The Future of FDA Quality Assessment
Knowledge-Aided Assessment & Structured Application - KASA

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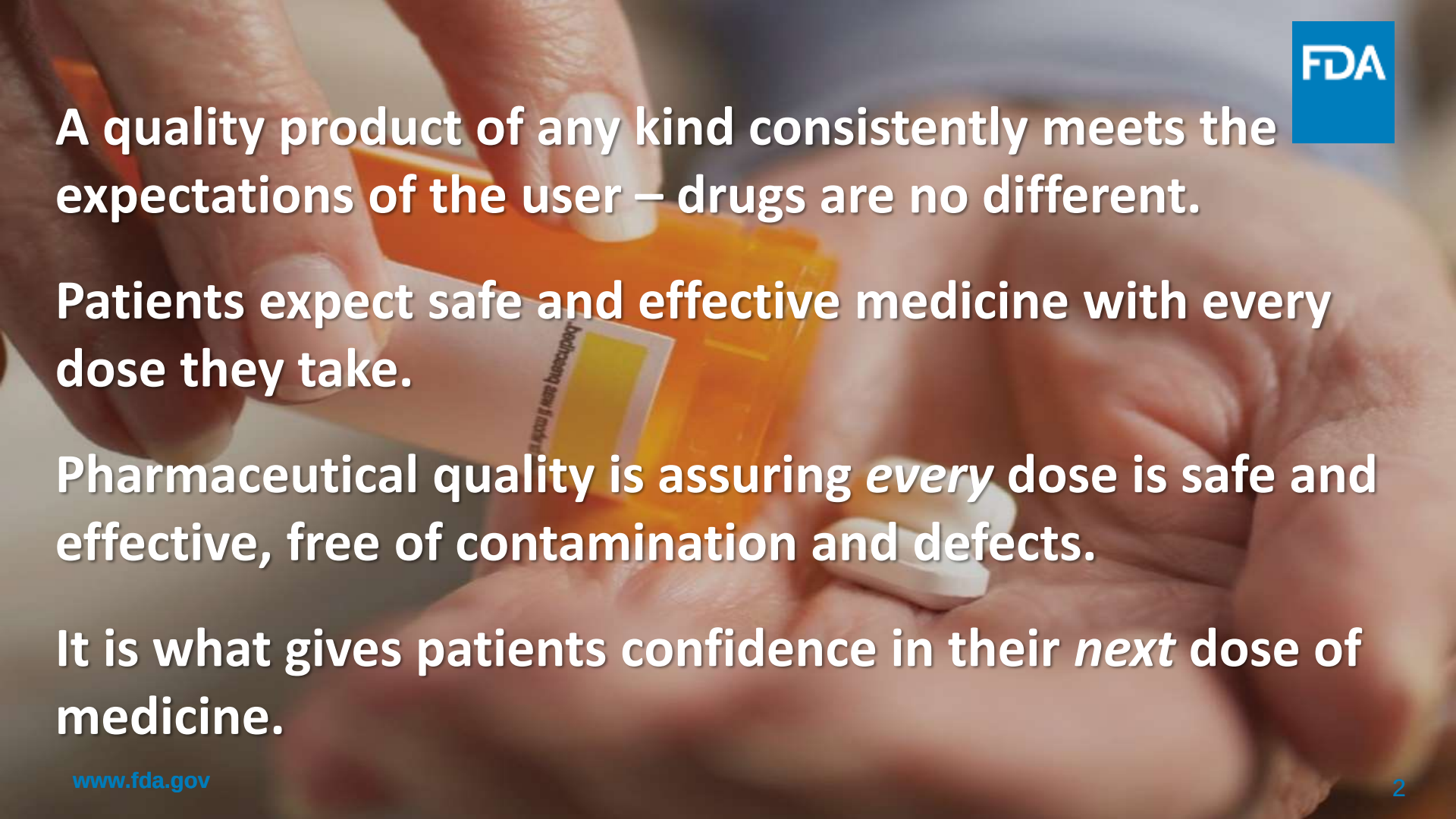
Center for Drug Evaluation and Research, U.S. Food and Drug Administration

DMF Workshop: GDUFA III Enhancements and Structured Submissions
November 30, 2022



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

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

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

Quality Assessment Transformation: KASA

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

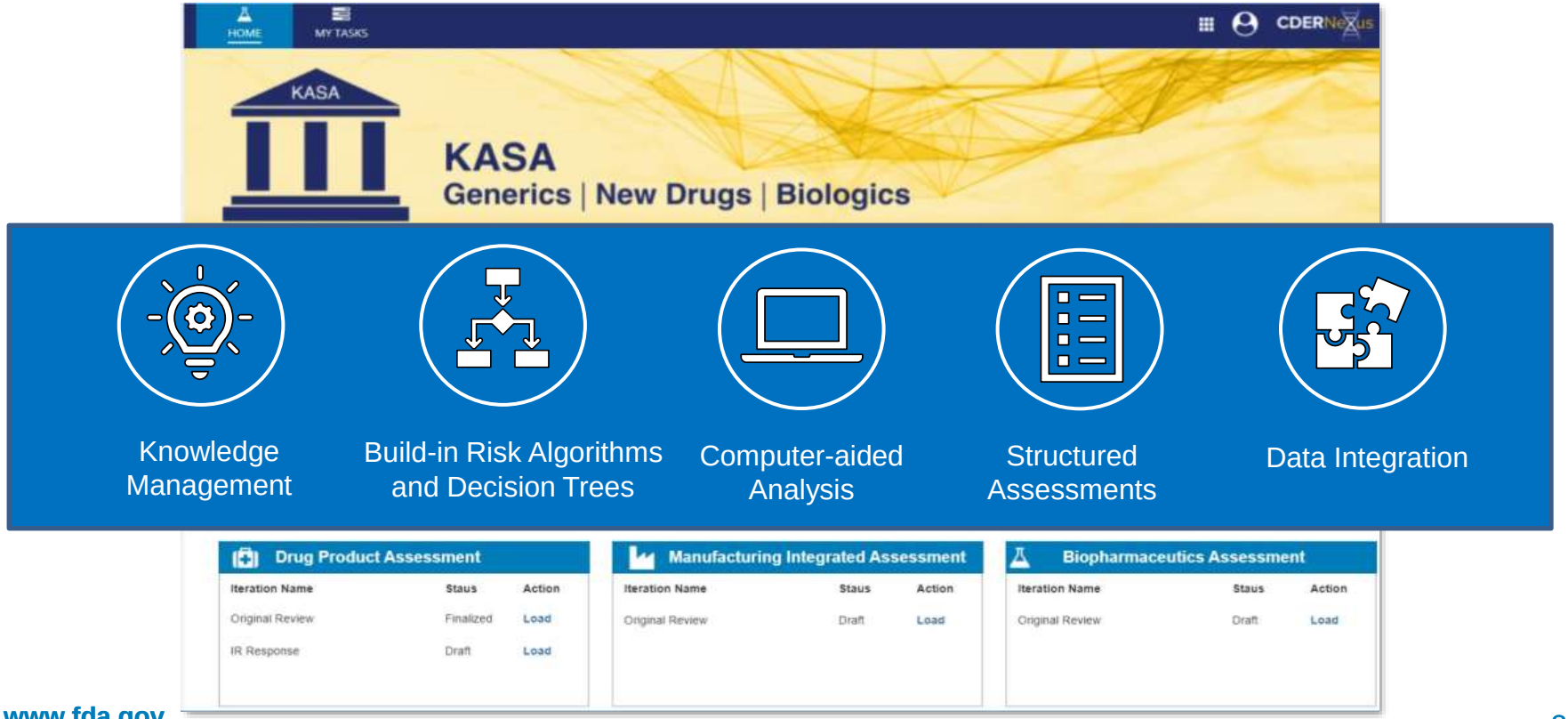
KASA = **K**nowledge-aided **A**ssessment and **S**tructured **A**pplication

