U.S. FOOD & DRUG ADMINISTRATION

Knowledge-aided Assessment & Structured Application (KASA):

A New Approach that Modernizes FDA's Quality Assessment of Regulatory Drug Applications

Food and Drug Administration
Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee

November 3, 2022

U.S. FOOD & DRUG ADMINISTRATION

Quality Assessment Modernization: Vision and Future Roadmap

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

November 3, 2022

Sau Larry Lee, PhD
Deputy Director of Science
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

A quality product of any kind consistently meets the expectations of the user – drugs are no different.

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.

Quality Assessment in Office of Pharmaceutical Quality

- Office of Pharmaceutical Quality (OPQ) evaluates how a drug is formulated, how it is manufactured, and the facilities used in the manufacturing process to ensure a safe and effective medication is being delivered to the intended population.
- OPQ also looks at formulation and manufacturing changes made after a drug is approved to ensure quality is maintained throughout the product's lifecycle.

Challenges to Assessing Quality

- There has been an increase in submission number and complexity with accelerated timelines.
- Annually, OPQ reviews ~ 3,000 INDs, ~240 NDAs/BLAs, ~900 ANDAs, ~10,000 supplements, submitted in **unstructured** PDF format.

P.2 Pharmaceutical Development

Formulation Development and Product Design

Drug Substance

Particle size distribution: XXX hydrochloride drug substance supplied by XXX was used for the development of XXX Delayed-Release Capsules 20 mg, 30 mg and 60 mg. The vendor XXX provides drug substance with consistent particle size. The proposed three tier particle size specification is summarized below.

Particle size distribution	d(0.1) µm	d(0.5) µm	d(0.9) µm
Specifications	NMT x µm	NMT x µm	NMT x µm

Solid state form: As confirmed by XXX, XXX Hydrochloride manufactured by XXX is the Anhydrous Crystalline Form A. It is characterized by the following 2θ values x, x, x, x, x, x, x and x ± 0.2° and also matches the P-XRD pattern in the patent US XXX.

The XRPD evaluation for XXX reveals that the innovator has used the XXX hydrochloride representing the 2Θ values of Polymorphic Form A. The same polymorphic form of drug substance obtained from XXX was used for the product development.

Section P.2 in this actual example contains 9 pages of freestyle narrative in unstructured text

Challenges to Assessing Quality

A freestyle narrative-based quality assessment means:

- unstructured information;
- a summarization of application information; and
- "copy & paste" data

Such system can result in:

- risk assessment and evaluation of the applicant's mitigation approaches dispersed in lengthy text;
- inconsistency and ineffectiveness, and encumbered ability to share knowledge and efficiently manage FDA's repertoire of approved drug products and facilities;
- hindered decision-making capabilities because assessors evaluate each application in relative isolation without fully assessing the wealth of information at FDA's disposal.

Advancing Forward

- For a regulatory assessment focused on quality (Chemistry, Manufacturing, and Controls), a lifecycle approach that underscores good knowledge management is essential.
- To be most efficient, OPQ needs to take advantage of modern IT tools and platforms that:
  - emphasize structured data* and the ability to capture critical information;
  - enable a systematic approach to risk assessment, resulting in a more consistent high-quality evaluation and decision making.

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

Advancing Forward

We recognize the need to modernize

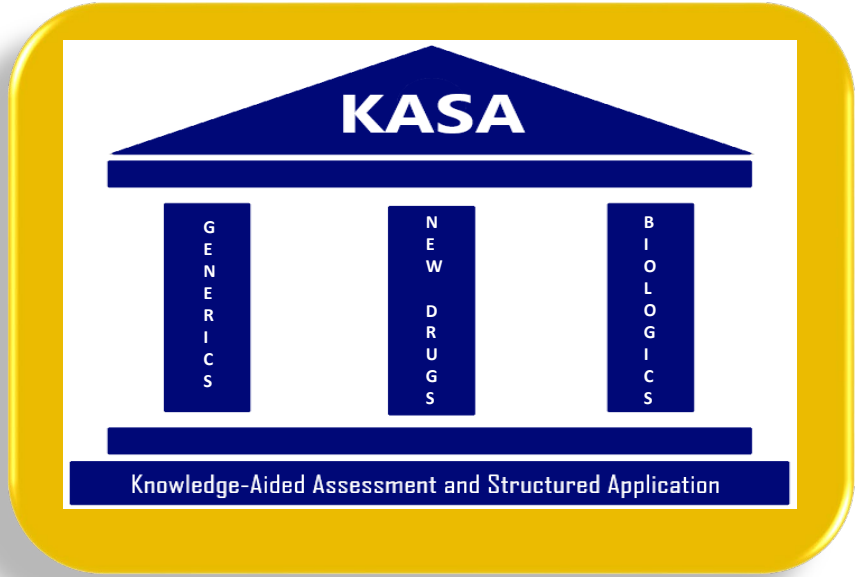
(20th → 21st century technology)

Quality Assessment

moves from narrative information to **structured data and systematic approach for risk assessment powered by IT tools** to best capture/manage knowledge

This concept was envisioned in 2016 and discussed at the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting on September 20, 2018, as KASA.

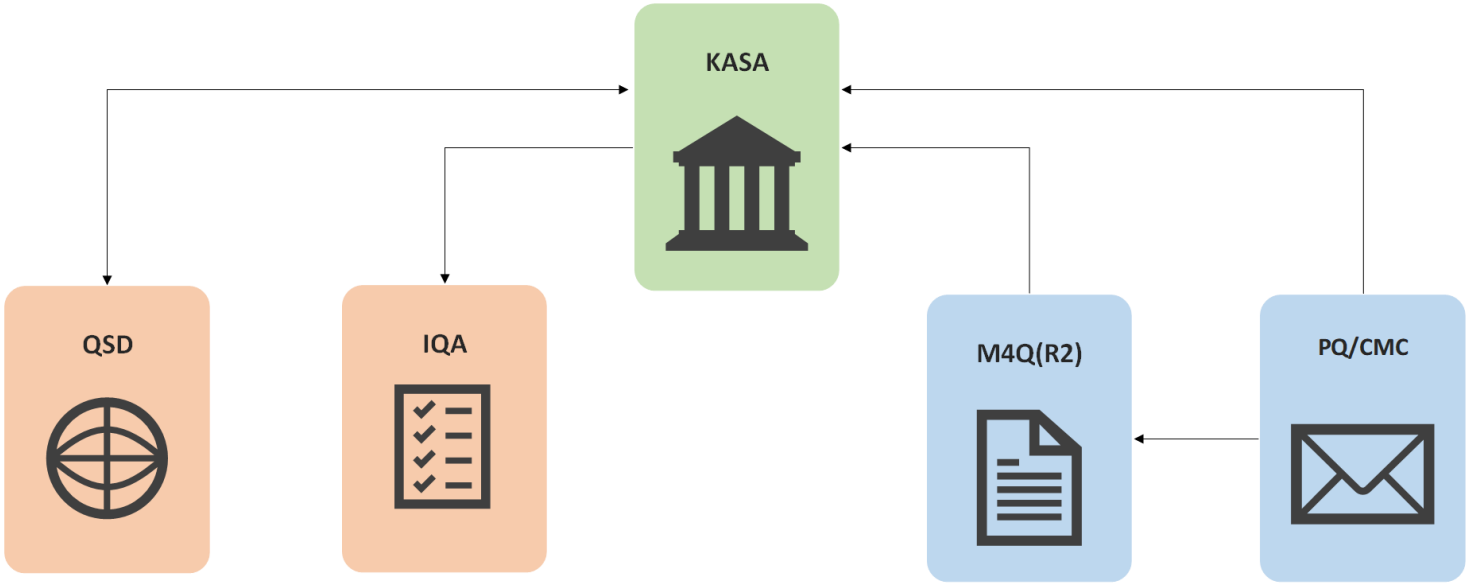
Quality Assessment Transformation: KASA



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

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

How does KASA Connect to other Relevant OPQ Initiatives/Programs?



What is KASA?

Knowledge-Aided Assessment and Structured Application

- 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

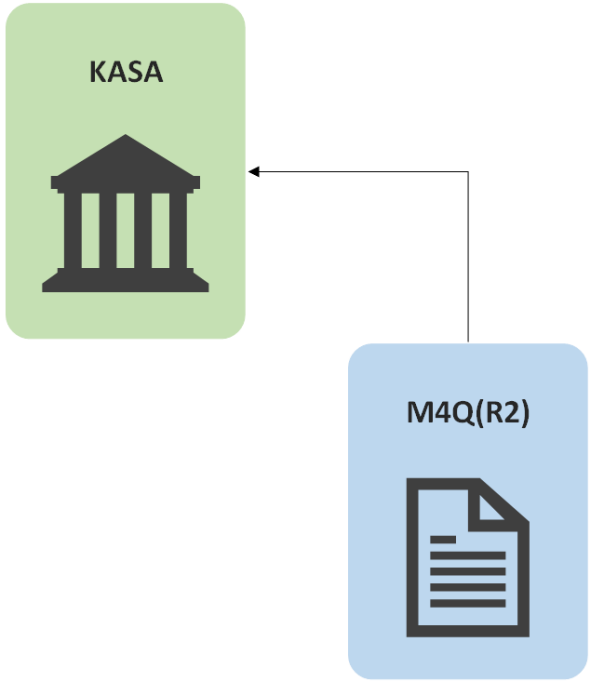
KASA Overview

What is ICH M4Q(R2)?

The Common Technical Document – Quality

- Modernize and optimize the Common Technical Document (CTD) Quality section in Modules 2 and 3
- Incorporate ideas presented in International Council for Harmonisation (ICH) Q8-14 and promoting emerging concepts
- Address regional diversity in requirements
- Organize the information in a structured format to promote knowledge management

KASA Connection to M4Q

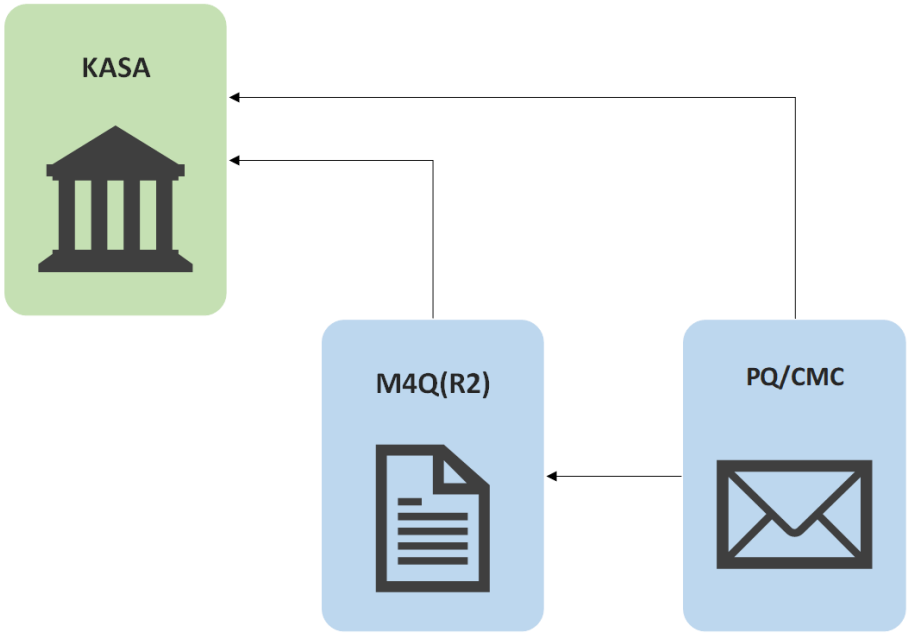


What is PQ/CMC?

Pharmaceutical Quality/Chemistry Manufacturing and Controls

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

KASA Connection to PQ/CMC

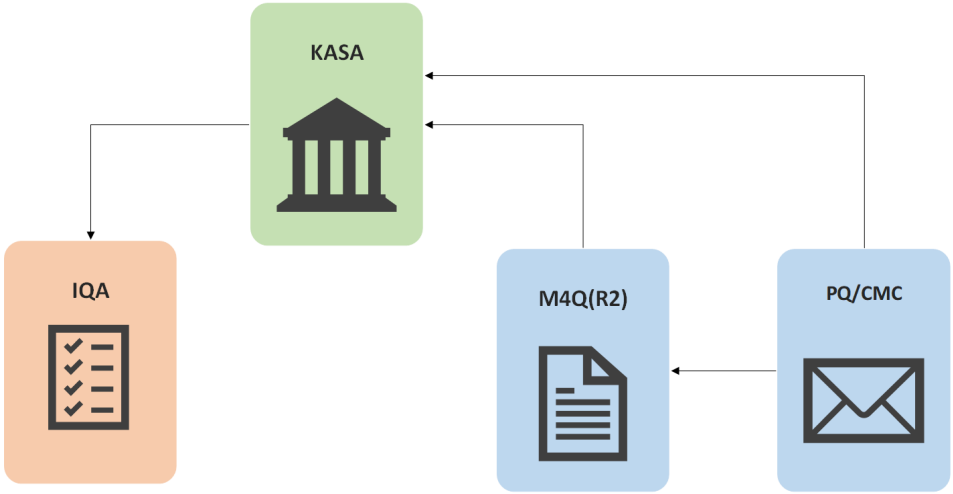


What is IQA?

Integrated Quality Assessment

- Ensure effective and efficient assessment of drug applications by multi-disciplinary teams
- Define business process and operational workload distribution
- Delineate roles and responsibilities
- Establish internal milestones/timelines to meet user fee commitments

KASA Connection to IQA

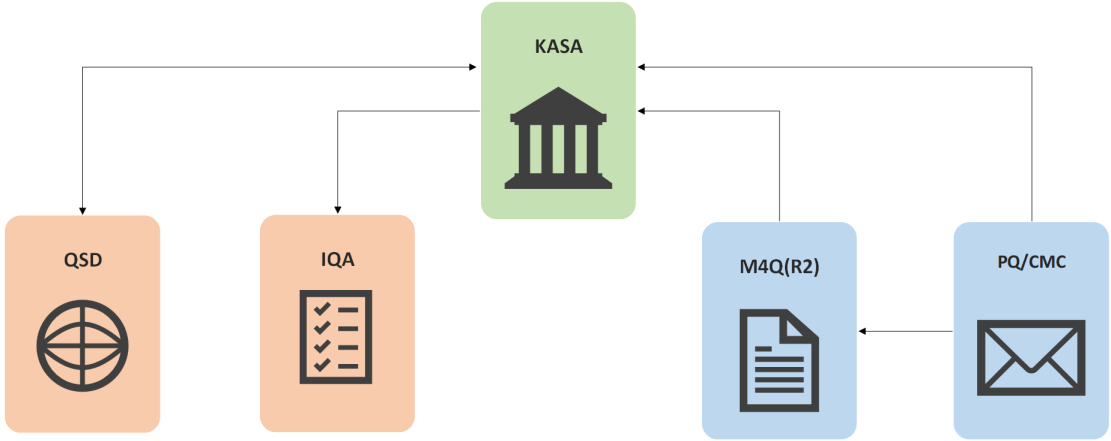


What is QSD?

