



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

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DMF Workshop: GDUFA III Enhancements and Structured Submissions
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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 = Knowledge-aided Assessment and Structured Application

What is KASA?

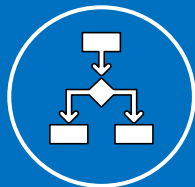
Knowledge-Aided Assessment and Structured Application

- 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



Knowledge Management



Build-in Risk Algorithms and Decision Trees



Computer-aided Analysis



Structured Assessments



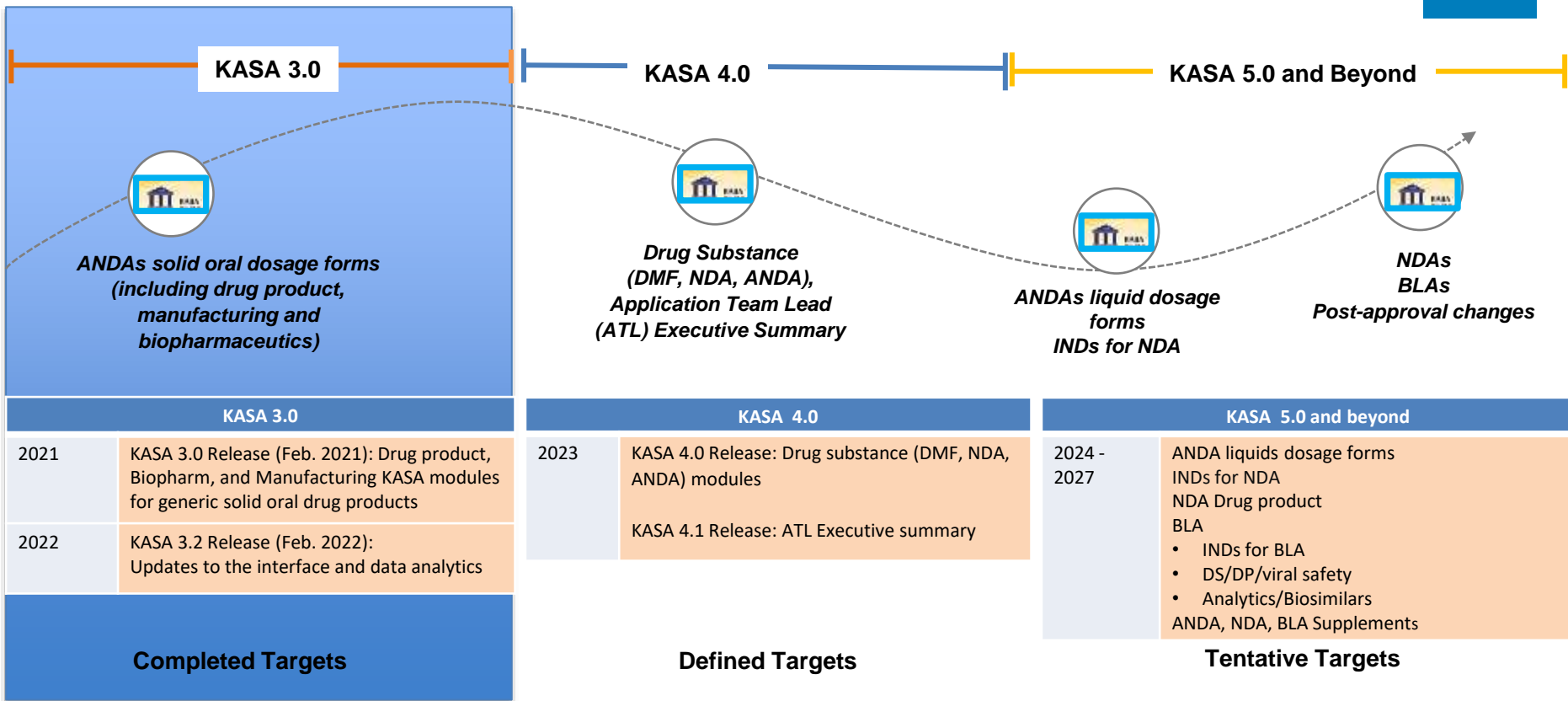
Data Integration

Drug Product Assessment		
Iteration Name	Status	Action
Original Review	Finalized	Load
IR Response	Draft	Load

Manufacturing Integrated Assessment		
Iteration Name	Status	Action
Original Review	Draft	Load

Biopharmaceutics Assessment		
Iteration Name	Status	Action
Original Review	Draft	Load

Roadmap for KASA IT Production





KASA

Generics | New Drugs | Biologics

KASA: Knowledge-aided Assessment and Structured Application

 CONTACT HELP DESK

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	Staus	Action
Original Review	Finalized	Load
IR Response	Draft	Load