What is KASA?

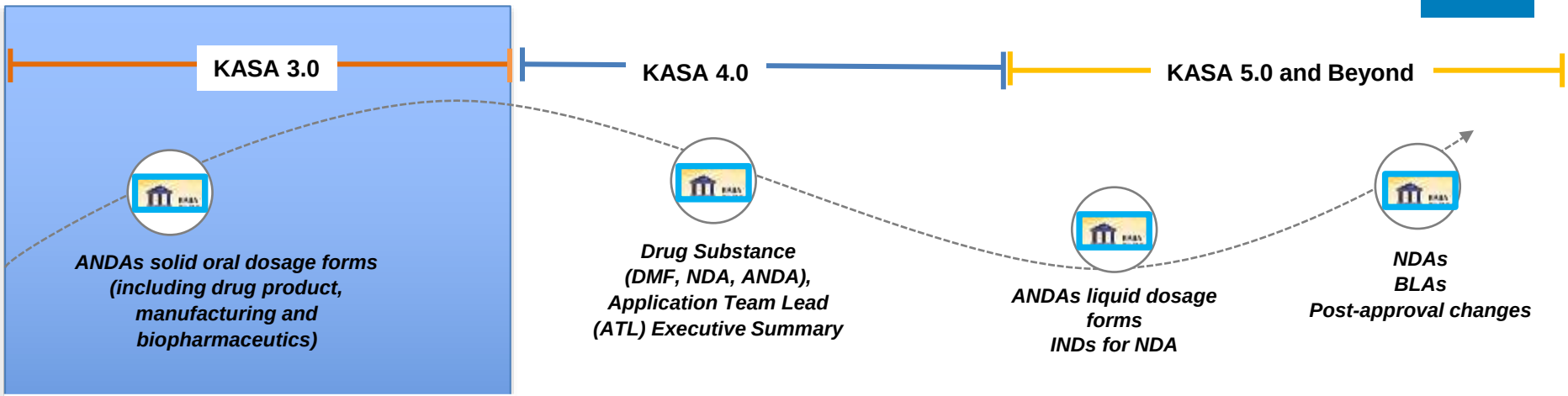
Knowledge-Aided Assessment and Structured Application