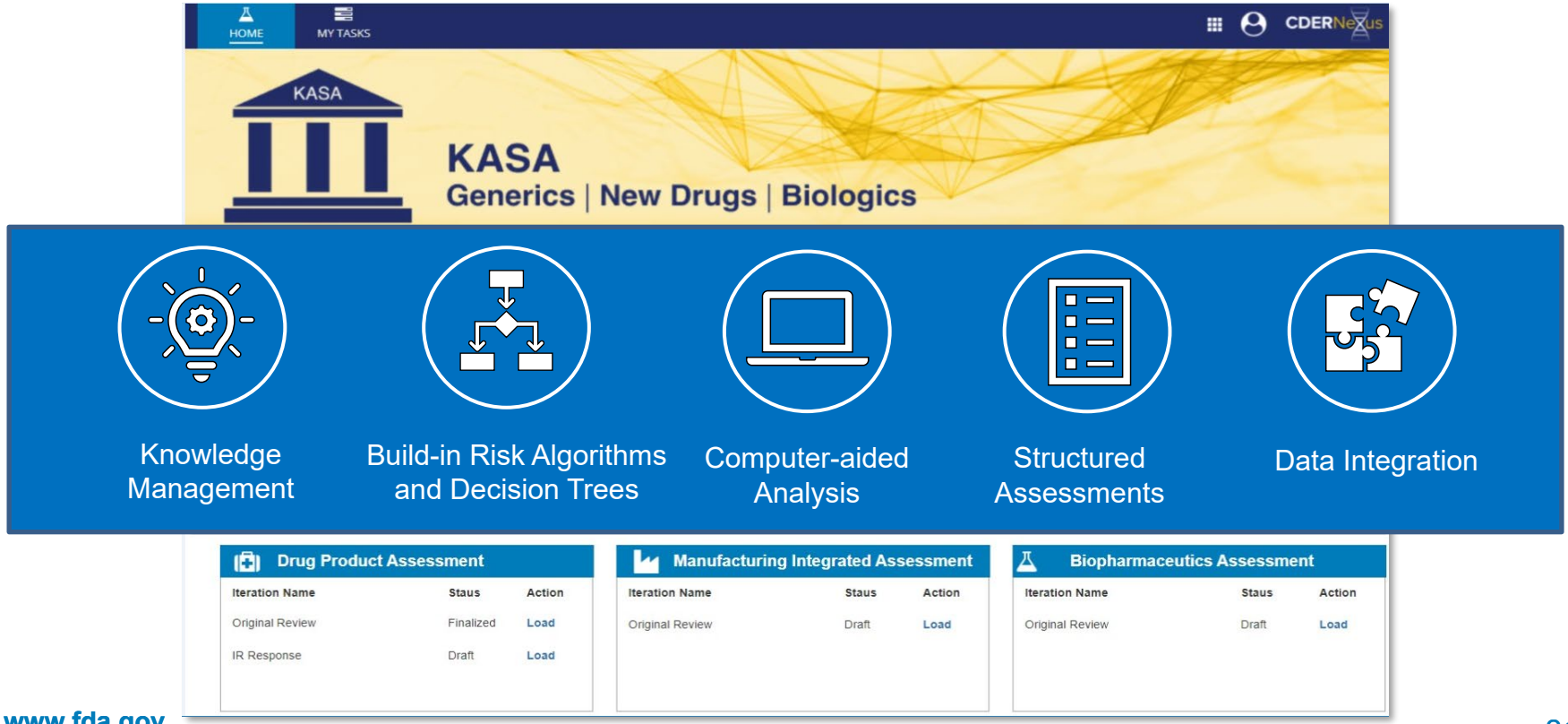
Quality Surveillance Dashboard

- Provide framework for consistent evaluation of facilities and potential quality signals within a product's lifecycle
- Incorporate interactive visualizations that enable users to discover and share insights regarding facilities, manufacturing capabilities, and product quality issues
- Utilize predictive analytics and natural language processing to enable efficient and risk-based assessments
- Integrate and govern facility and postmarket product quality data from across multiple systems

KASA Connection to QSD



KASA for generic solid oral dosage forms is live as of Feb 2021



Plans for KASA's Future

OPQ is focused on continuing KASA's development (creation, testing, refinement) and expanding it to include:

- Drug Substances (for new and generic drugs)
- Liquid-based dosage forms for generics
- INDs
- NDAs
- BLAs
- Post-Approval Supplements (ANDAs, NDAs, BLAs)

Conclusion

- The KASA system enables the use of 21st century technology and is driving innovation for FDA.
- KASA has been successful thanks to the efforts of countless OPQ employees, Office of Business Informatics (OBI) staff, and contractors, plus the steady support of CDER leadership.

Thank You


Effective leadership
Collaborative relationships
Encourage innovation
Risk-based approaches
One Quality Voice
Patients first
Team-based processes
Developing and utilizing staff expertise
Scientifically-sound quality standards

KASA Accomplishments to Date

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

November 3, 2022

Andre Raw, PhD
Associate Director of Science and Communication
Office of Lifecycle Drug Products (OLDP)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

The Why of KASA

- Historically, assessments (or reviews) in CDER have relied upon freestyle narrative text (e.g., Word documents) consisting of:
    1. unstructured information;
    2. a summarization of application information; and
    3. “copy & paste” data.

- This is not an effective system, and it encumbers our ability to share knowledge and manage FDA’s repertoire of approved drug products and facilities.

- And hinders our decision-making capabilities because assessors (or reviewers) evaluate each application in relative isolation without fully assessing the wealth of information at FDA’s disposal.

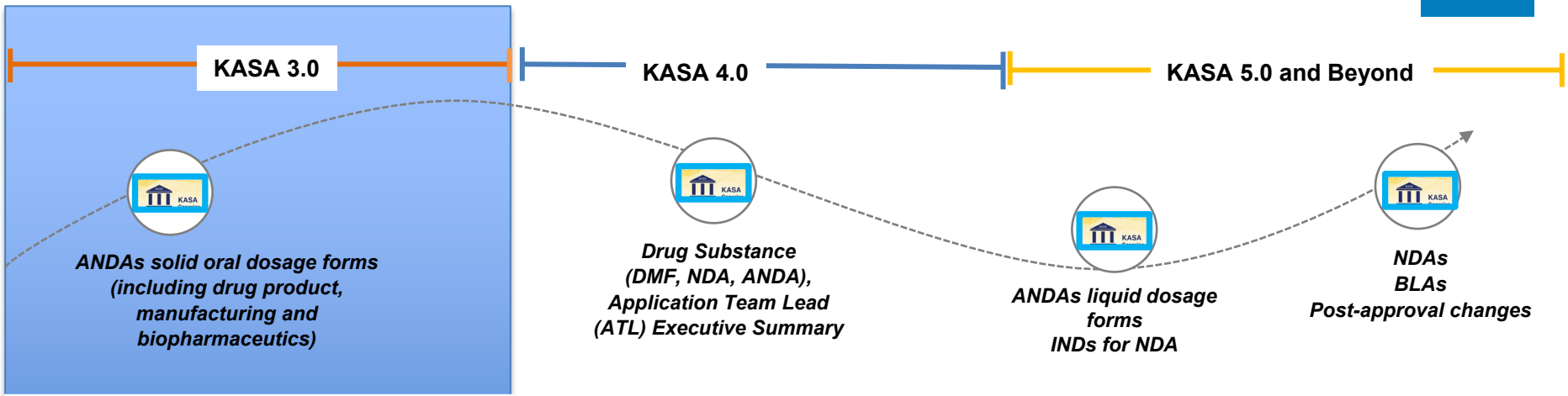
The Why of KASA

- In 2016 OPQ's KASA system was envisioned as a means of modernizing FDA's assessment (or review) by taking advantage of:
    1. Structured data (as opposed to narrative information);
    2. Advanced analytics; and
    3. Knowledge management.

- Over the course of 6 years, subject matter experts (SMEs) at all levels (grassroots and beyond) have worked to develop, test, implement, and refine various KASA prototypes.

- Major Milestone: On February 1, 2021 KASA was launched in NEXUS for generic solid oral dosage forms.

Roadmap for KASA IT Production



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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

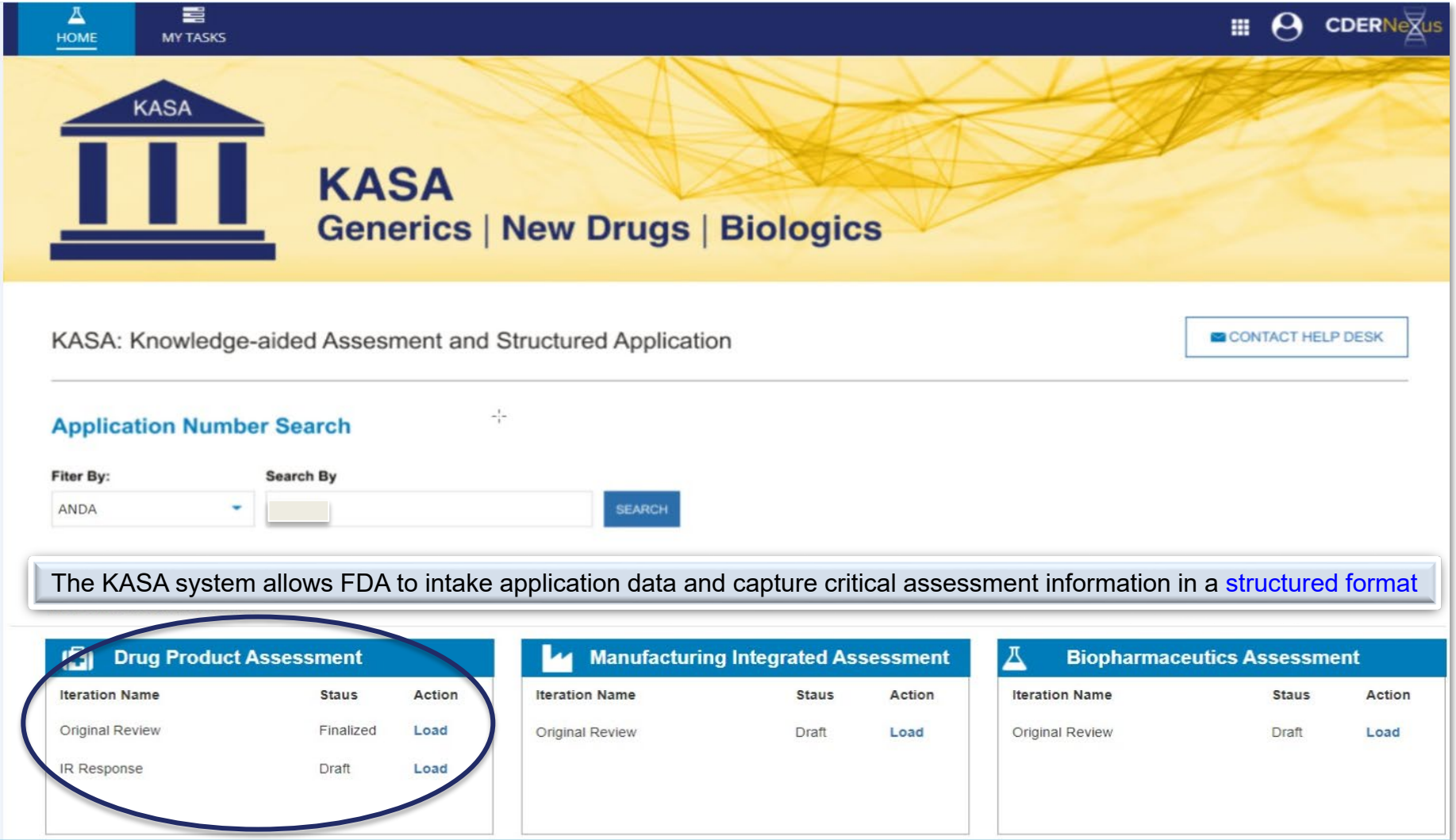
Completed Targets

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

Defined Targets

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

Tentative Targets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The KASA system allows FDA to intake application data and capture critical assessment information in a structured format
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Manufacturing Integrated Assessment
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Biopharmaceutics Assessment
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KASA Captures Inherent Drug Product Risk Using Algorithms and Control in a Structured Format

	Initial Risk FMECA	Risk Control Dropdown Menu		Explanation Applies to NDA/ANDA	Supporting Information Linked to EDR Submission
CQA1/ Dissolution	Low/ Medium/ High	Design	Approach A Approach B Approach C		
		Measurement	Approach H Approach I Approach J		
CQA2/ Impurities	Low/ Medium/ High	Design	Approach M Approach N Approach O		
		Measurement	Approach S Approach T Approach V		

Descriptors:
Structured Knowledge of Formulation Design and/or Control Strategy

KASA Enables a Compact Assessment

	Initial Risk FMECA	Risk Control Dropdown Menu		Explanation Applies to NDA/ANDA	Supporting Information Linked to Electronic Submission
CQA1/ Dissolution	Low/ Medium/ High	Design	Approach A Approach B Approach C		
		Measurement	Approach H Approach I Approach J		
CQA2/ Impurities	Low/ Medium/ High	Design	Approach M Approach N Approach O		
		Measurement	Approach S Approach T Approach V		

Assessor Briefly Describes How Fundamental Risk Control Approach Selected from Drop-Down is Specifically Applied in NDA/ANDA

Detailed Supporting Information is Linked to Specific Page in Electronic Submission

Drug Product Risk Analytics

ANDA x

	Initial Risk		Risk Control Strategy	Residual Risk
CQA/ Assay	High	Product Design	None	Medium (High)
		Measurement	Traditional Product Release/Stability Testing	

ANDA y

	Initial Risk		Risk Control Strategy	Residual Risk
CQA/ Assay	High	Product Design	Approach A	Medium
		Measurement	Traditional Product Release/Stability Testing	

NDA

	Initial Risk		Risk Control Strategy	Residual Risk
CQA/ Assay	High	Product Design	Approach A	Low
		Product Design	Approach B	
		Product Design	Approach D	
		Measurement	Traditional Product Release/Stability Testing	