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Iteration Name	Staus	Action
Original Review	Draft	Load

Biopharmaceutics Assessment		
Iteration Name	Staus	Action
Original Review	Draft	Load

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	<p><i>Assessor Briefly Describes How Fundamental Risk Control Approach Selected from Drop-Down is Specifically Applied in NDA/ANDA</i></p>	<p><i>Detailed Supporting Information is Linked to Specific Page in Electronic Submission</i></p>
		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		

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

KASA Informatics

ANDAs/NDAs for a Drug Product Line



Pending A/NDA Control Strategy

Within Criteria: Low Risk

Outside Criteria: More Scrutiny



KASA

Generics | New Drugs | Biologics

KASA: Knowledge-aided Assessment and Structured Application

[CONTACT HELP DESK](#)

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Results for: ANDA 202345

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Iteration Name	Status	Action
Original Review	Finalized	Load
IR Response	Draft	Load

Manufacturing Integrated Assessment		
Iteration Name	Status	Action
Original Review	Draft	Load

Biopharmaceutics Assessment		
Iteration Name	Status	Action
Original Review	Draft	Load

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	<u>Descriptors:</u> Process Design & Development, In-Process Controls, Scale up approaches	
			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	<u>Descriptors:</u> Prior experience, Site History	

Integrated Manufacturing Risk Analytics



Access information on approved sites: (a) site's capability to manufacture various dosage forms; (b) CGMP history; (c) approved control strategy for available unit operations



Compare

Pending application facility assessment

Proposed site has demonstrated capability, proposed process control strategy is in alignment with prior information: **Low Risk**

Proposed site has not demonstrated capability, proposed process control strategy is not in alignment with prior information: **More Scrutiny**



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Results for: ANDA 202345



Drug Product Assessment

Iteration Name	Status	Action
Original Review	Finalized	Load
IR Response	Draft	Load