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



Roadmap for KASA IT Production



KASA 3.0	
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

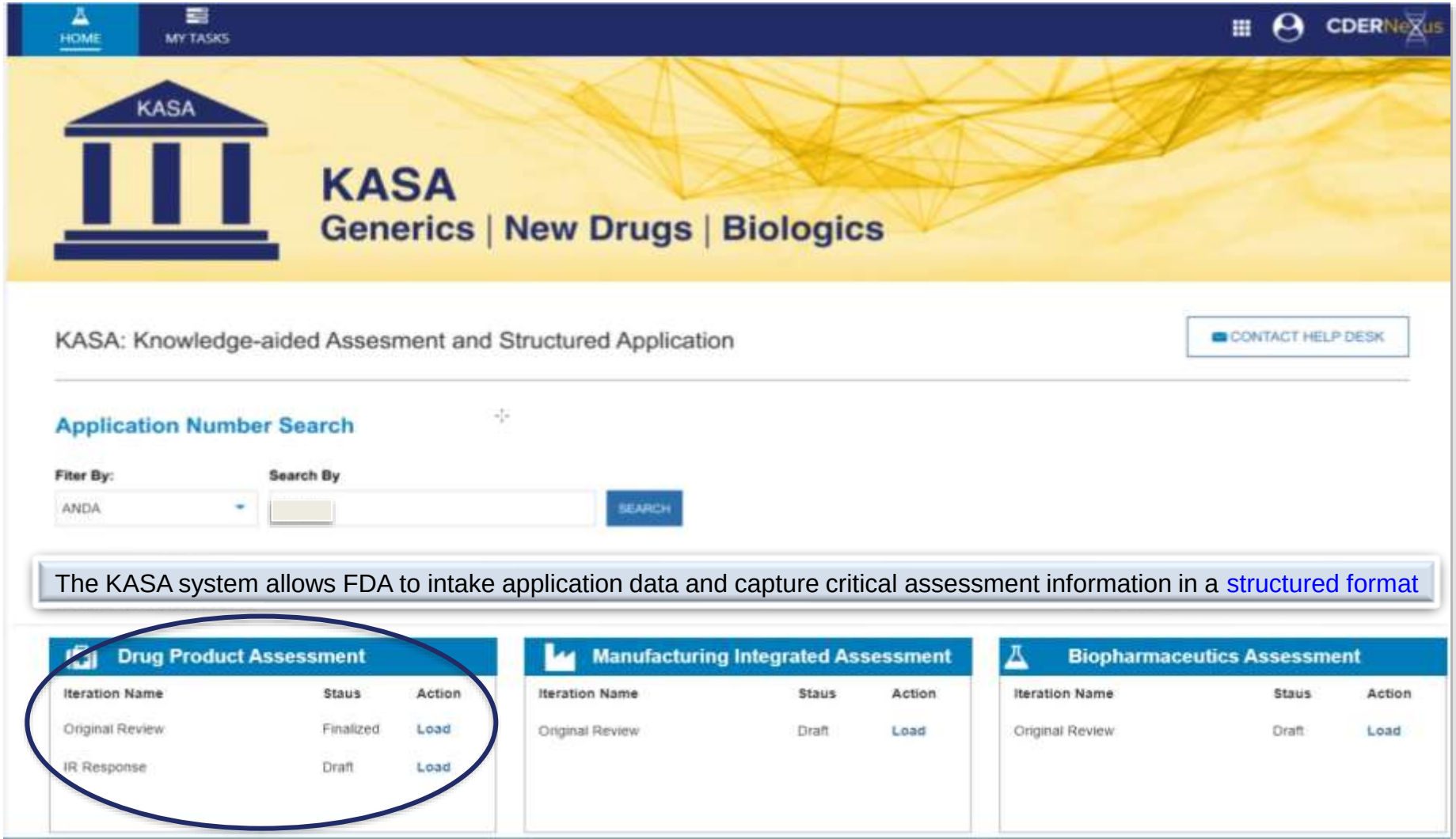
Completed Targets

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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KASA: Knowledge-aided Assesment and Structured Application
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Application Number Search
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The KASA system allows FDA to intake application data and capture critical assessment information in a structured format
Drug Product Assessment
Iteration Name
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Original Review
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IR Response
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Manufacturing Integrated Assessment
Iteration Name
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Biopharmaceutics Assessment
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Draft
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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		Explanaon Applies to ND/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