Same Initial Inherent Risk

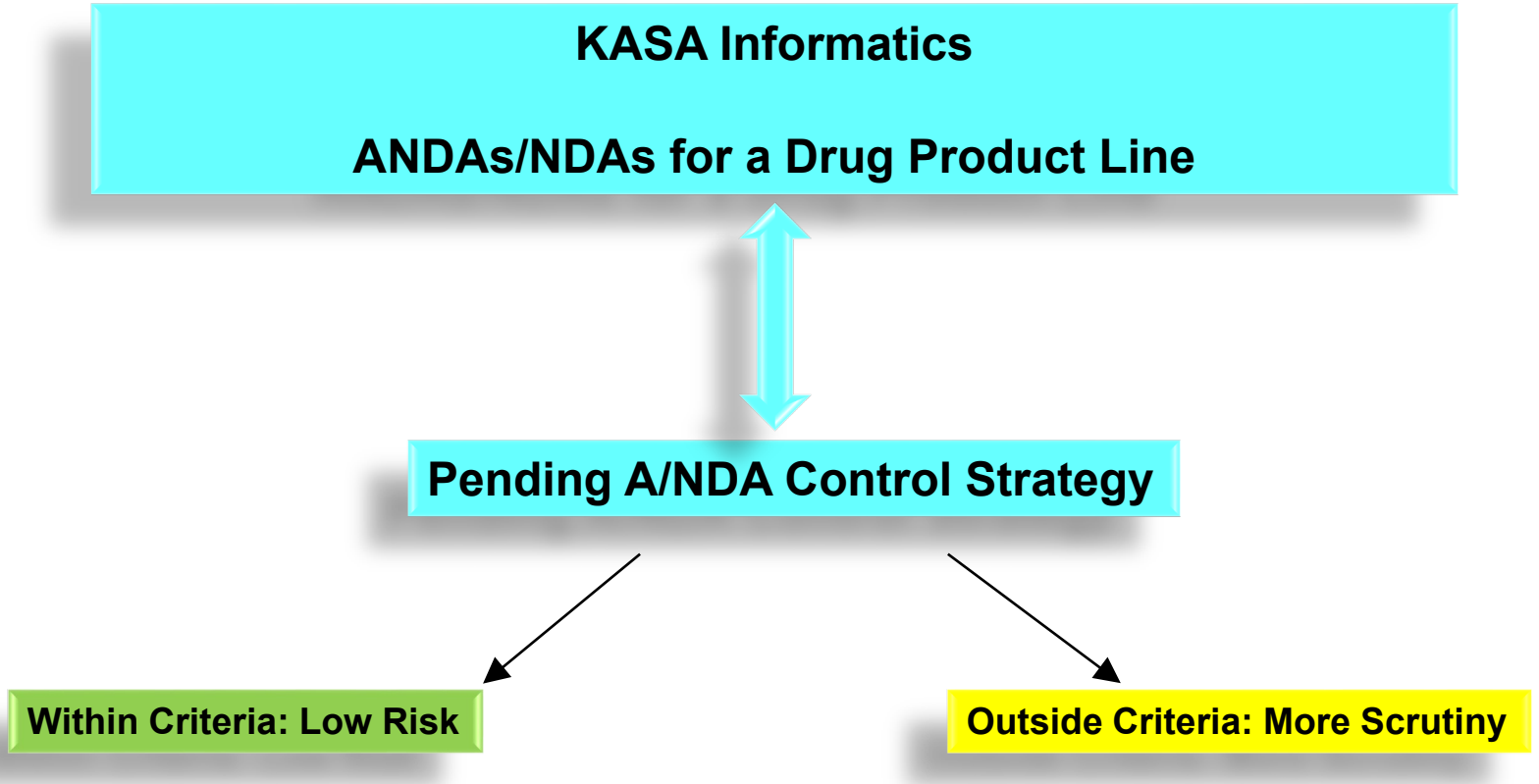
Increasing Level of Risk Control

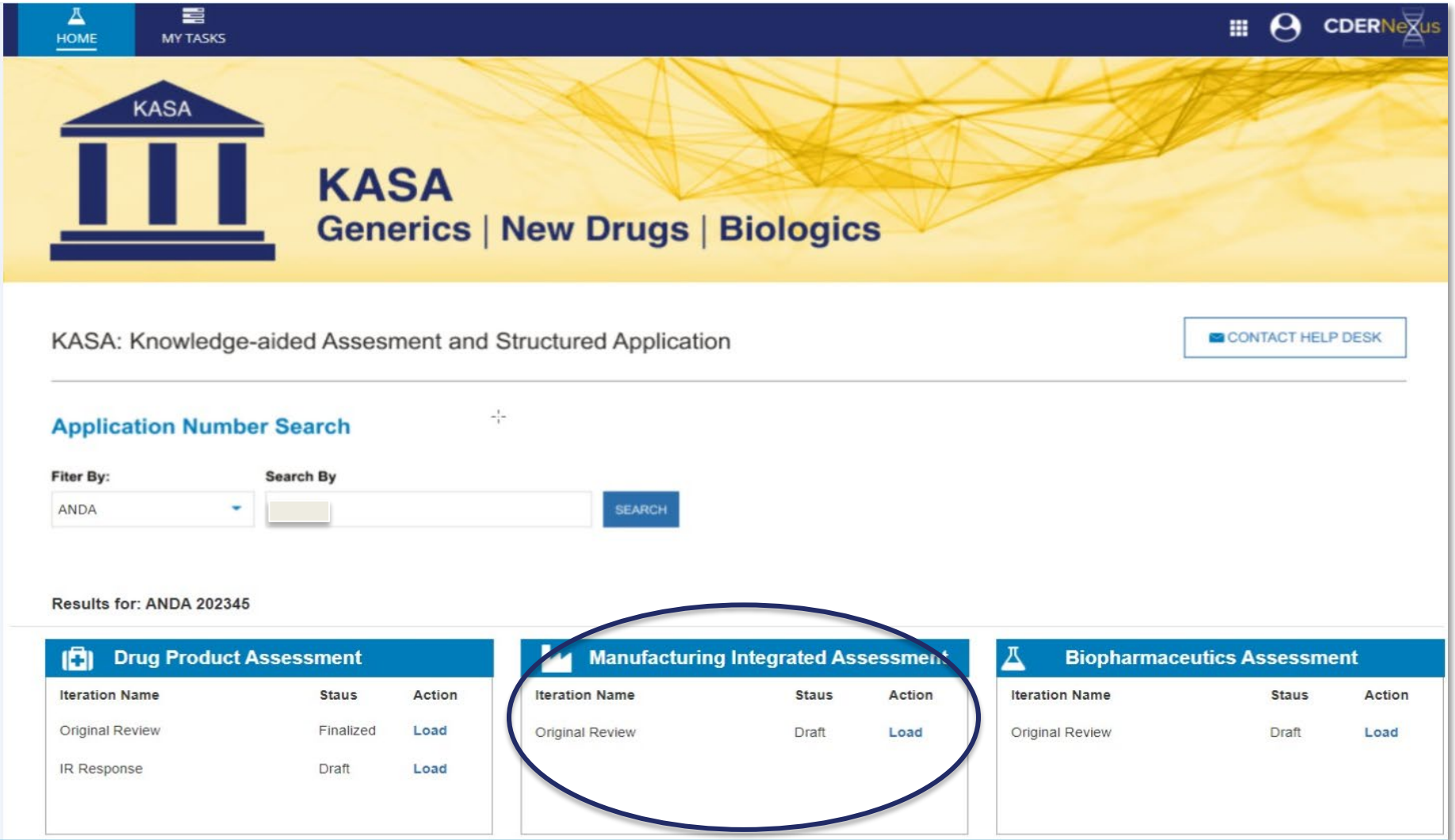
"Structured Descriptors" to Capture Control Strategy

Control Strategy	Acceptance Criteria	Generalizable Rationale for Control Strategy	Explanation Applies to A/NDA	Supporting Information Linked to Submission
Raw Material CMA	NMT X%	Rationale A Rationale B Rationale C		
Drug Product Specification Attribute A B C	Impurity Limit %	Approach D Approach E Approach F		

Descriptor:
Structured Knowledge for Control Strategy/Rationale

Informatics to Detect Control Strategy/ Attribute Outliers

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Biopharmaceutics Assessment
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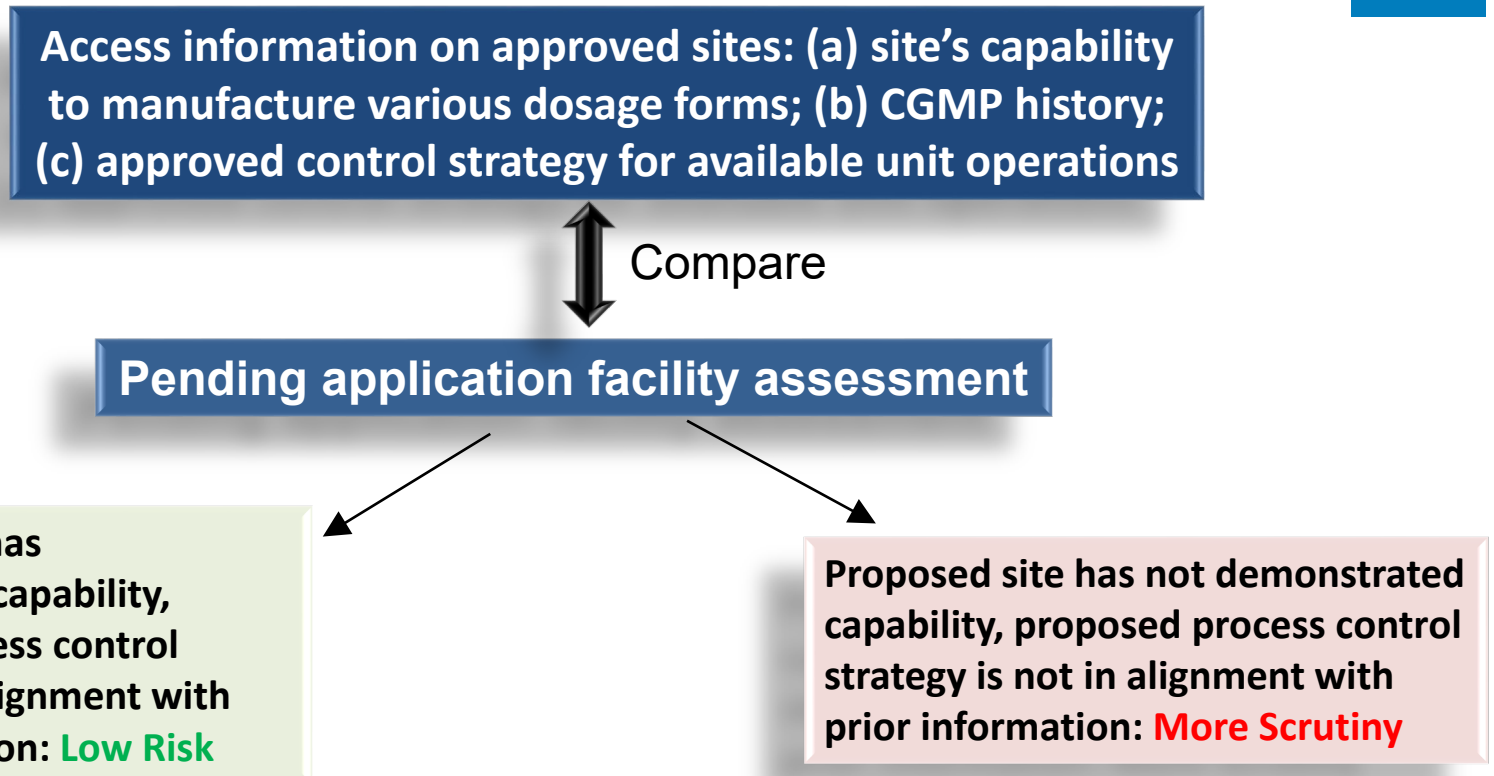
KASA Captures Manufacturing Risk Control in a Structured Format

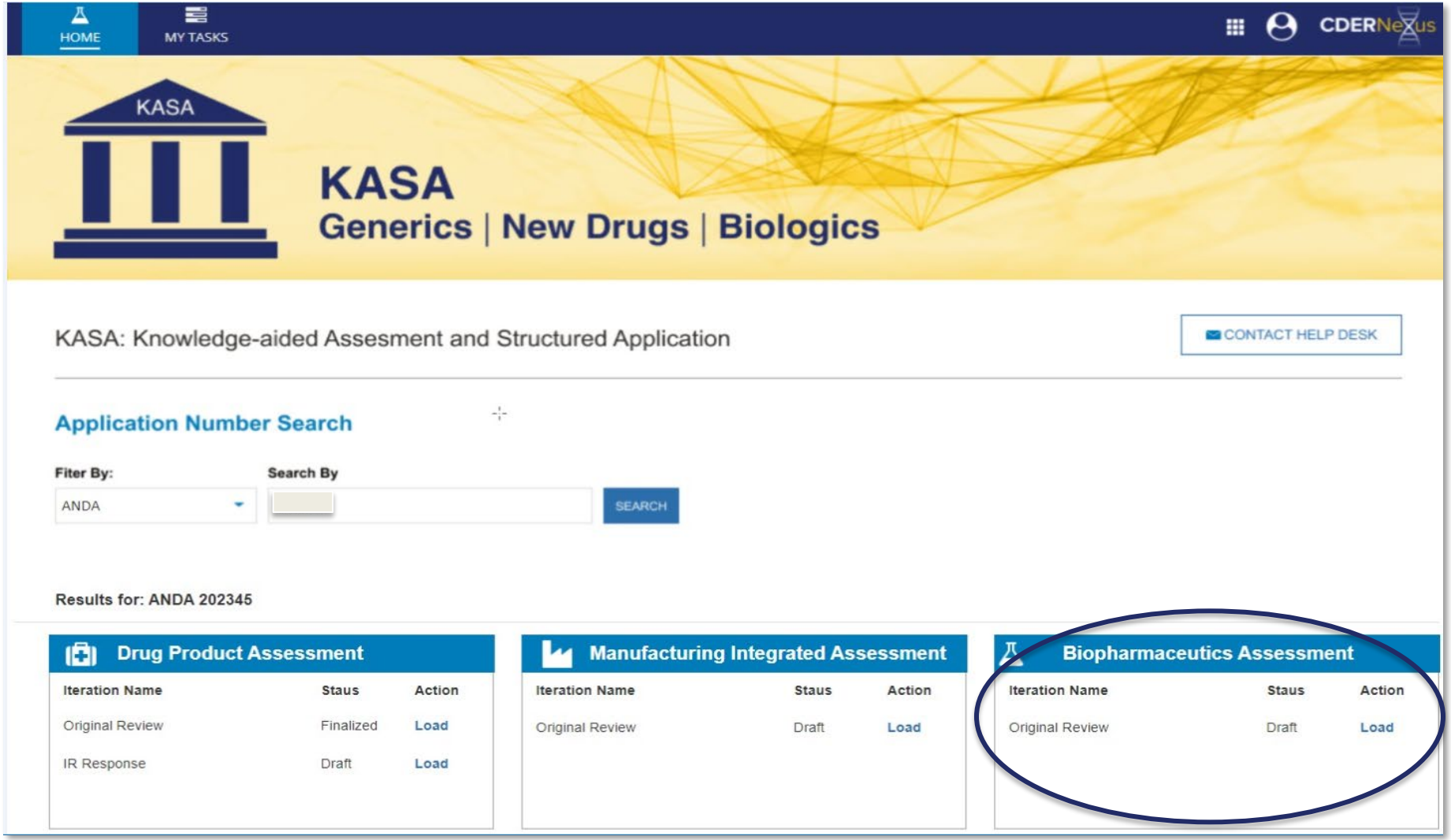
	Initial Risk	Unit Operation	Manufacturing Risk Control Dropdown Menu		Assessment Comment	Supporting Information Link
CQA 1 / Dissolution	High/ Medium/ Low	Wet Granulation	Process Factor	Approach A Approach B Approach C		
			Facility Factor	Approach H Approach I Approach J		
		Compression	Process Factor	Approach M Approach N Approach O		
			Facility Factor	Approach S Approach T Approach V		

Descriptors:
Process Design & Development, In-Process Controls, Scale up approaches

Descriptors:
Prior experience, Site History

Integrated Manufacturing Risk Analytics

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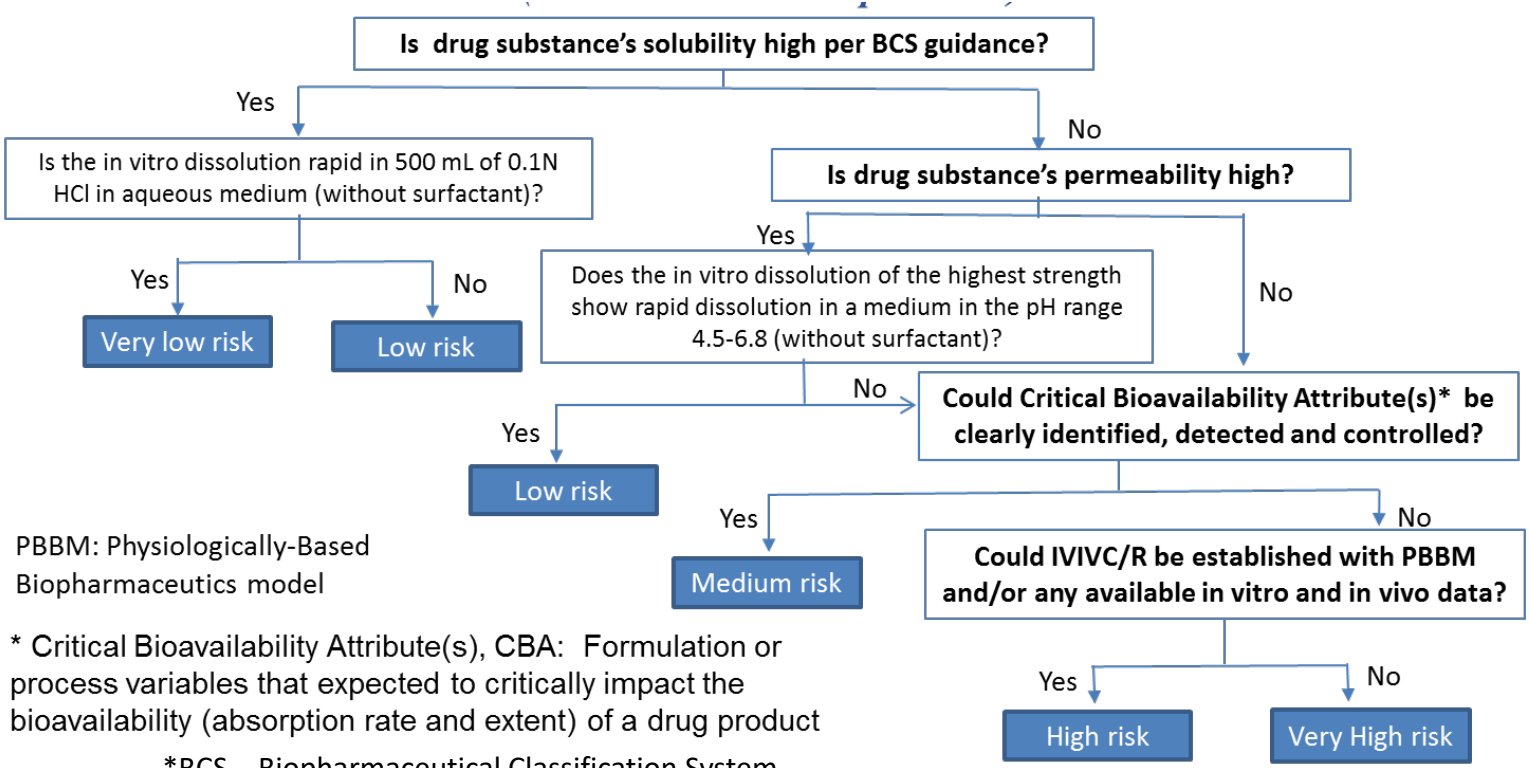
Initial Biopharmaceutics Risk Categories

