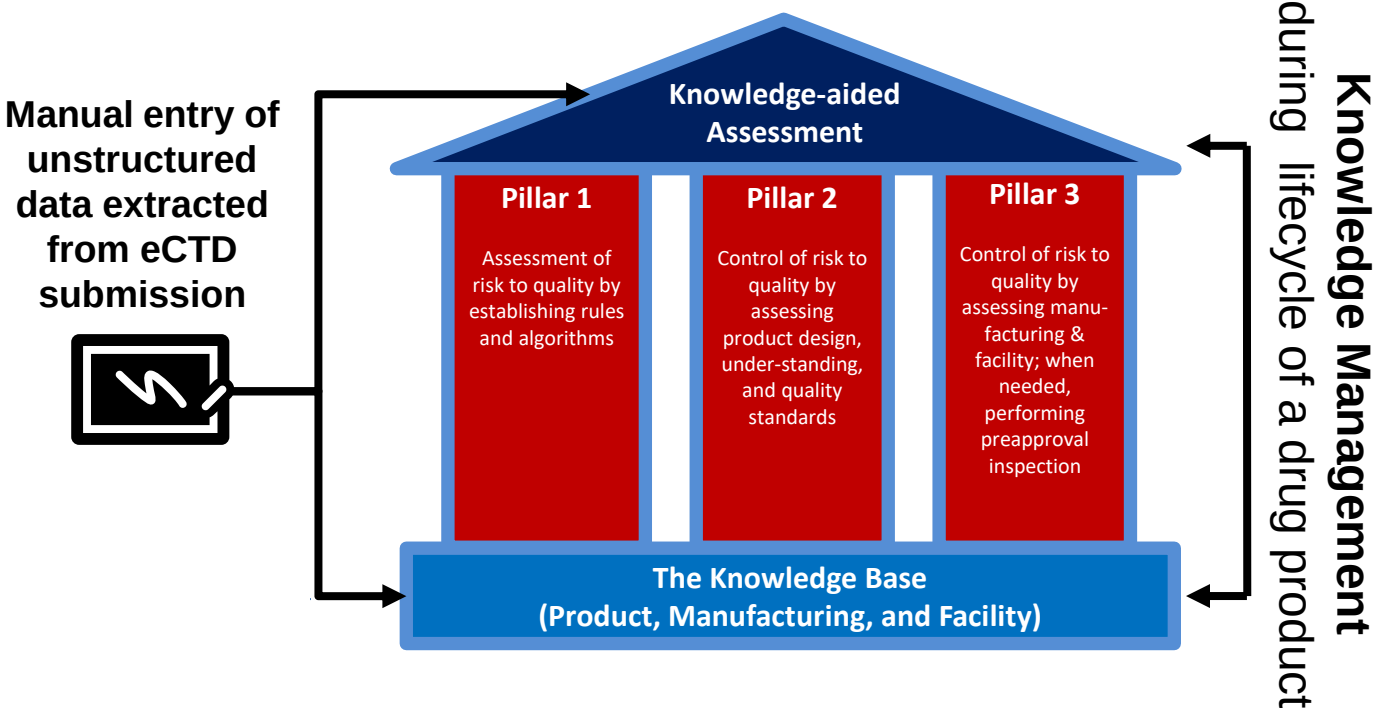
Data for each DS synthetic route captured in the KASA for DS platform is:

- searchable
- visualizable
- comparable

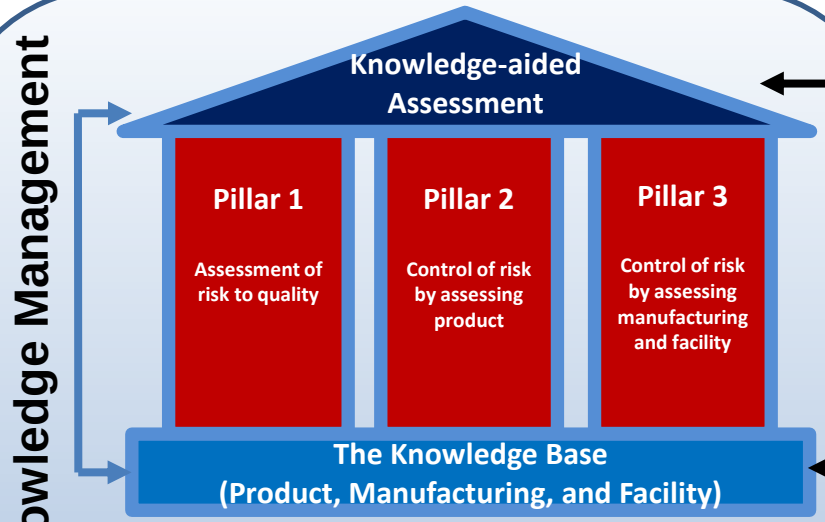
KASA improves overall efficiency and excels regulatory decision by improving the DS knowledge management



Current KASA System

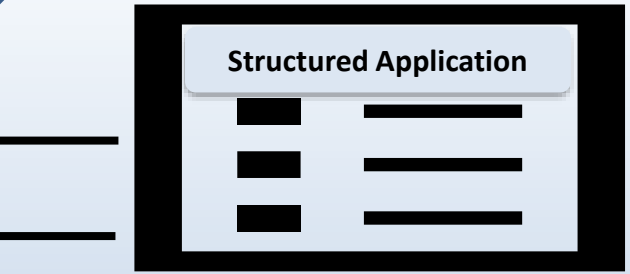


Future KASA System



KA

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



What information is submitted?