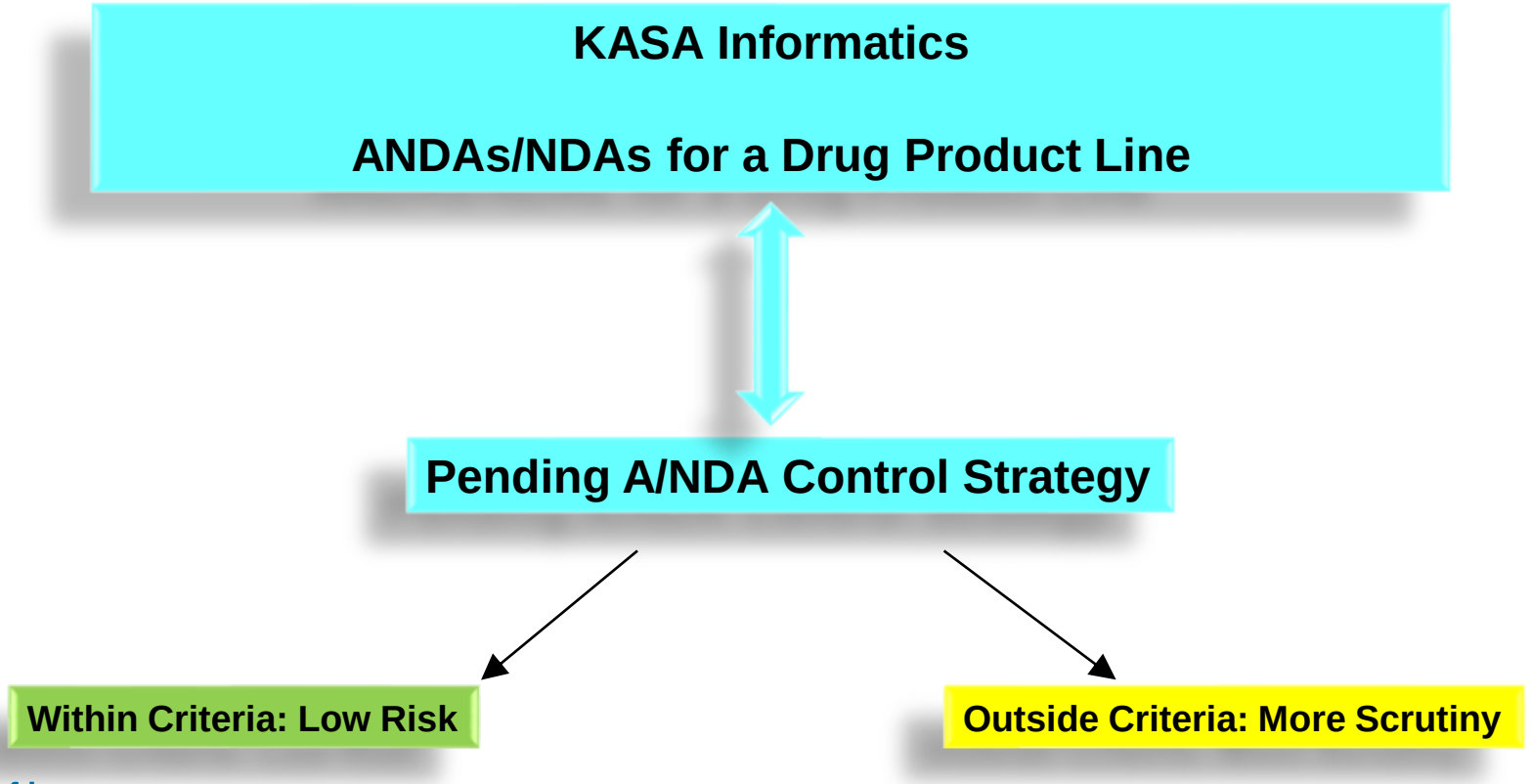
Increasing Level of Risk Control

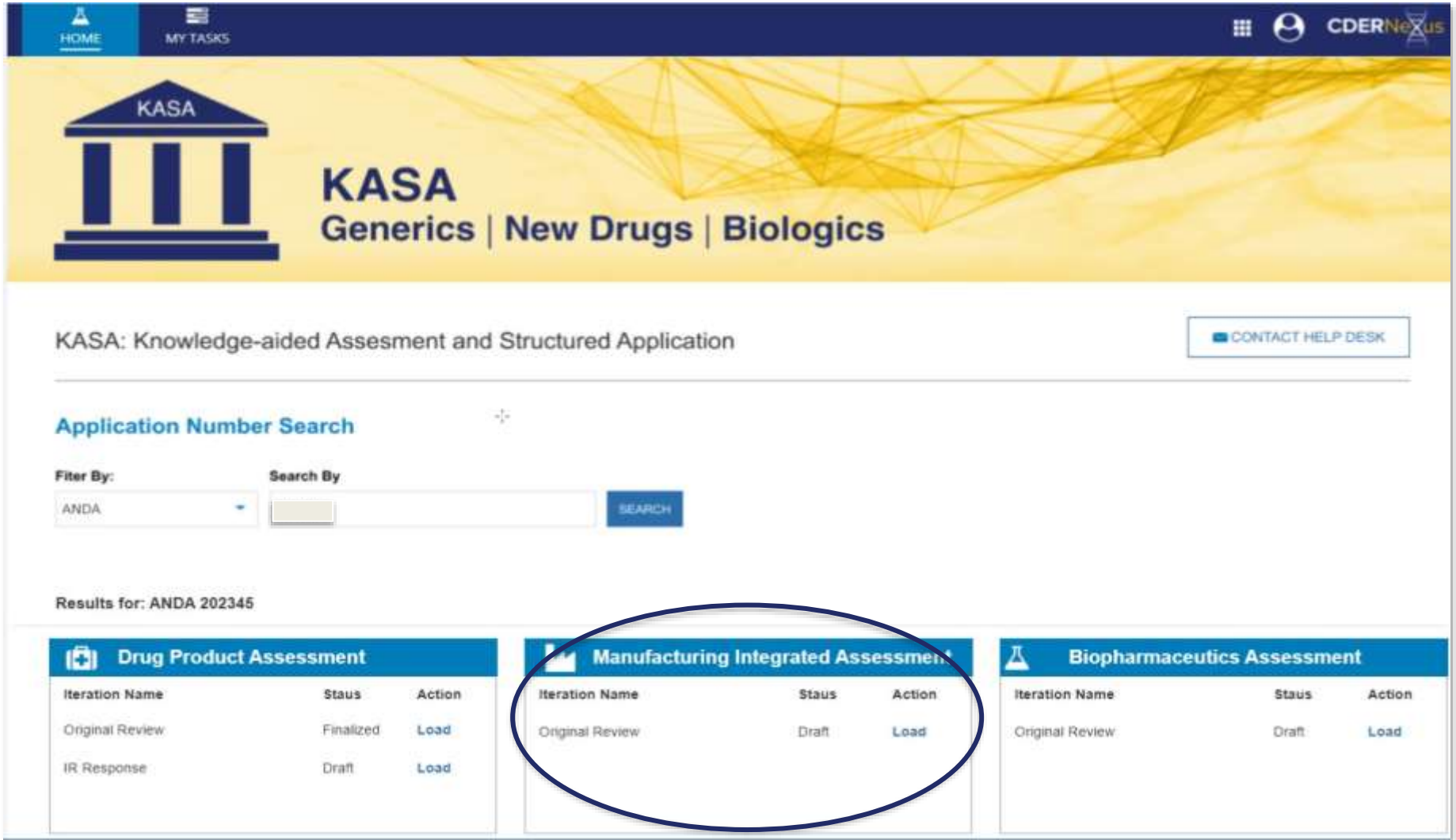
"Structured Descriptors" to Capture Control Strategy

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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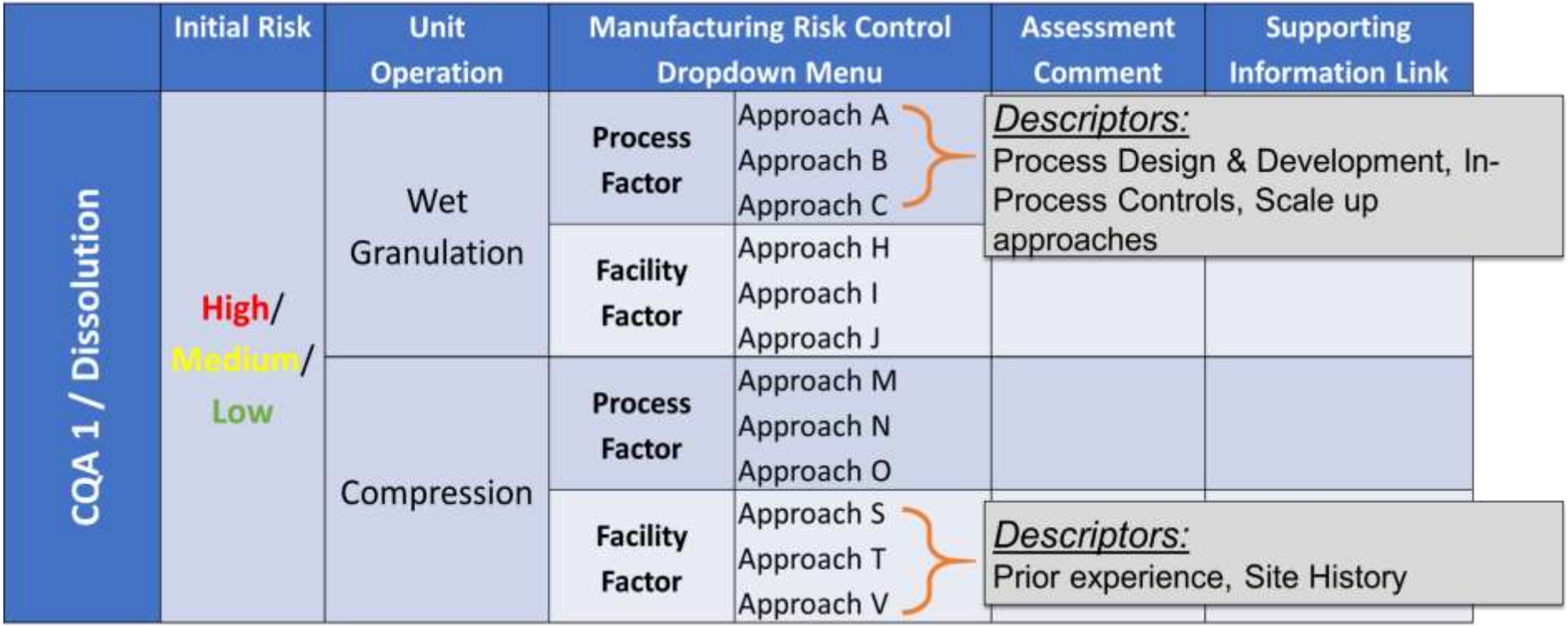
KASA Captures Manufacturing Risk Control in a Structured Format