Biopharmaceutics Risk Level	Examples of Biopharmaceutics Risk Mitigation Approaches
Very Low	Standardized dissolution test
Low	Adequate method development to justify dissolution method and acceptance criterion
Medium	In vitro approach is used to mitigate the biopharmaceutics risk. Dissolution test should target to detect meaningful changes in identified critical bioavailability attributes to provide insight into the in vivo performance
High	IVIVR is used to support patient-centric dissolution test (Based on available in vitro/in vivo data and/or PBBM)
Very High	In vivo studies are used to develop IVIVC/R to support patient-centric dissolution test

KASA Capture Biopharmaceutics Risk Using Defined Decision Tree Algorithms



PBBM: Physiologically-Based Biopharmaceutics model

* Critical Bioavailability Attribute(s), CBA: Formulation or process variables that expected to critically impact the bioavailability (absorption rate and extent) of a drug product

*BCS – Biopharmaceutical Classification System

Where is KASA Today

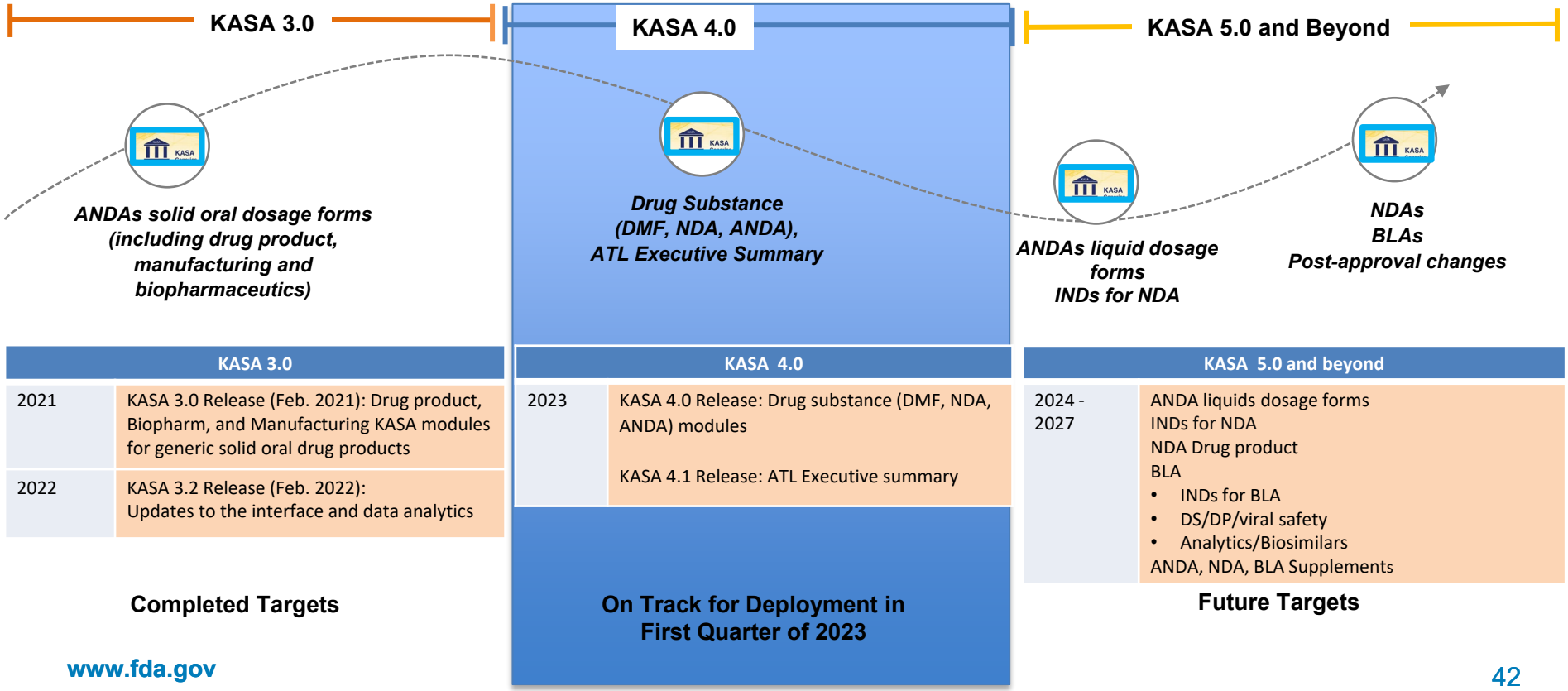
- KASA Enables the Vision of Knowledge Management

To date, KASA has Analytical reports (17) that provide assessors with critical information for making informed decisions based upon KASA's structured knowledge of drug products/facilities.

- OPQ has taken significant steps towards solidifying the use of KASA among assessor since Go-Live in 2021:

Assessments Finalized	Drug Product Assessment	Manufacturing Integrated Assessment	Biopharmaceutics Assessment
	535	505	396

Roadmap for KASA IT Production



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On Track for Deployment in First Quarter of 2023

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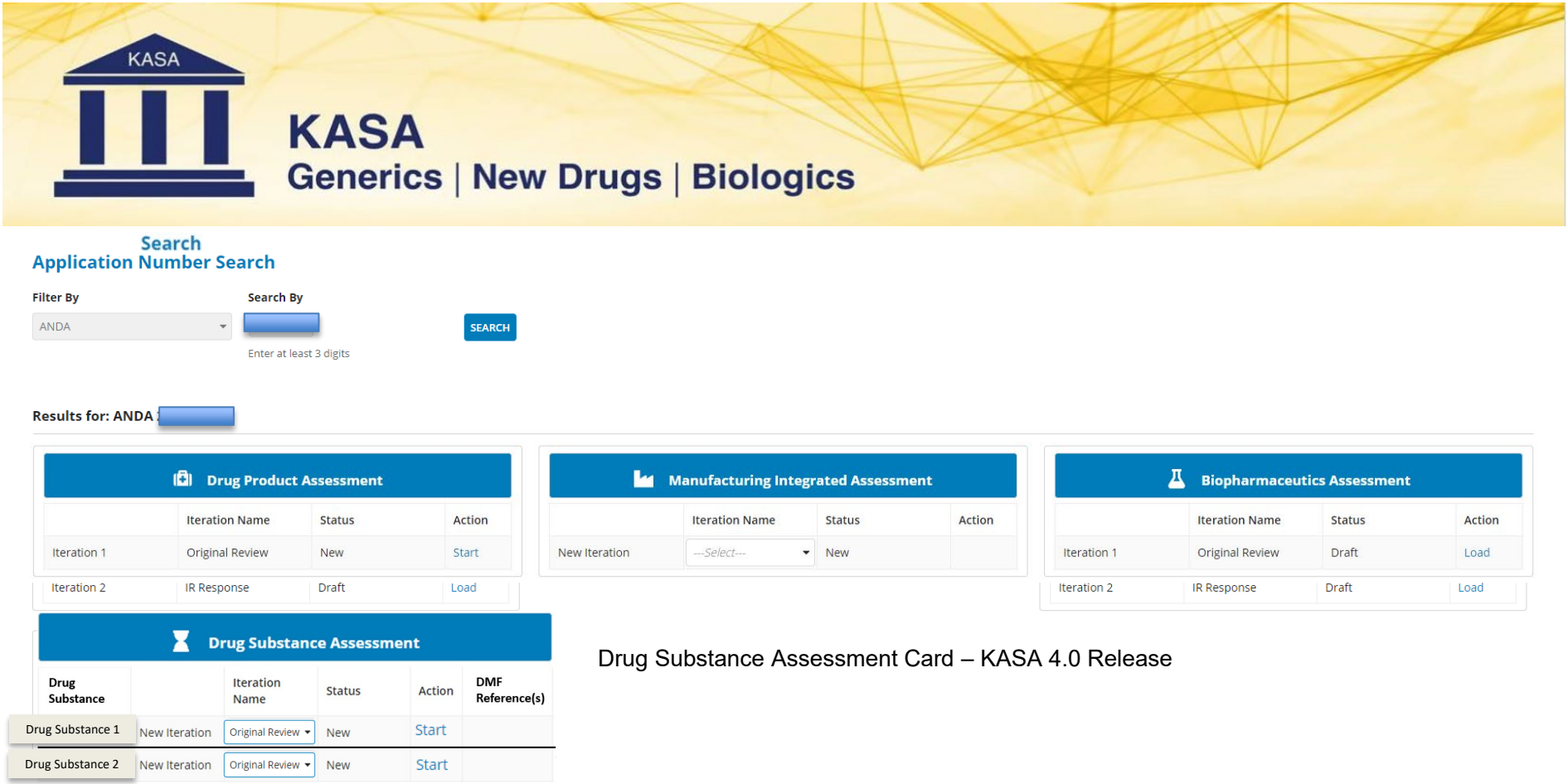
Future Targets



Drug Substance Assessment Card – KASA 4.0 Release

KASA

KASA

Generics | New Drugs | Biologics

Application Search

Filter By

NDA

Search By

SEARCH

Enter at least 3 digits

Results for: NDA

Drug Substance Assessment

Drug Substance		Iteration Name	Status	Action	DMF Reference(s)
Drug Substance 1	New Iteration	Original Review	New	Start	
Drug Substance 2					

KASA System

Measures risk associated with how a product is designed and manufactured (established rules and algorithms)

Evaluates how risk is mitigated and controlled through product design features and applied quality standards

Assesses manufacturing controls and the demonstrated capability of facilities involved

Takes knowledge management to a whole new level and emphasizes quality throughout the product's lifecycle

KASA and Manufacturing/Facility Evaluation

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

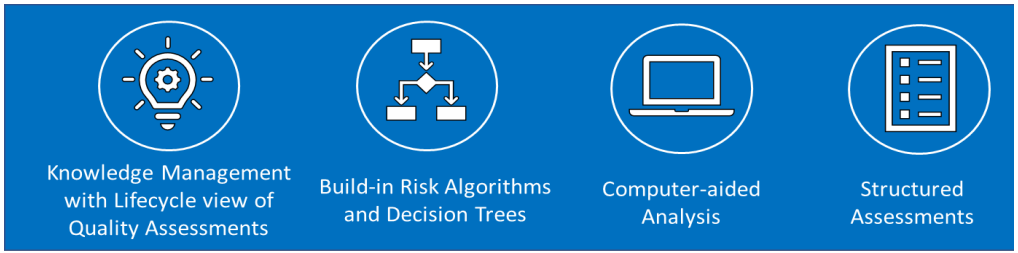
November 3, 2022

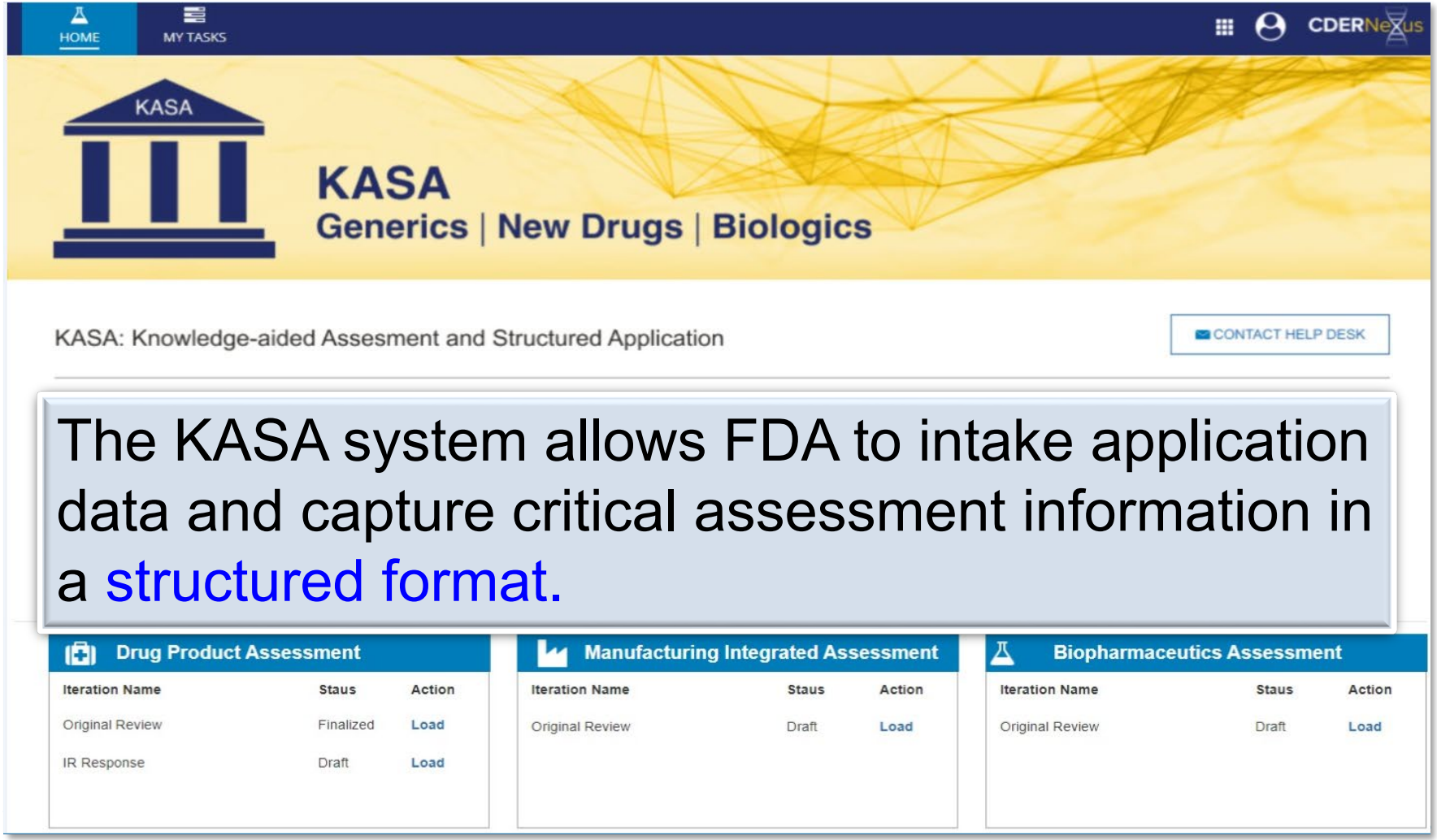
Stelios Tsinontides, PhD
Director
Office of Pharmaceutical Manufacturing Assessment (OPMA)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Rakhi B. Shah, PhD
Associate Director of Science & Communication
Office of Pharmaceutical Manufacturing Assessment (OPMA)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

- KASA tool & Integrated quality assessments
- KASA roadmap for manufacturing
- KASA analytics
- Summary

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KASA for Manufacturing Assessment

Measure risk associated with product design and manufacturing (established rules and algorithms)

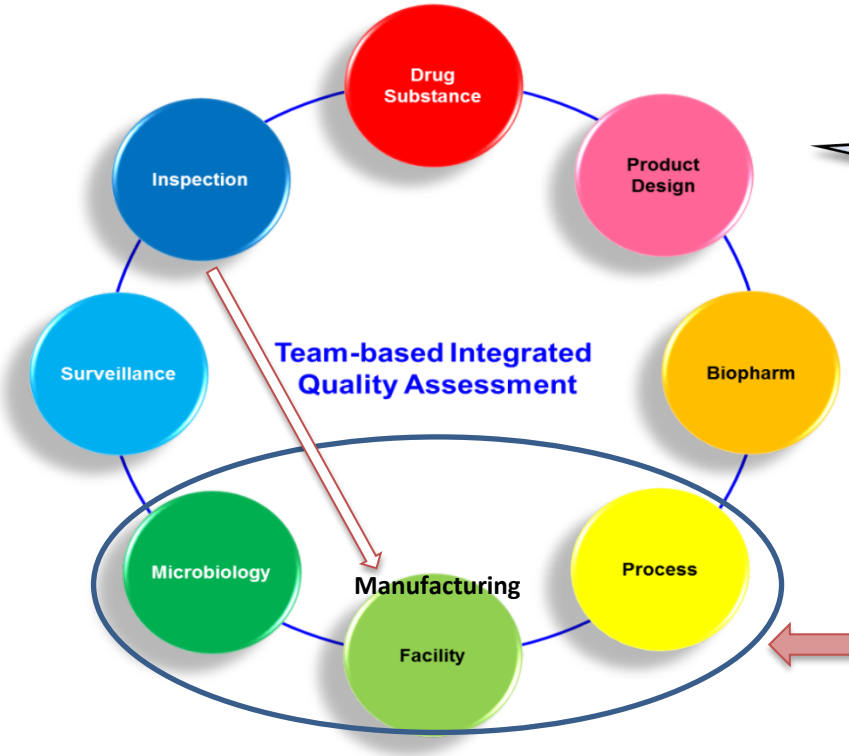
Evaluate risk mitigation and control through product design features and applied quality standards