Manufacturing Integrated Assessment

Iteration Name	Status	Action
Original Review	Draft	Load



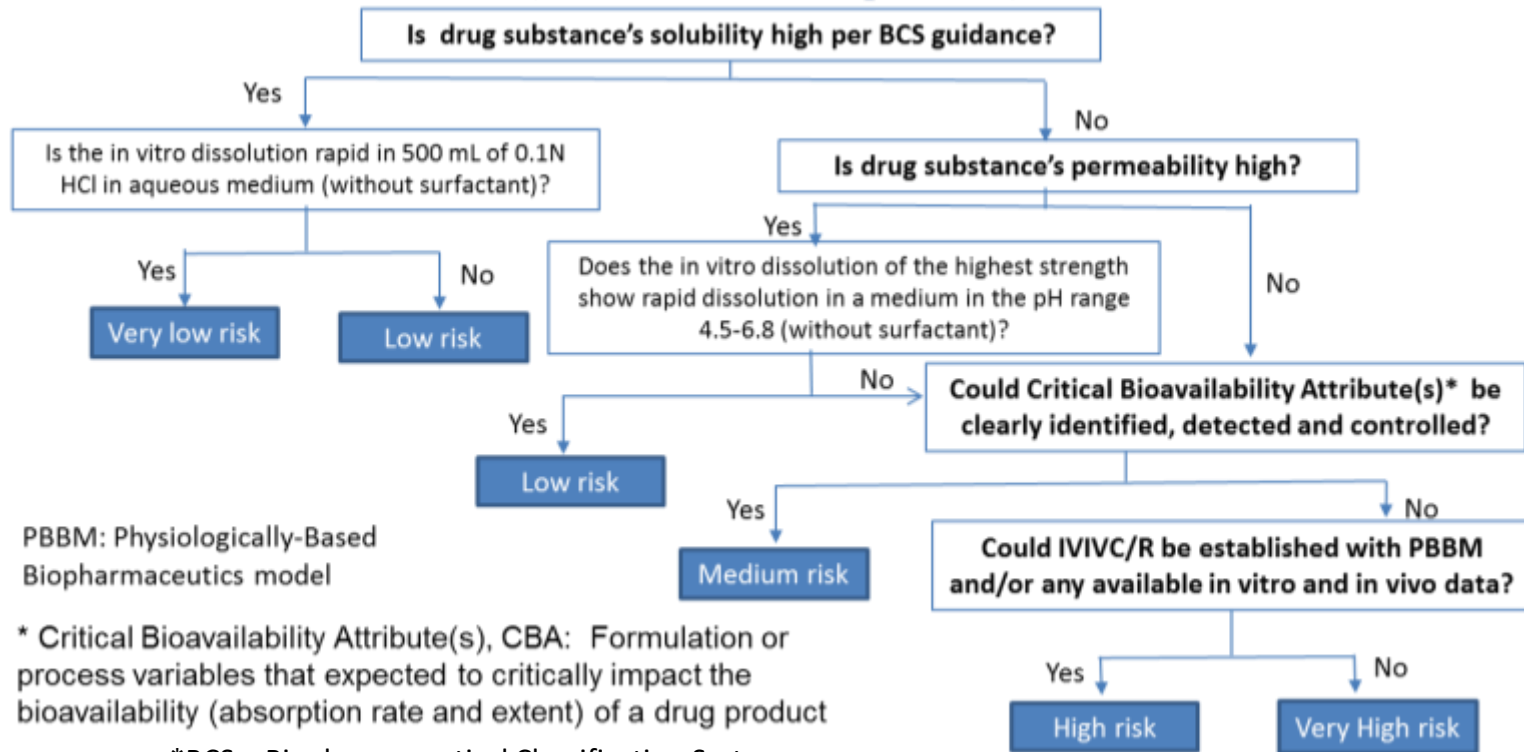
Biopharmaceuticals Assessment

Iteration Name	Status	Action
Original Review	Draft	Load

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 Biopharmaceuticals 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

KASA 3.0

KASA 4.0

KASA 5.0 and Beyond



ANDAs solid oral dosage forms
(including drug product,
manufacturing and
biopharmaceutics)



Drug Substance
(DMF, NDA, ANDA),
ATL Executive Summary



ANDAs liquid dosage forms
INDs for NDA



NDA's
BLAs
Post-approval changes

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

On Track for Deployment in First Quarter of 2023

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

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



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 Chemical Structures

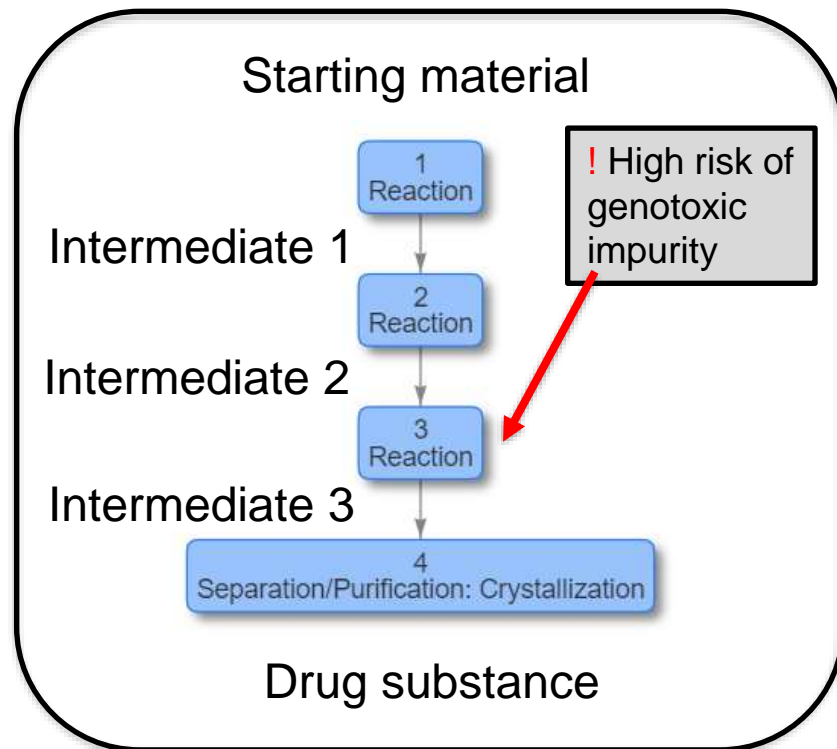
- Chemical structures captured and retrieved through integration with GSRS database

Chemical name	Structure	Role	Identifiers	Additional note	Edit
ID: Chemical Name: aspirin		Drug Substance	CID: 2244 UNII: Smile: <chem>CC(=O)OC1=CC=CC=C1C(=O)O</chem>	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

Generics | New Drugs | Biologics

Search Application Number Search

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ANDA

Search By

Enter at least 2 digits

SEARCH

Results for: ANDA



Drug Product Assessment

	Iteration Name	Status	Action
Iteration 1	Original Review	New	Start
Iteration 2	IR Response	Draft	Load



Manufacturing Integrated Assessment

	Iteration Name	Status	Action
New Iteration	—Select—	New	



Biopharmaceutics Assessment

	Iteration Name	Status	Action
Iteration 1	Original Review	Draft	Load
Iteration 2	IR Response	Draft	Load



Drug Substance Assessment

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

Drug Substance Assessment Card – KASA 4.0 Release



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	Critical Review	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.