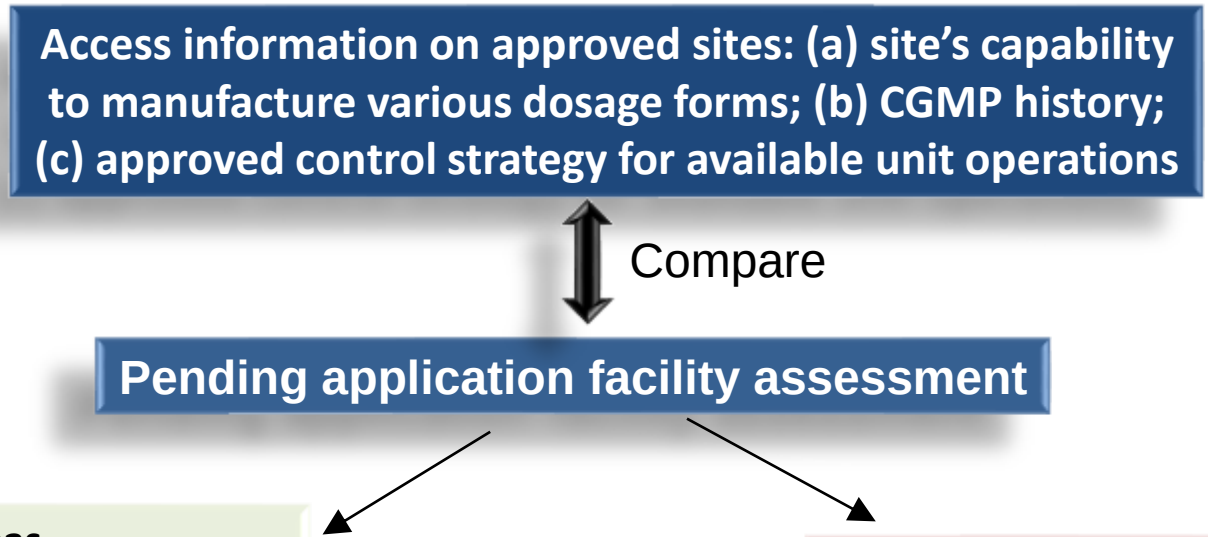


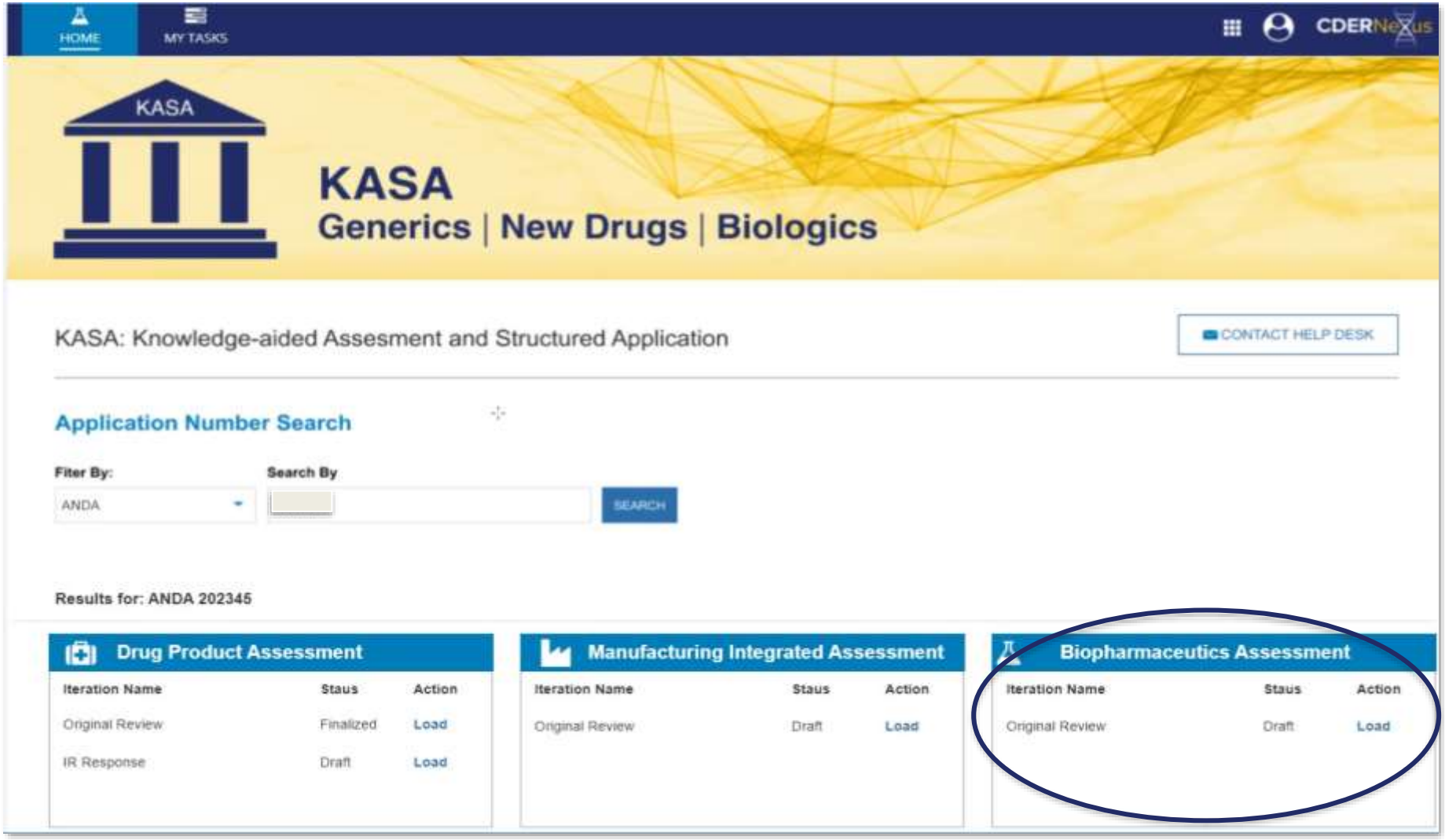
	Initial Risk	Unit Operation	Manufacturing Risk Control Dropdown Menu		Assessment Comment	Supporting Information Link
CQA 1 / Dissolution	High/ Medium/ Low	Wet Granulation	Process Factor	Approach A Approach B Approach C		
			Facility Factor	Approach H Approach I Approach J		