Assess manufacturing controls and the capability of facilities

Take knowledge management to a whole new level and emphasize quality throughout the product's lifecycle

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

Integrated Quality Assessment (IQA)



Inclusive of drug substance, drug product, manufacturing, and facilities, and maximizes each team member's expertise

OPMA

- Pre-marketing applications:
  - ❑NDA
  - ❑ANDA
  - ❑BLA
- Post-marketing applications – (A)NDA, BLA supplements

Science- and Risk-Based approach that is patient-focused

Manufacturing KASA Roadmap

KASA 3.0

FY 2021

Manufacturing modules for generic solids; data analytics

KASA 5.0

FY 2023

Manufacturing, micro modules for generic liquids; data analytics

KASA 7.0

FY 2025

Manufacturing modules for NDA solids including Established conditions; data analytics

Liquids will go next

KASA 8.0

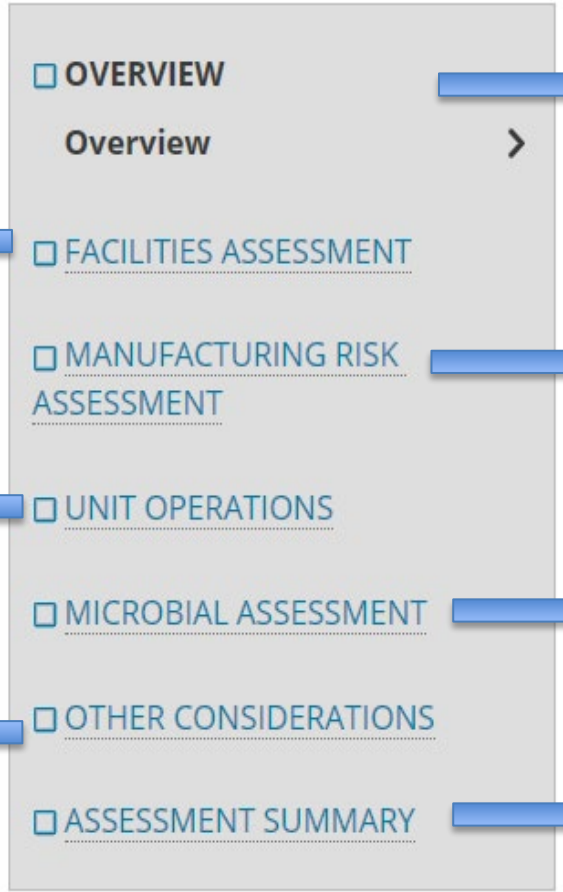
FY 2025+

Biologics micro and facilities modules

Implemented

OPQ Internal development and evaluation & implementation in IT platform

Manufacturing KASA for Solid Generics



Basic ANDA Information, drug substance, drug product, facilities list

Facilities risk assessment for all commercial drug substance and drug product manufacturing, testing, and primary packaging facilities

Initial risk for drug product manufacturing assessment include factors for drug product, drug substance, facilities, unit operations

Each drug product unit operation assessment includes type, equipment, in-process controls, process parameters, design & development consideration, process development, scale up

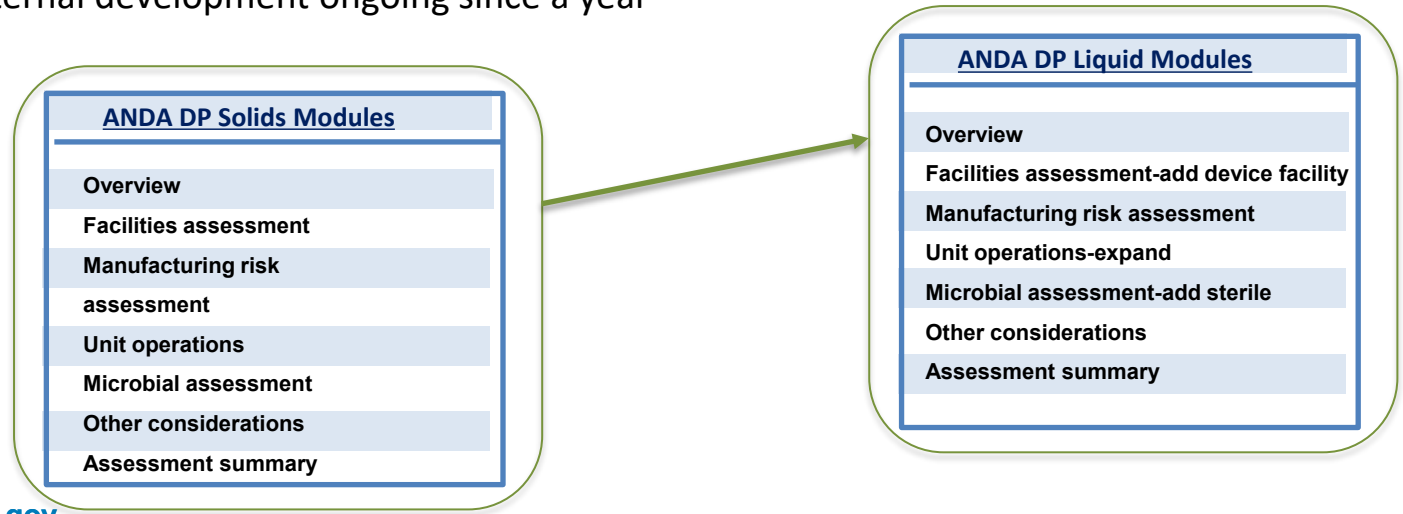
Microbial assessment for drug product control (non-sterile)

Executed and master batch records, yield, reconciliation, hold time, comparability protocol, process validation (if applicable)

Assessment discipline summary and risk update table

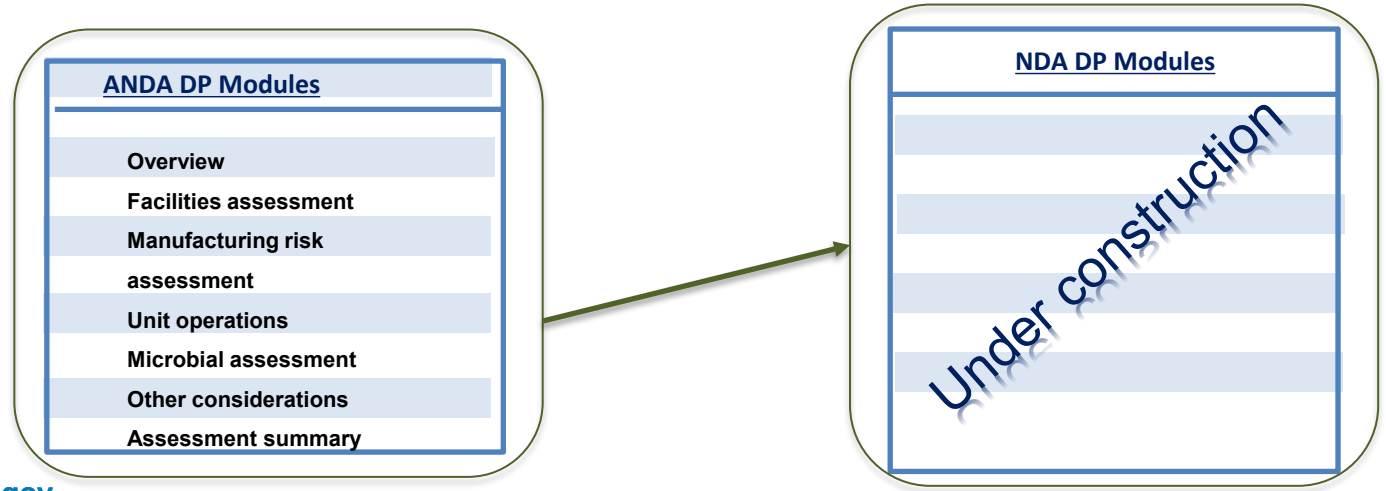
Manufacturing KASA for Liquid Generics

- Start with developing interface for ANDA liquid products by leveraging existing generic solids module
- Develop combination products module
- Develop sterile microbiology module- aseptic and terminally sterilized products
- Develop extractable/leachable module
- Expand/enhance/align unit operations for liquid products
- Internal development ongoing since a year



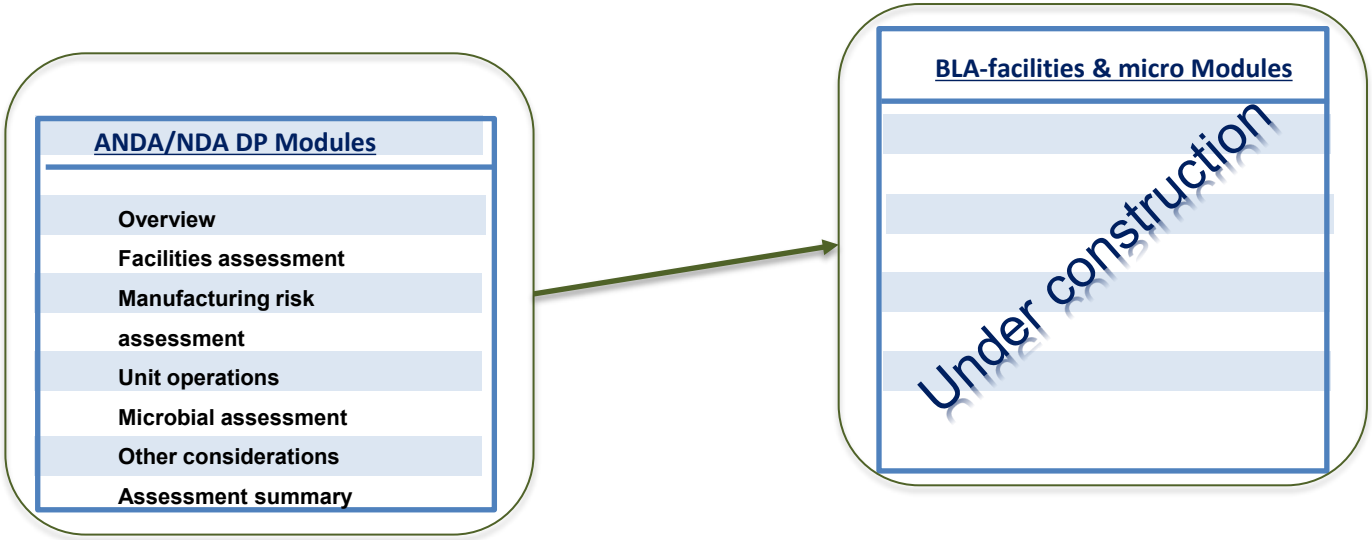
Manufacturing KASA for New Drugs

- Start with developing interface for NDA solid oral products leveraging existent generic manufacturing module, then develop liquids
- Use Project Orbis, Product quality assessment aid, Real-time oncology review programs into consideration when developing NDA modules
- Develop non-sterile microbiology module-prototype developed
- Integrate established conditions and Post Approval Change Management Protocols in KASA modules
- Add complex products and other unit operations not covered in generics platform: e.g.: Transdermal, Topicals



KASA for Biologics-Facilities & Micro

- Identify areas from A/NDA micro and facilities modules needed incorporate in the biologics KASA
- Modify risk assessment for facilities to make them suitable for biologics
- Integrate established conditions and Post Approval Change Management Protocols in KASA modules
- Close collaboration with Office of Biotech Products in developing KASA modules for biologics



Manufacturing Risk Control

	Initial Risk	Unit Operation	Manufacturing Risk Control Dropdown Menu		Assessment Comment	Supporting Information Link
CQA1 / Dissolution	High / Medium / Low	Wet Granulation	Process Factor	Approach A Approach B Approach C		
			Facility Factor	Approach H Approach I Approach J		
		Compression	Process Factor	Approach M Approach N Approach O		
			Facility Factor	Approach S Approach T Approach V		

Descriptors:
Process Design & Development, In-Process Controls, Scale up approaches

Descriptors:
Prior experience, Site History

Manufacturing Facilities Data Analytics

Input

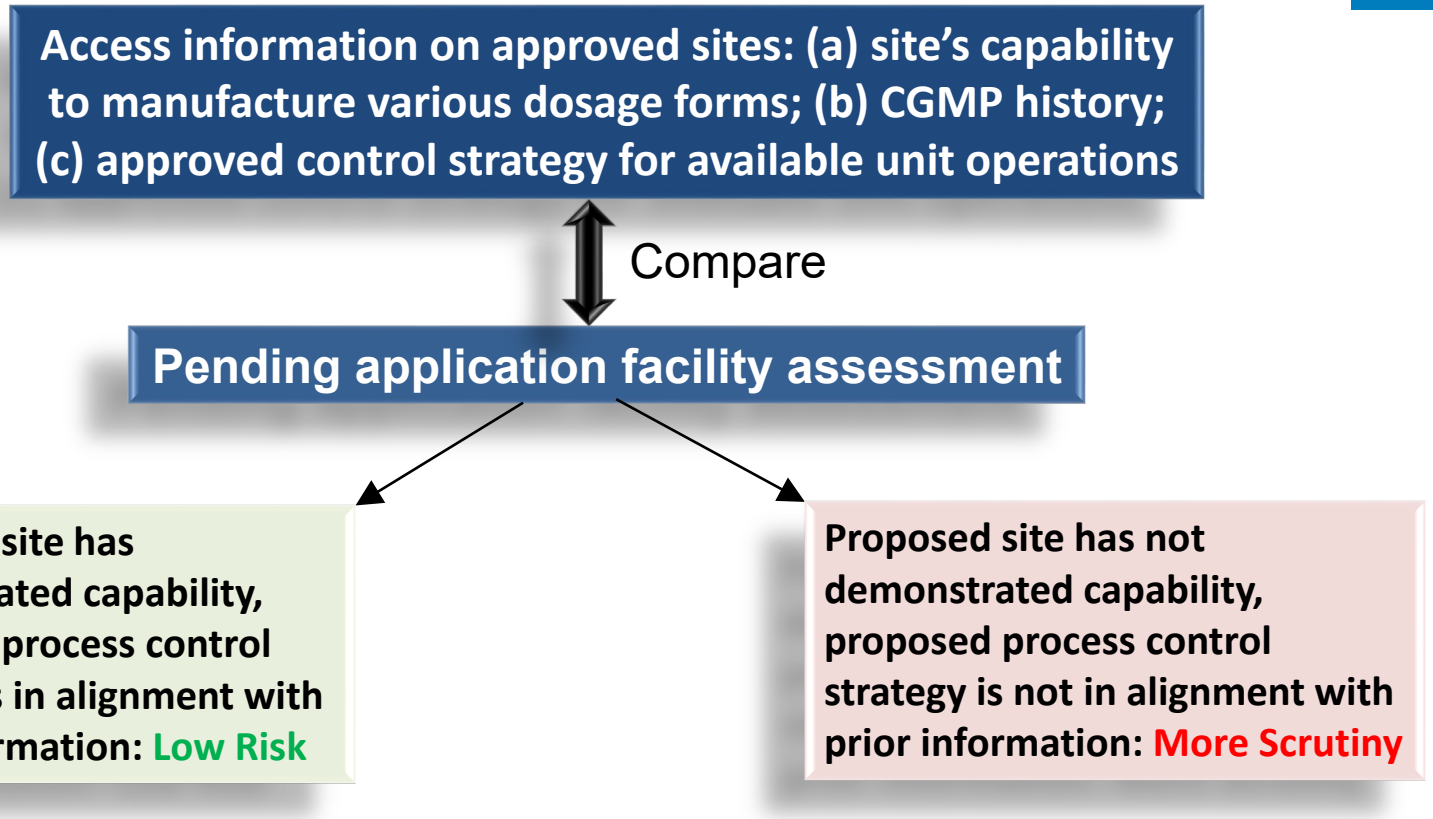
Application ID		xxx			
FEI		yyy			
Profile Code		TCM			
Unit Operations of Interest		Wet Granulation-Drying-Milling	Blending	Compression	Coating-functional

Output

Table : Other applications at FEI yyy with relaed product profile codes and unit operations of interest