How is information organized?

ICH M4Q revision

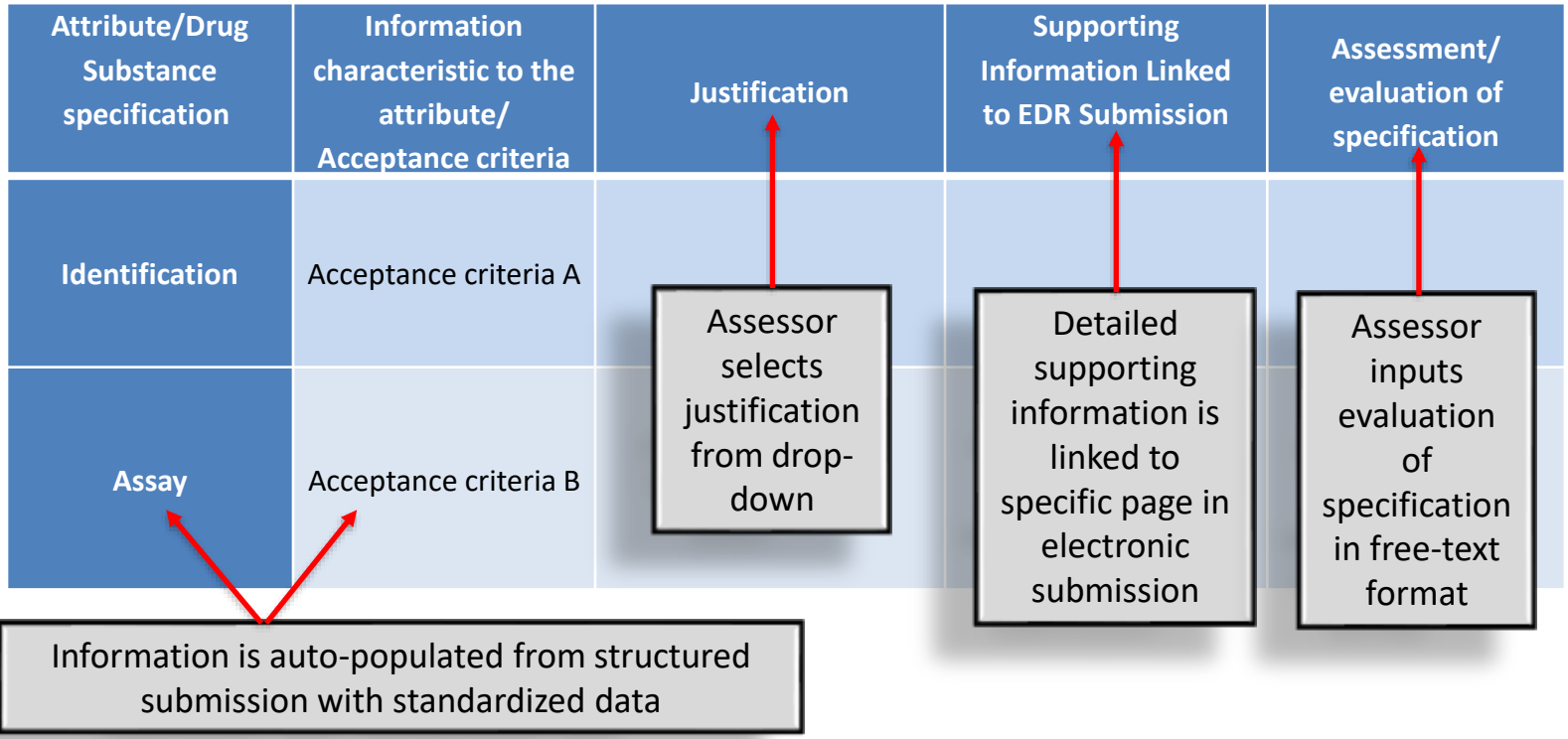
Electronic data standards

PQ-CMC

SA

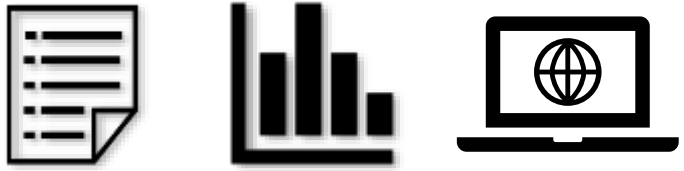
content and organization of submission and electronic data standards

KASA with Standardized Data



Benefits of KASA for DS System (1)

Benefits to FDA



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

Benefits of KASA for DS System (2)

Benefits to Industry and Patients

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

Thank You!

- Please type questions regarding the content of this presentation into the “Q&A Box” so that they can be addressed during the panel Q&A after this session.

- Send questions regarding this presentation to: DMFWorkshop2021@fda.hhs.gov by 3/19/2021 for inclusion in the follow-on webinar April 9, 2021.

- Please refer to the following poster for cross-referenced materials: *Completeness Assessments (CAs): Current CA Status, KASA for CA, Common Issues & GDUFA Commitment Letter Statistics*, Yingzi Wang, Jayani R. Perera, Jason Crawford, Larisa Wu, and Xiang Yu