		Compression	Process Factor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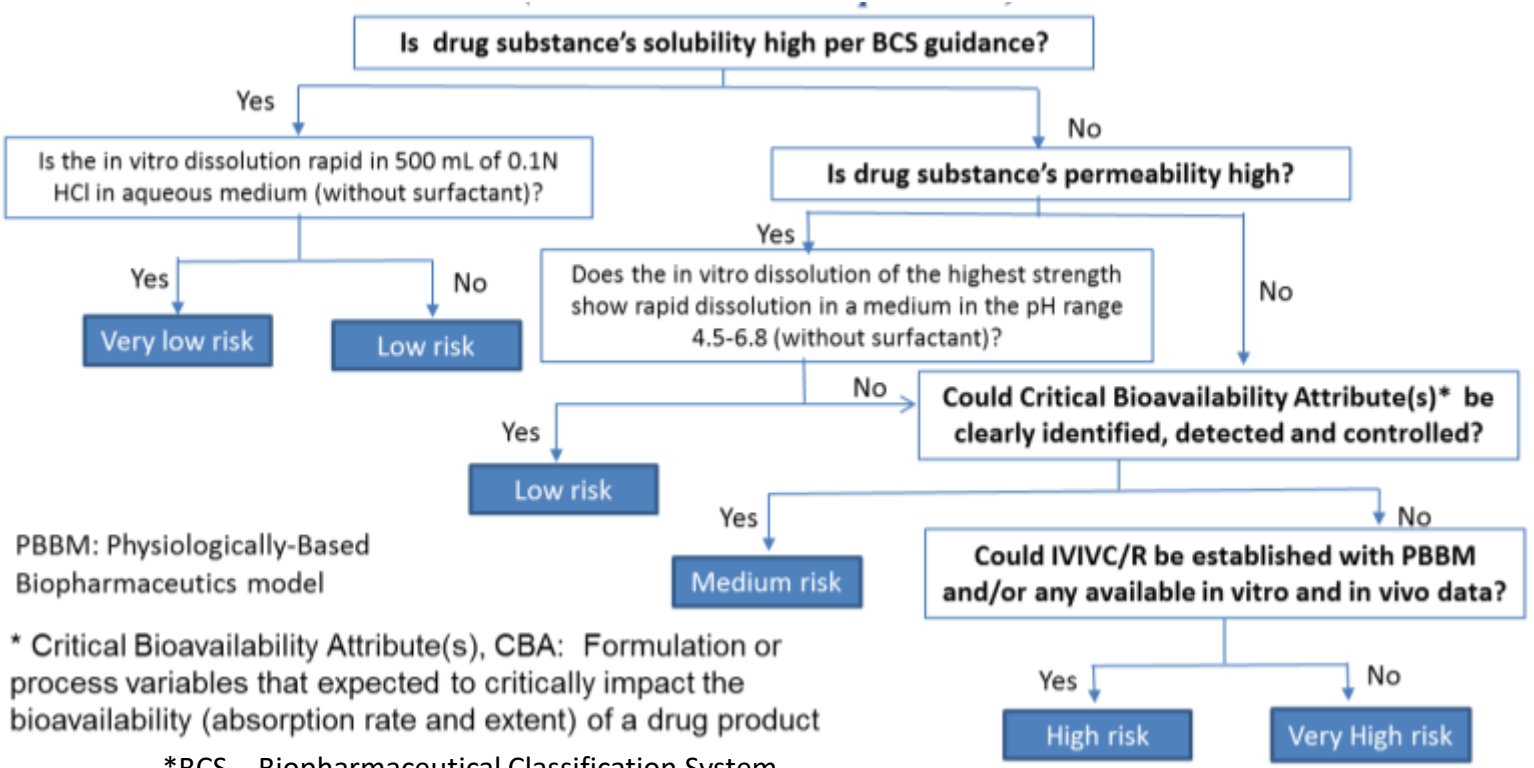
Initial Biopharmaceutics Risk Categories

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

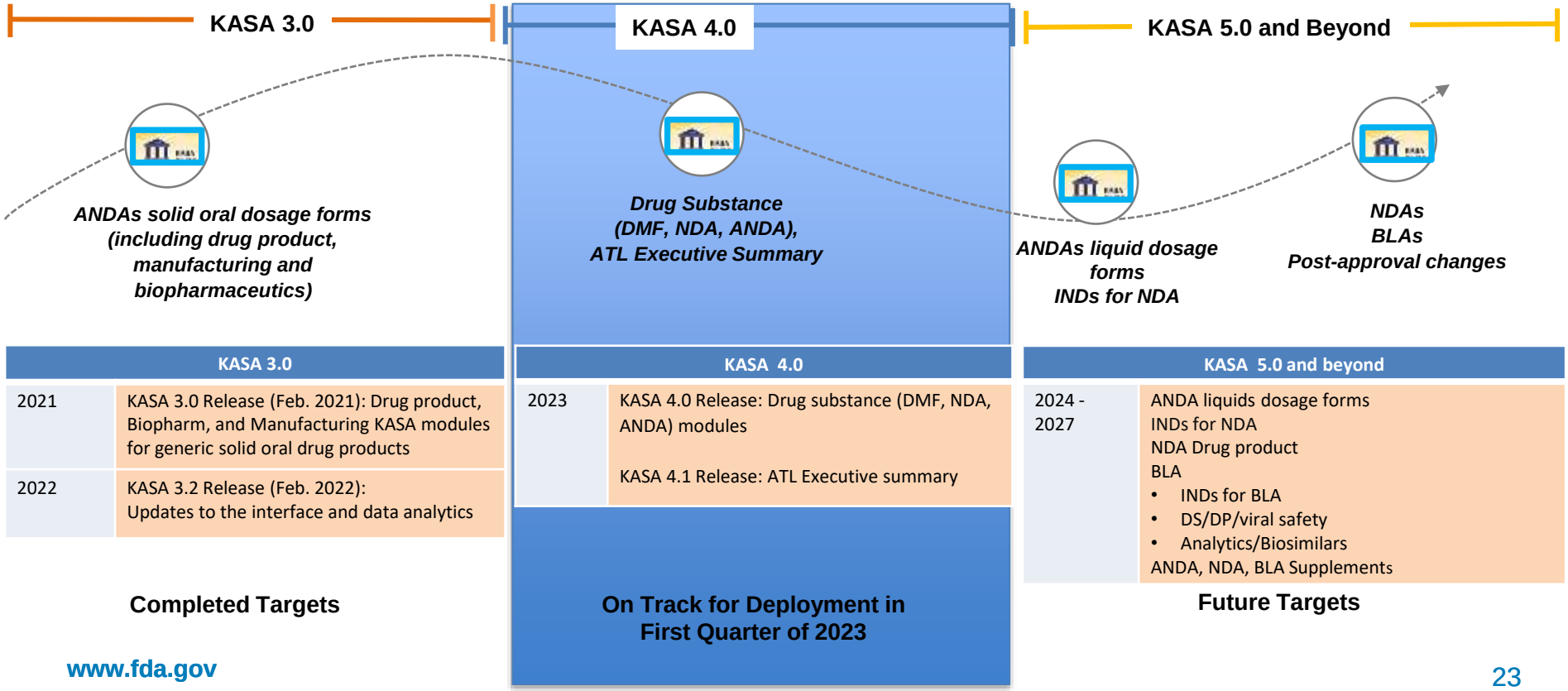
- KASA Enables the Vision of Knowledge Management