Application ID/Link to Assessment	Drug Product Name	Profile Code	Outcome of Facility Assessment	Date of Facility Assessment	PAI/704(a)(4) Indicated	Drug Load	Post Approval Inspection	Unit Operations					
								Wet Granulation-Drying-Milling	Blending	Compression	Coating || functional	Roller Compaction	Encapsulation
xxx	XXX Tablets, USP 1 g	TCM	Pending					X	X	X	X		
aaa	Headache tablets, 10 mg	TCM	Pending		Yes 704(a)(4)	Med	Yes		X	X			
bbb	Blood pressure tablets, 2.5 mg	TCM	Approve	date	No	Low	Yes		X	X			
ccc	Headache tablets 200 mg	CHG	Approve	date	No	High	No		X				**X**
eee	Def Tablets, 6.25 mg and 12.5 mg	TCM	Approve	date	Yes PAI	Med	No		X	X			
Experience on Unit Operations in current application with solid oral Products								Yes	Yes	Yes	No		

KASA Analytics - Facilities



Summary

- ✓ KASA improves overall efficiency and helps making regulatory decision by improving the manufacturing and facilities knowledge management

- ✓ KASA for liquids, new drug products manufacturing modules are build using the same approach as KASA for generics, but include unique elements and analytics tools

- ✓ Emphasizes concept of integrated assessment with respect to manufacturing process and facilities throughout the drug product lifecycle (from NDA to latest ANDA)

Application of KASA to New Drugs

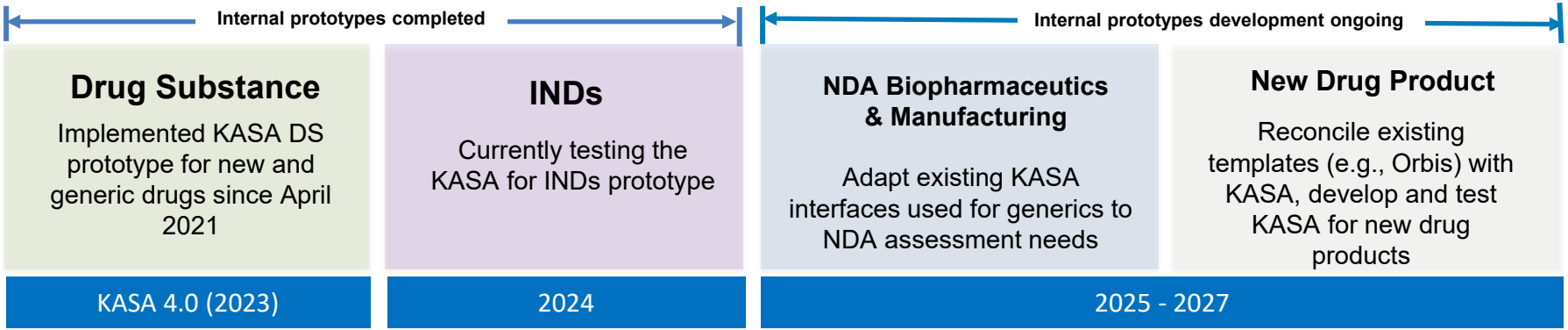
Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

November 3, 2022

Larisa Wu, PhD
Associate Director of Science and Communication
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

KASA for New Drugs

- Build on the success of KASA for generics and expand to new drug assessment.
- Involve the users (assessors) in all stages of development, testing, implementation, refinement, and communication of IT requirements for KASA interfaces.



KASA for Drug Substance (DS)

Goal

To create and implement KASA for DS applicable for assessment of API information submitted in NDAs, ANDAs, and DMFs.

- Quickly identify problems with the DS synthetic pathways that can potentially generate high risk impurities
- Apply consistent standards for assessment of DS information in NDAs, ANDAs, DMFs
- Inform decision making and increase efficiency of assessment
- Complete IQA review for generic solid oral dosage forms in KASA

KASA for DS Roadmap

Development of KASA for DS prototype

Dec 2019 – Mar 2021

- ***KASA for DS (NDAs, ANDAs, and DMFs)***

Implementation of KASA for DS prototype

Apr 1, 2021 – present

To date, dozens of APIs assessments completed

KASA for DS in CDER IT platform

KASA 4.0
KASA for DS modules

2023

KASA 4.2
KASA for DS analytics

2024+

Ongoing discussions with CDER IT and GSRS* on KASA for DS modules and analytics

OPQ Internal development and implementation

CDER IT platform

*GRSR – Global Substance Registration System

Highlights of KASA for DS

Drug Product Modules | **Manufacturing Modules** | **Biopharm Modules**

KASA 3.0 and enhancements

ATL Executive Summary

Summary Overview

Drug Substance Modules

- Overview
- Drug Substance Risk Assessment
- Drug Substance Manufacturing*
- Drug Substance Characterization
- Drug Substance Specification
- Drug Substance Stability

- *Structured DS Synthetic Pathway, Chemical lookup and registration* (developed in GSRS and integrated with KASA)
- Analytics - *to search, visualize, and analyze DS synthetic pathways*

KASA 4.0 and enhancements

Structured DS Synthetic Pathway

	Format	Function of Synthetic Step	Manufacturing Risk Control		Assessment Comment	Supporting Information Link
Assessment of Synthetic Steps	Full	Reaction	**Synthetic inputs & outputs**	Substance name A Substance name B		
			Control	Approach 1 Approach 2 Approach 3		
	Simplified	Separation/ Purification	**Synthetic inputs & outputs**	Substance name C Substance name D		

Chemical Structures Library/GSRS

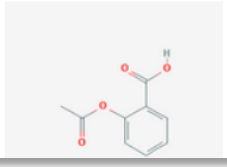
Synthetic Process Design & Development, Critical Process Parameters, In-Process Controls

Chemical Structures Library/GSRS

+ control of starting materials, intermediates, reagents, impurities

Structured Chemical Structures

- Chemical structures captured and retrieved through integration with GSRS database

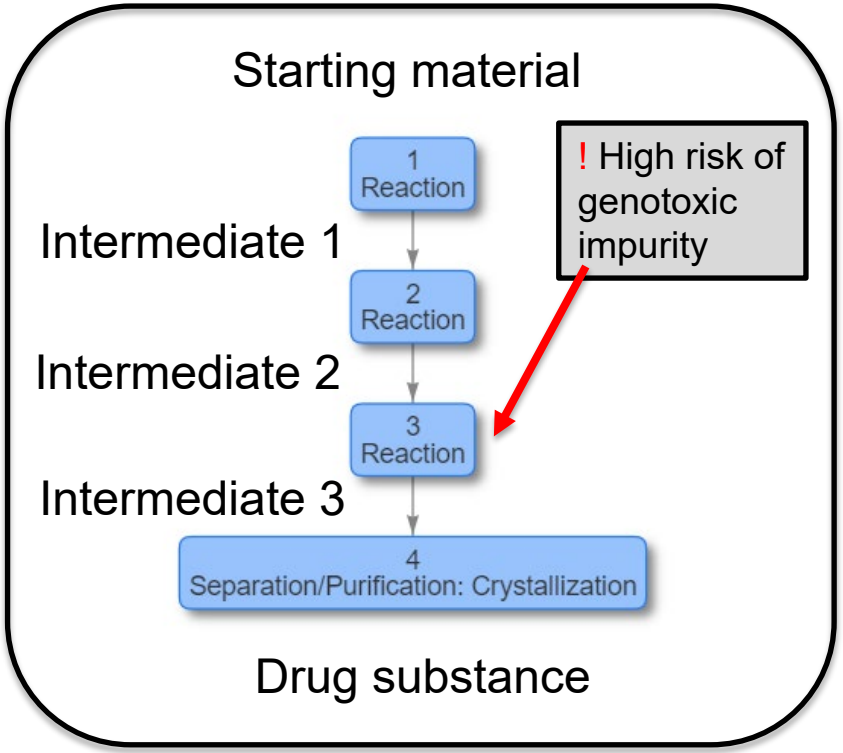
Chemical name	Structure	Role	Identifiers	Additional note	Edit
ID: *Chemical Name:* aspirin		Drug Substance	*CID:* 2244 *UNII:* *Smile:* CC(=O)OC1=CC=CC=C1C(=O)O	N/A	Edit + x

SD files - Chemical **structure-data file** format that can associate data with one or more chemical structures;
Tables of information can be translated into structures which can then be searched.

KASA for DS Analytics

- DS synthetic routes in KASA can be:
  - Visualized
  - Searched
  - Analyzed
- Analytics tools will enable KASA to search based on DS, reagents, solvents, impurities and display synthetic pathways

- Goal: Identify reactions/combinations of chemicals that potentially generate high risk impurities,
  e.g., nitrosamines.



KASA for IND Roadmap

Development of KASA for IND prototype

2022

Modules of KASA for IND small molecules were developed

Implementation of KASA for IND prototype

2022 - 2023

KASA for IND prototype will be tested, refined and implemented internally

KASA for IND in CDER IT Platform

2024 - 2025

Discussions with CDER IT to communicate requirements of KASA for IND

OPQ Internal development and implementation

CDER IT Platform

Highlights of KASA for IND

1. Streamlines review documentation for future IND assessments
2. Contains a built-in decision tree for selection of IND assessment template
   - Full template
   - Abbreviated template
3. Contains built-in risk assessment considerations to facilitate a consistent review approach across assessors
4. Is expected to enhance assessment efficiency
5. Paves the way for future knowledge management integration which spans a product's lifecycle from the initial IND phase.

KASA for New Drug Product (NDP) Roadmap

Development of KASA for NDP prototype

2022 - 2023

Ongoing discussions to develop modules of KASA for NDP prototype

Implementation of KASA for NDP prototype

2024

KASA for NDP prototype will be tested, refined and implemented internally

KASA for NDP in CDER IT Platform

2025 +

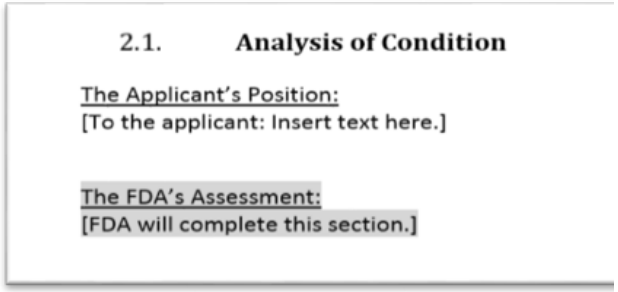
Discussions with CDER IT to communicate requirements of KASA for NDP

OPQ Internal development and implementation

CDER IT Platform

Highlights of KASA for NDP

- Built on the experience with Project Orbis and Product Quality Assessment Aid (PQAA)
  - ORBIS = 'collaborative' assessment of critical oncology drugs between FDA and other regulatory agencies (TGA, HC, Swissmedic, HSA, ANVISA, MHRA)
  - PQAA = unified template that allows applicant to provide the data and analysis, which is followed by FDA commentary and analyses, as needed; application assessment focused on critical analysis, and minimizes copy/paste, and formatting in Word.
- Reconciled the PQAA template and existent KASA interfaces (DS, Manufacturing, Biopharmaceutics)



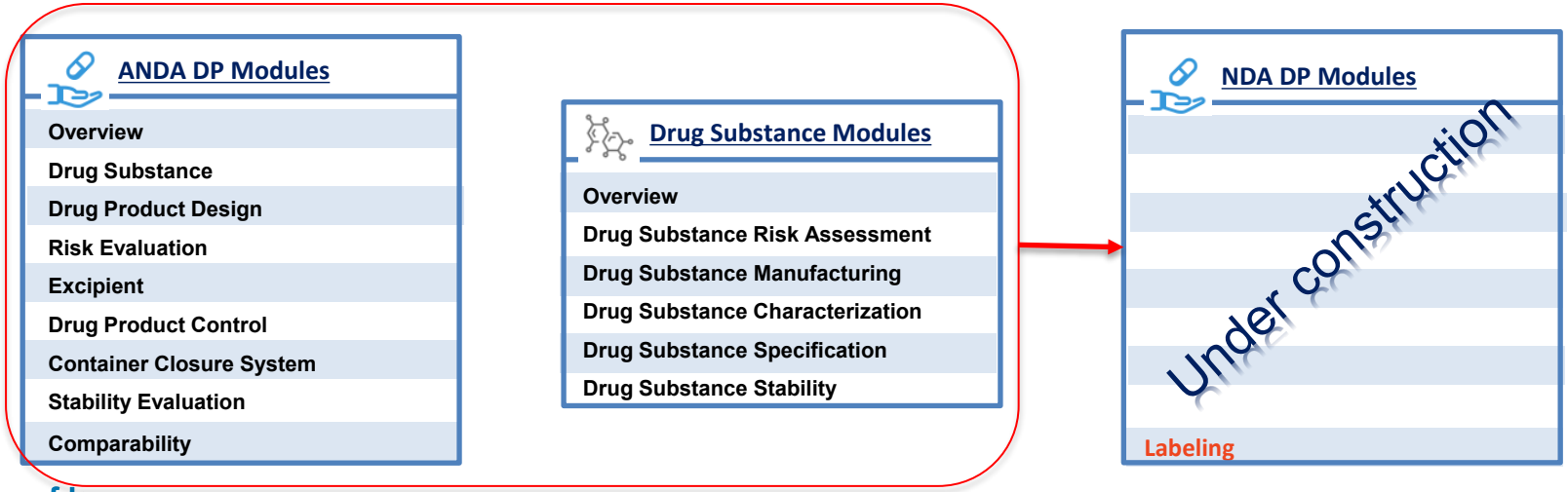
2.1. **Analysis of Condition**

The Applicant's Position:
[To the applicant: Insert text here.]

The FDA's Assessment:
[FDA will complete this section.]

Highlights of KASA for NDP

- Start with developing interface for NDA solid oral products and leverage existent interfaces
- Use the same KASA interface for new molecular entities (NMEs) and 505b2, but develop different analytics
- Develop a separate KASA module for labeling assessment



Conclusions

- KASA for new drug products presents opportunities for knowledge management, consistency in decision making, and improved assessment efficiency
- KASA for new drug products modules are build using the same approach as KASA for generics, but include unique elements and analytics tools based on the needs of new drug products assessment

Application of KASA to Biologics

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

November 3, 2022

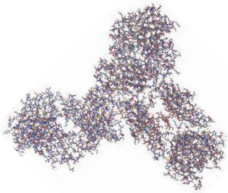
Joel Welch, Ph.D.
Associate Director for Science & Biosimilar Strategy
Vice Chair for Emerging Technology Team
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Key Objectives of KASA System

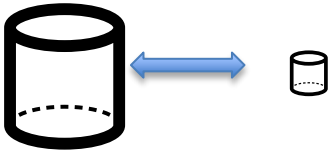
1. Capture and **manage knowledge** during the lifecycle of a drug product (Applicable for biological products)
2. **Establish rules and algorithms to facilitate** risk identification, mitigation, and communication for the drug product, manufacturing process, and facilities (Applicable for biological 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)

How Will KASA for Biological Products Be Different?