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

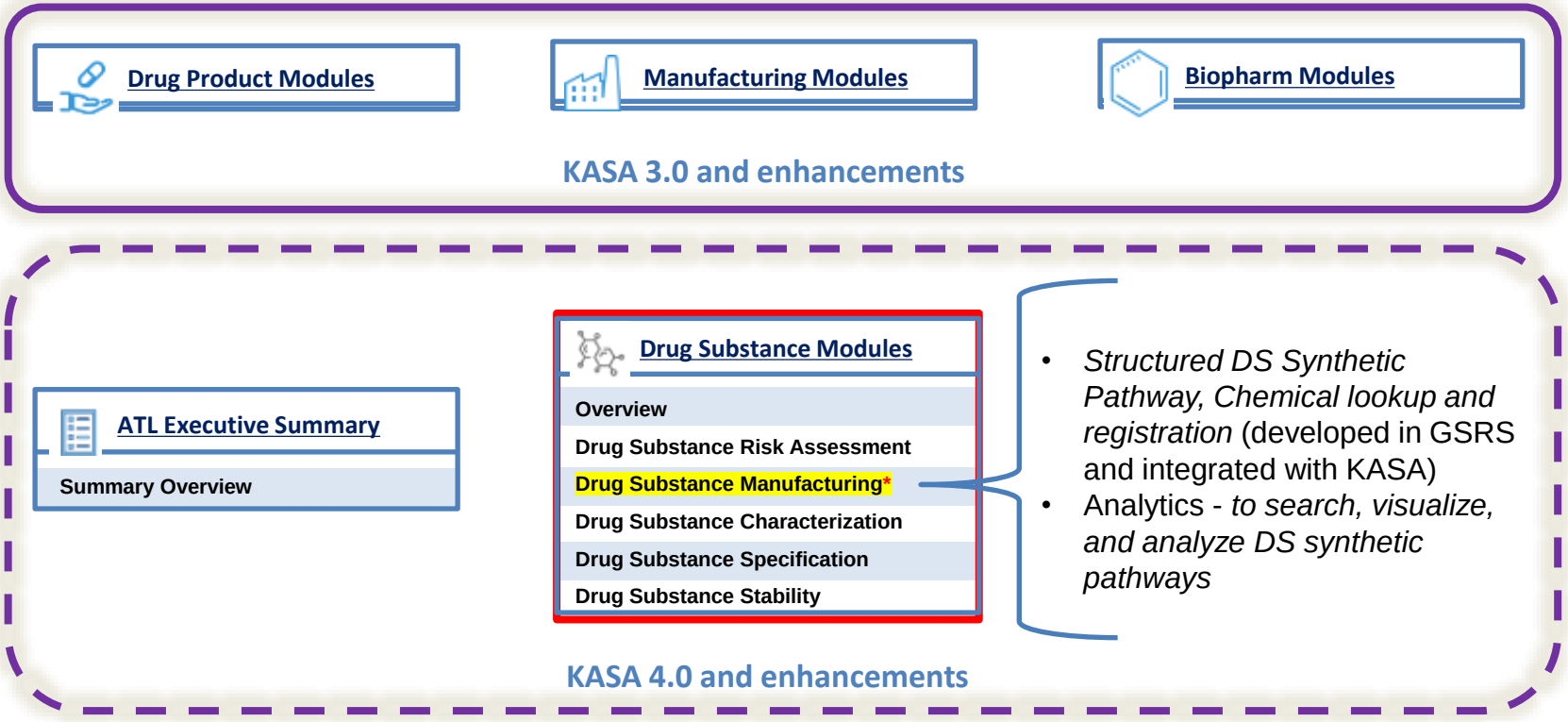
KASA for Drug Substance

Goal

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

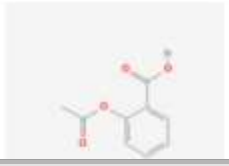
- Quickly identify problems with the DS synthetic pathways that can potentially generate high risk impurities
- Apply consistent standards for assessment of DS information in NDAs, ANDAs, DMFs
- Inform decision making and increase efficiency of assessment

Highlights of KASA for DS



Structured Chemical Structures

- Chemical structures captured and retrieved through integration with GSRS database