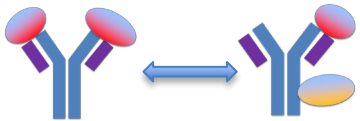
Biological Products can be highly complex



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

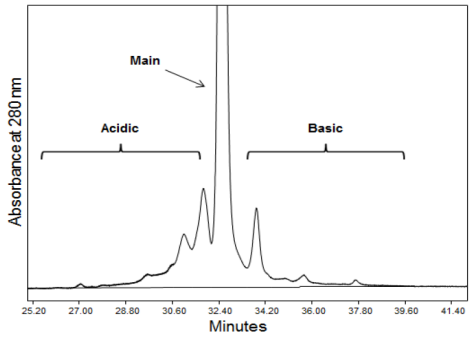


Molecules may have indication specific CQAs



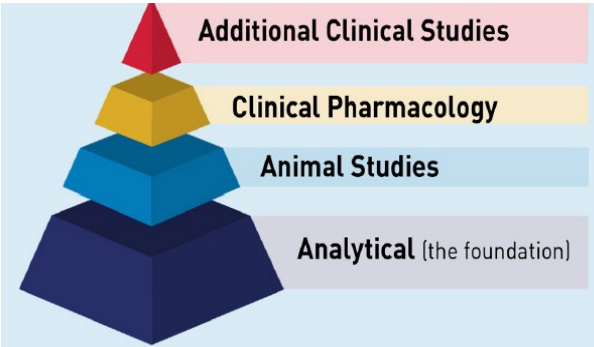
Biological products may contain product-related substances (retaining activity) as well as product-related impurities

CQAs make not always be fully resolved by a given method

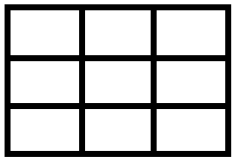


Biological Products Offer Unique Opportunities

Biosimilars and role of analytics



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

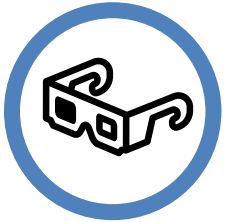


Explosion in use of “Platform” and “Modular” manufacturing approaches

Informatics power in identifying molecules of same target/pathway

KASA for Biologics Roadmap

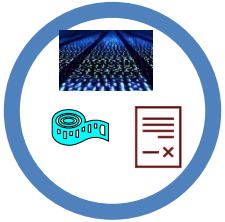
Development of Early Prototype Approach



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)

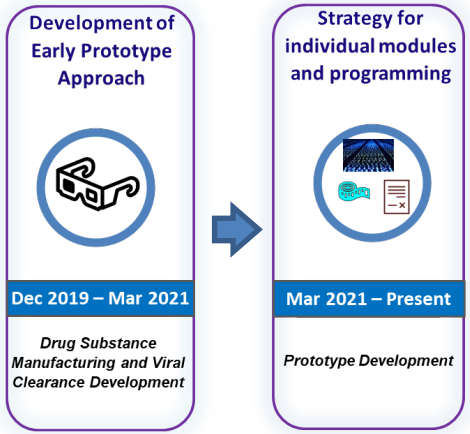
FY 2025+

Phased Integration

OPQ Internal development and evaluation

Implementation

Biotechnology KASA First Prototype Modules



- Designed for new fed-batch Monoclonal antibodies BLAs
- The majority of BLA submissions
- Prototypes apply to new BLAs (though framework can be adapted for supplements)
- Two prototype modules created
    1). A risk-based assessment module for DS manufacturing
    - Designed to capture description for manufacturing steps
    - Process parameter Range evaluation
    - Key elements that aren't characterized, but need to be described

    2). Viral Clearance/Adventitious Agents Testing

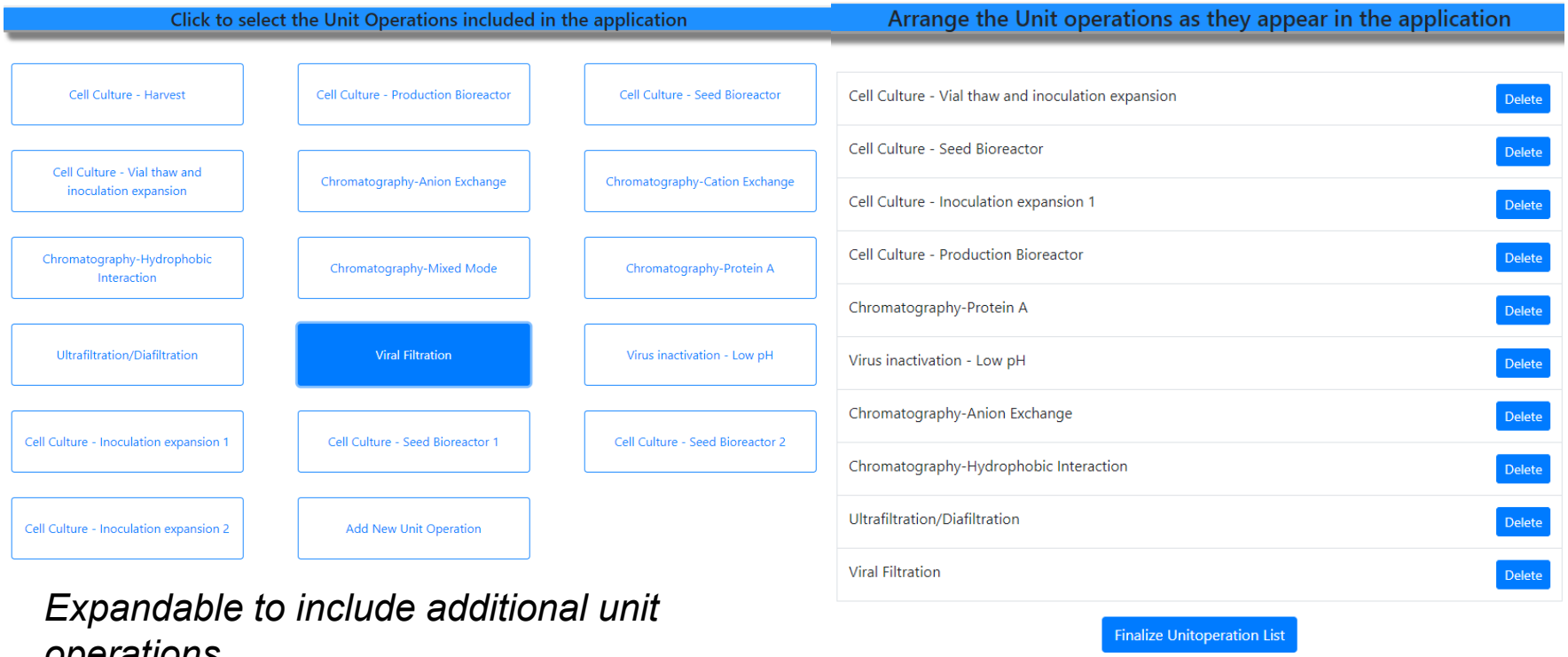
Key Features of Prototypes

- For risk-based assessment module 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
- For both DS Manufacturing and Viral Clearance/Adventitious Agents Module:
  - 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

Piloting and Ongoing Development

- Will include testing of system using already submitted applications as well as new applications
- Identifying gaps and outcomes from pilot experience
- Effort with focus on areas to continue developing
  - Expansion of pilot modules to additional cell substrates (e.g., e Coli) and additional unit operations (e.g., perfusion systems)
  - Identification of additional modules to consider developing (e.g., methods)

Example: Selection for Unit Operations



Expandable to include additional unit operations

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

Drag and rearrange based on manufacturing process

Example: Summary – Viral Clearance

Unit Operation	Claimed LRV (log value)	Include in Total LRV (checkbox)
Chromatography-Cation Exchange	4.3	☑
Chromatography-Protein A	2.9	☑
Viral Filtration	5.9	☑
Virus Inactivation - Low pH	6.6	☑

Capturing Critical Values

Step		Location	Unit Consideration
A	Total LRV	19.7	log_{10}
B	Maximum load of RVLPs in unprocessed bulk (worst case) – "If method other than TEM used, provide justification"	1700000	particles/mL
C	Product titer in cell culture supernatant	1.65	mg/mL
D	Product Yield	70.0	%
E	Maximum Potential Single Dose of DP	2900	mg
F	Volume of Unprocessed Bulk required for single dose	25.11	mL/dose
G	Maximum Potential viral load	42683982.68	particle/dose
H	Log transformed maximum potential viral load	7.63	log_{10}
I	Safety Factor	12.07	log_{10}

Automated Calculations

Adequate Safety Factor

Flag versus Expectation

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

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
- Anticipate a phased implementation where inter-related topics are introduced in groups

Conclusions

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

U.S. FOOD & DRUG ADMINISTRATION

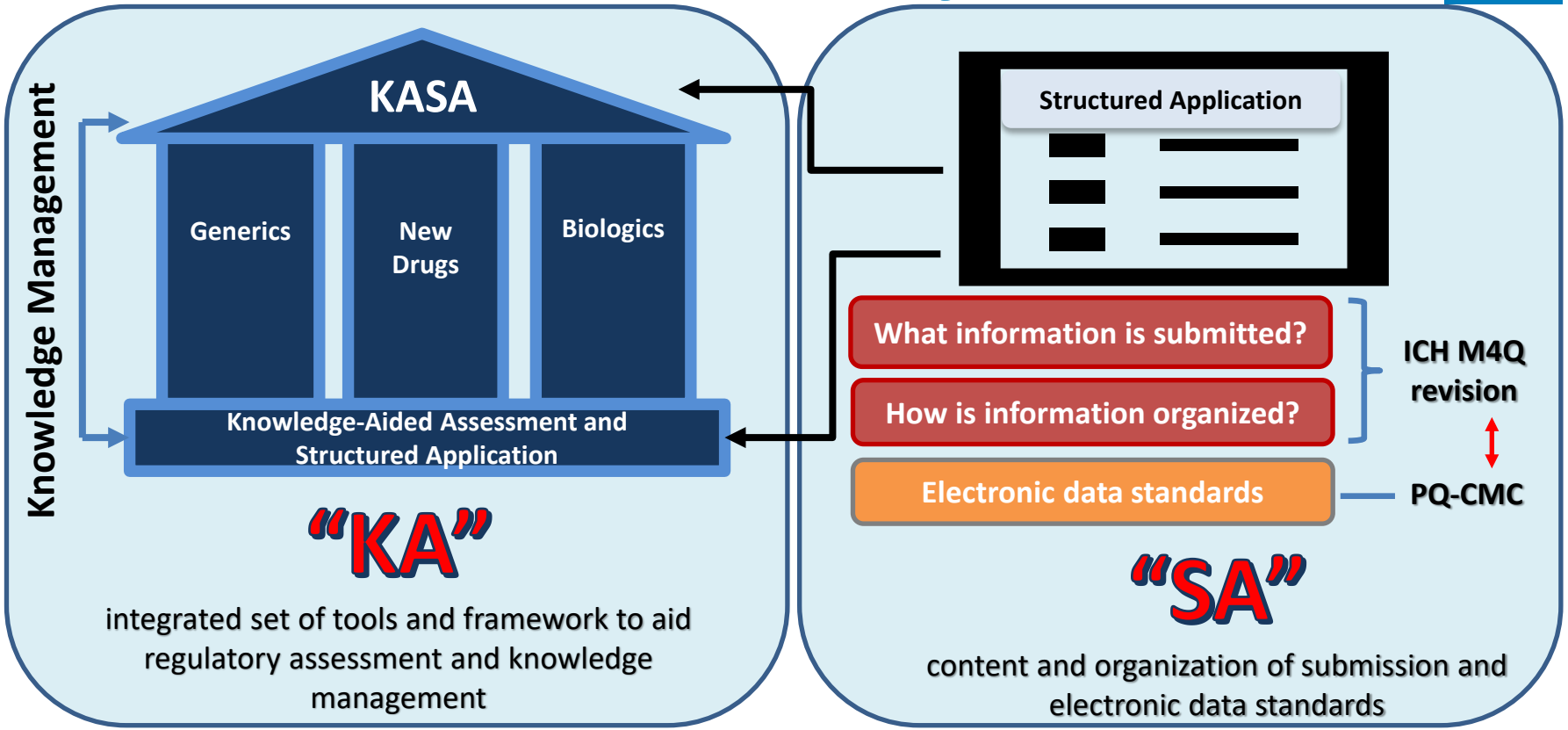
Cloud-based Assessment and Structured Application

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

November 3, 2022

Lawrence Yu, PhD
Director
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rapporteur, ICH M4Q(R2) Expert Working Group

The FDA KASA System



2018 Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

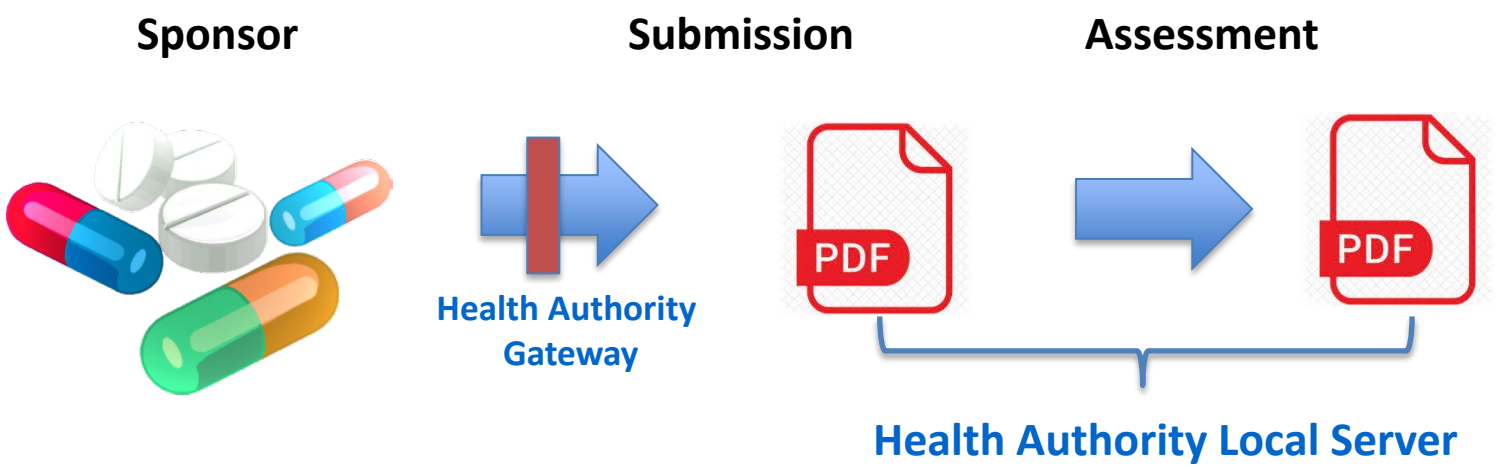
VOTE: Relating to the KASA initiative, should the FDA consider the enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment?

Vote Result: ***YES: 10*** ***NO: 0*** ***ABSTAIN: 0***

Committee Discussion*: The committee unanimously agreed that, relating to the KASA initiative, the FDA should consider enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment under the KASA initiative. Several members stated that this would increase communication while making submissions from industry easier and more transparent. Brand and generic industry representatives on the committee also agreed that KASA would be good for industry and FDA. Members encouraged a flexible design, so data is searchable, easily transposable and exportable for further analysis. Please see the transcript for details of the Committee discussion.*

Vision for future regulatory submission and assessment

Current Regulatory Submission and Assessment

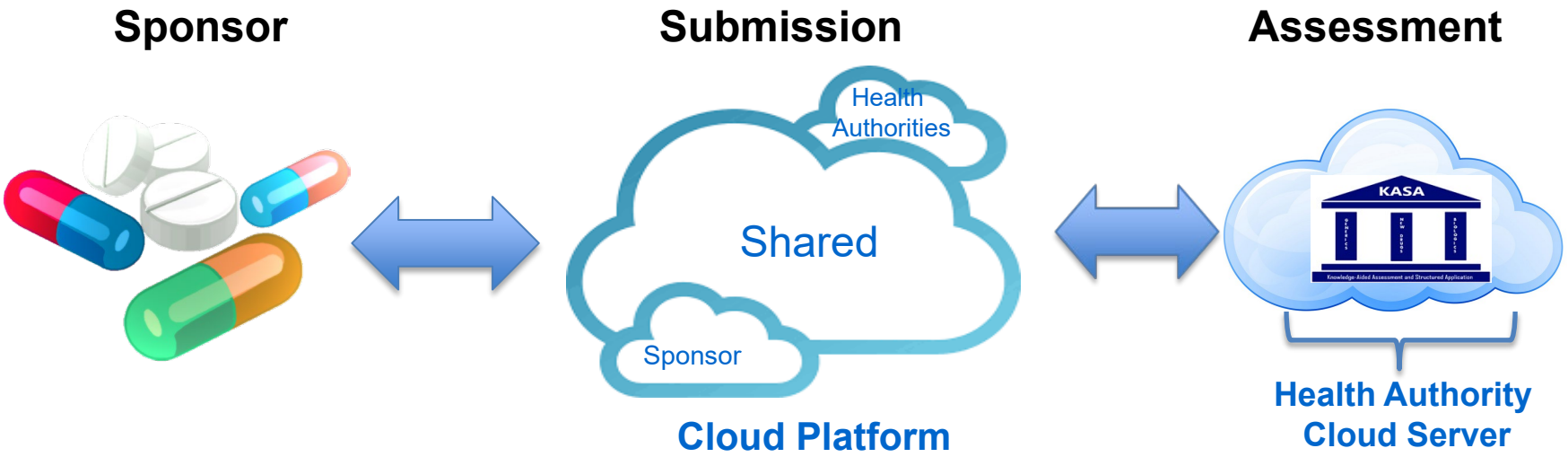


Characteristics: Lengthy unstructured text narrative with dispersed information and the lack of efficient information sharing, knowledge management, and data analytics

FDA's Pharmaceutical Quality Assessment is Moving into Cloud

Characteristics: Lengthy submission with unstructured text narrative and the lack of efficient information exchange. Regulatory assessment moves to structured data enabling efficient information sharing, knowledge management, and data analytics, resulting efficient regulatory assessment

Future Regulatory Submission and Assessment



Characteristics: Both regulatory submission and assessment move to structured data format enabling efficient regulatory submission and assessment, information sharing, knowledge management, and data analytics

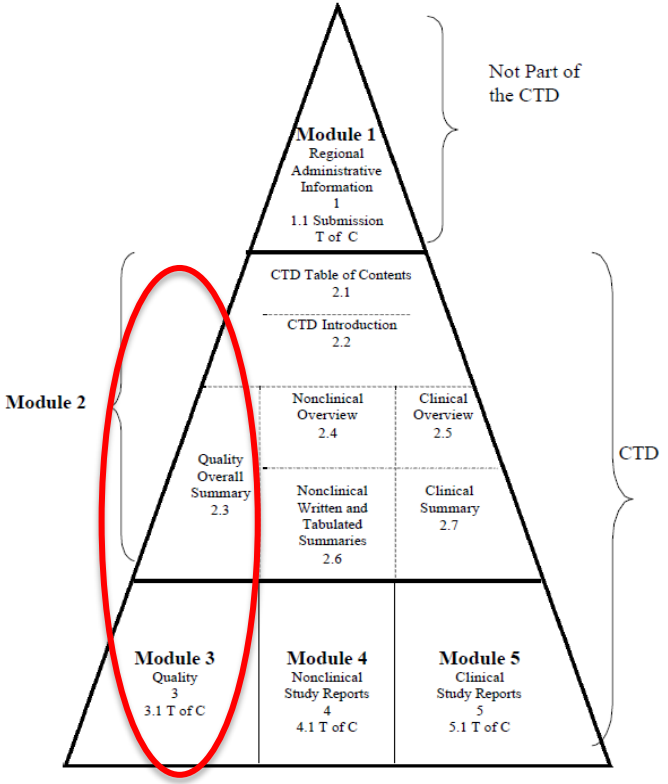
How to Get There?

- Regulatory Assessment Transformation
  - Knowledge-aided Assessment and Structured Applications (KASA)
- Regulatory Submission Transformation
  - Revision of ICH M4Q
  - Pharmaceutical Quality electronic data standards

ICH M4Q(R2): Opportunity for modernization of regulatory submission

What is the ICHM4Q Designed to Do?

- Provides a harmonized structure and format for presenting quality information in Common Technical Document (CTD)/electronic CTD for registration of pharmaceuticals for human use
  - **Module 2 Quality Overall Summary (QOS)**
  - **Module 3 Quality**
- M4Q(R1) was developed in 2002
- Major improvement over paper/local submission formats



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

FDA Guidance for Industry M4Q: The CTD – Quality, August 2001

What Are Perceived Problems?

- M4Q(R1) is now due for revision to further improve registration and lifecycle management efficiency, leverage digital technologies, and accelerate patient and consumer access to pharmaceuticals. The specific drivers for this revision include:

  1. Several ICH regions have not fully implemented ICH M4Q(R1). The modernization will support and clarify global understanding of the CTD, enabling greater regulatory convergence and harmonization, and decrease redundancy.

  2. The M4Q(R2) guideline should align with modern quality guidelines Q8-Q14, and other relevant ICH guidelines that have been developed or given greater focus since the issuance of ICH M4Q(R1).

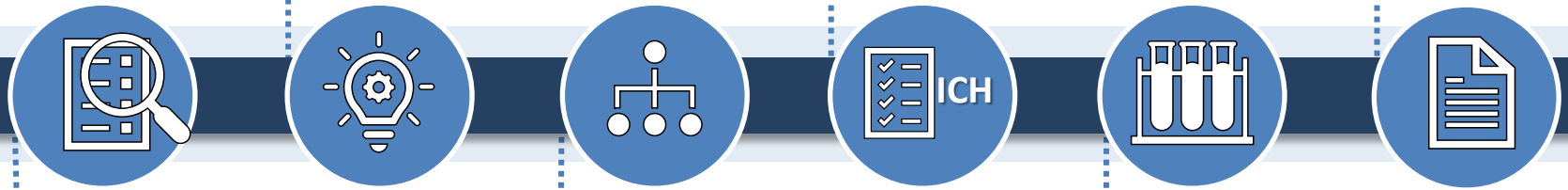
For your expanded interest see *Concept Paper M4Q(R2) Common Technical Document on Quality Guideline Endorsed by the Management Committee on 15 November 2021* ICH Official web site : ICH

What Are Perceived Problems (Continued)?

3. The M4Q(R2) guideline should provide guidance on the location of information supporting multicomponent and/or complex products, such as antibody-drug conjugates, vaccines, advanced therapy medicinal products (ATMPs)/Cell & Gene Therapies & Tissue Engineered Products or combination products that meet the definition of a pharmaceutical or biological product.
4. The M4Q(R2) guideline should facilitate leveraging advances in digital tools, data management and standardization, and analytics to enhance efficiencies and effectiveness of regulatory submissions and assessments, although the structured pharmaceutical quality submission is beyond the scope of M4Q(R2) guideline.

For your expanded interest see *Concept Paper M4Q(R2) Common Technical Document on Quality Guideline Endorsed by the Management Committee on 15 November 2021* ICH Official web site : ICH

What are the Issues to be Resolved?



Expanding the scope of M4Q(R1) guideline to include all pharmaceutical drug substances and products (both chemical and biological)

Establishing the role of M4Q(R2) as the main source of the structure and location of regulatory quality information.

Organizing product and manufacturing information in a suitable format for easy access, analysis, and knowledge management.

Incorporating concepts and data expectations presented in ICH Quality guidelines and aligning with currently recognized international standards and guidelines.

Better capturing the pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure.

Enhancing the Quality Module 2 to facilitate the efficiency and effectiveness of regulatory submissions and assessments.

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M4Q(R2) Objectives

- M4Q(R2) guideline will improve submission and assessment efficiency, resulting in accelerated access to pharmaceuticals by (6Es):
  1. Encouraging global convergence of science- and risk-based regulatory approaches in the preparation of dossiers.
  2. Explaining and defining the organization and positioning of information for Modules 2 and 3.
  3. Enriching communication between regulators and applicants and enhancing lifecycle and knowledge management.
  4. Embracing product and process innovation.
  5. Enabling efficient use of digital tools for submission and assessment and preparing for the closely linked, upcoming ICH guideline on structured pharmaceutical quality submission.
  6. Elucidating regulatory expectations and supporting efficient assessments, decision-making, and actions.

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Benefits of Revised M4Q

Benefits to Patients and Consumers

M4Q(R2) guideline would speed up patients and consumers' access to pharmaceuticals

Benefits of Revised M4Q

Benefits to industry

- Clarifies regulatory expectations
- Facilitates applying the enhanced ICH quality strategy/vision
- Streamlines regulatory application preparation
- Improves the quality of submissions
- Facilitates data and information management
- Promotes communication with regulators
- Fosters harmonization and standardization of information requirements, while increasing regulatory convergence

Benefits of Revised M4Q

Benefits to regulators

- Enhances benefit-risk considerations,
- Increases access to quality data and information
- Streamlines regulatory assessment
- Facilitates oversight of pharmaceutical product quality
- Increases consistency and efficiency in regulatory decision-making and actions
- Improves communication with industry and among regulators

M4Q(R2): Progress

- May 2020, ICH endorsed the M4Q(R2) Proposal
- April 2021, ICH approved the outline of Concept Paper
- Aug 2021, ICH formed M4Q(R2) Informal Working Group
- Nov 2021, ICH endorsed the Concept Paper and Business Plan and formed M4Q(R2) Expert Working Group
- May 2022, Agreement on the high-level conceptual thinking of M4Q(R2)

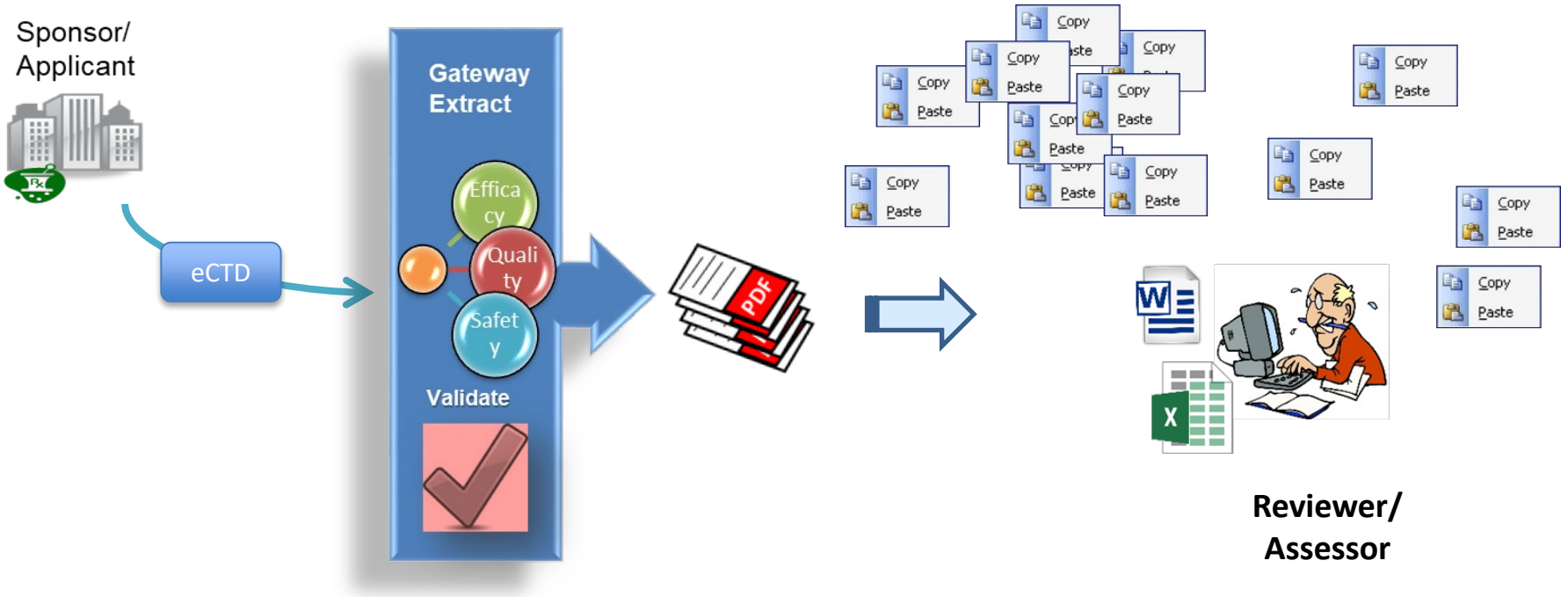
M4Q(R2) Work Plan

Expected Completion date	Deliverable
2021	✓ Final Concept Paper and Business Plan
2023	• ICH M4Q(R2) Step 1
2023	• ICH M4Q(R2) Step 2
2024	• Public workshops on M4Q(R2) Step 2
2025	• Step 3 and Step 4 Adoption of Final Guideline

Ongoing efforts related to structured applications

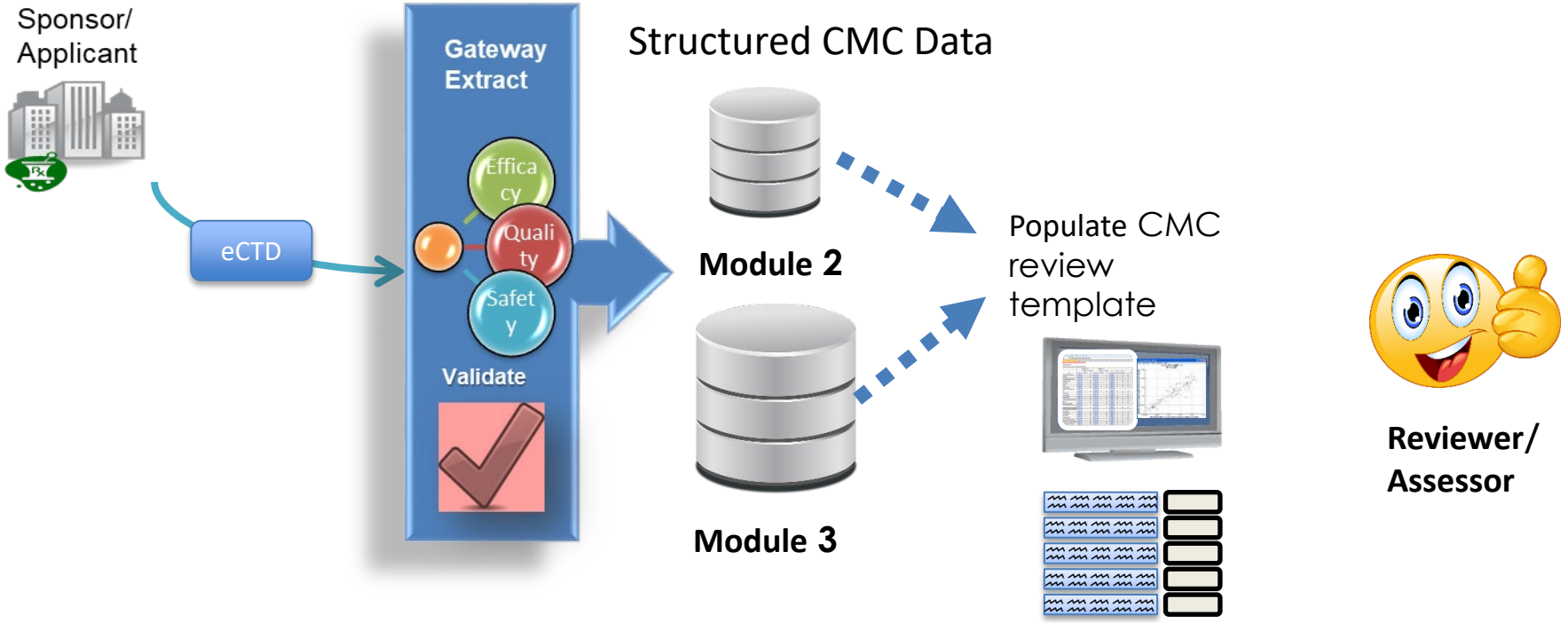
- **Pharmaceutical Quality Electronic Data Standards**

Current CMC Data Submissions and Review



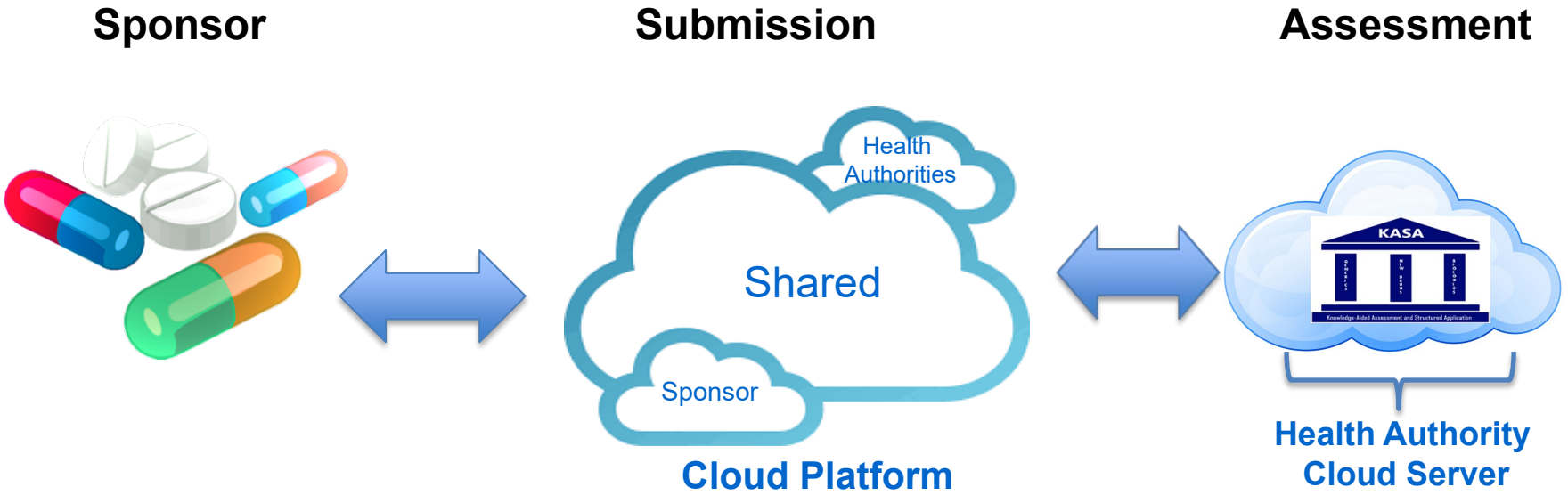
Structured CMC Data Submission (ICH SPQS)

Future Data Submissions and Review



The End Game

Cloud-based Regulatory Submission and Assessment

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