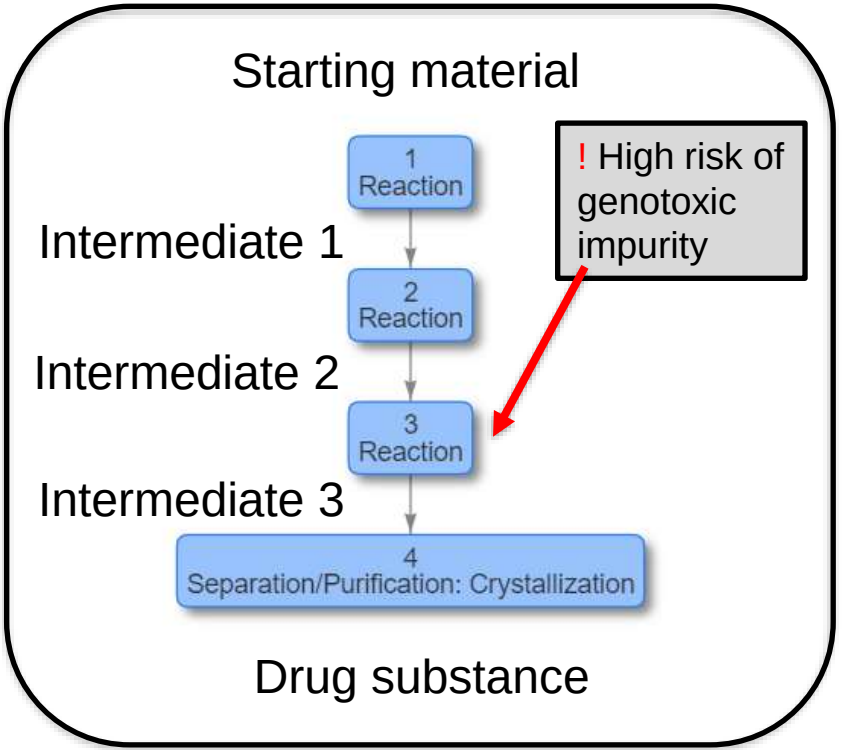
Chemical name	Structure	Role	Identifiers	Additional note	Edit
ID: Chemical Name: aspirin		Drug Substance	CID: 2244 UNII: Smile: CC(=O)OC1=CC=CC=C1C(=O)O	N/A	Edit + x

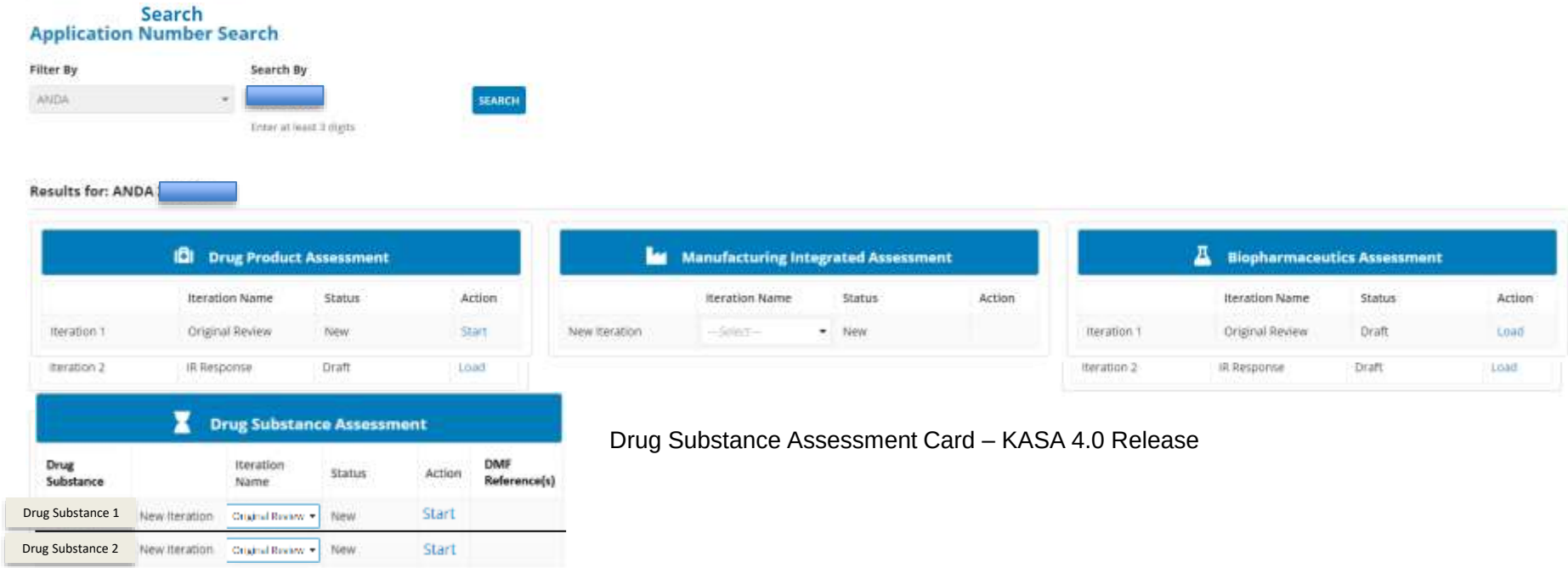
SD files - Chemical **structure-data file** format that can associate data with one or more chemical structures;
Tables of information can be translated into structures which can then be searched.

KASA for DS Analytics

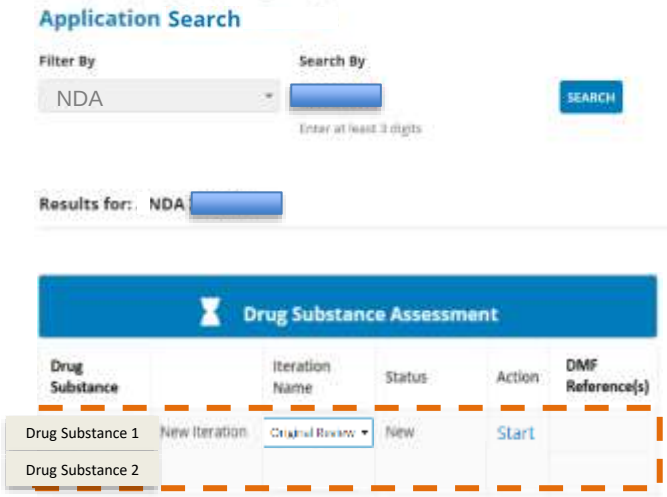
- DS synthetic routes in KASA can be:
  - Visualized
  - Searched
  - Analyzed
- Analytics tools will enable KASA to search based on DS, reagents, solvents, impurities and display synthetic pathways

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





Drug Substance Assessment Card – KASA 4.0 Release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Results for: NDA
Drug Substance Assessment
Drug Substance
Iteration Name
Status
Action
DMF Reference(s)
Drug Substance 1
New Iteration
New
Start
Drug Substance 2

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)

OPQ Advisory Committee Meeting (November 3, 2022)

Question: Do you support the long-term strategy for developing and implementing KASA at FDA and expanding the system from generic drugs to new drugs and biologics assessments?

Yes: Unanimous 13-0

https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-2-3-2022-pharmaceutical-science-and-clinical-pharmacology-advisory-committee-meeting

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.