The Future of FDA's Quality Assessment and Knowledge Management - KASA

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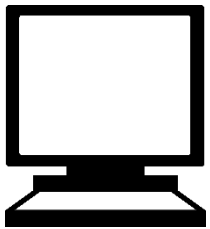
FDA U.S. FOOD & DRUG ADMINISTRATION

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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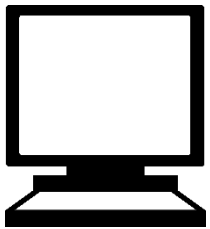



Drugs are no different.


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.

Current 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

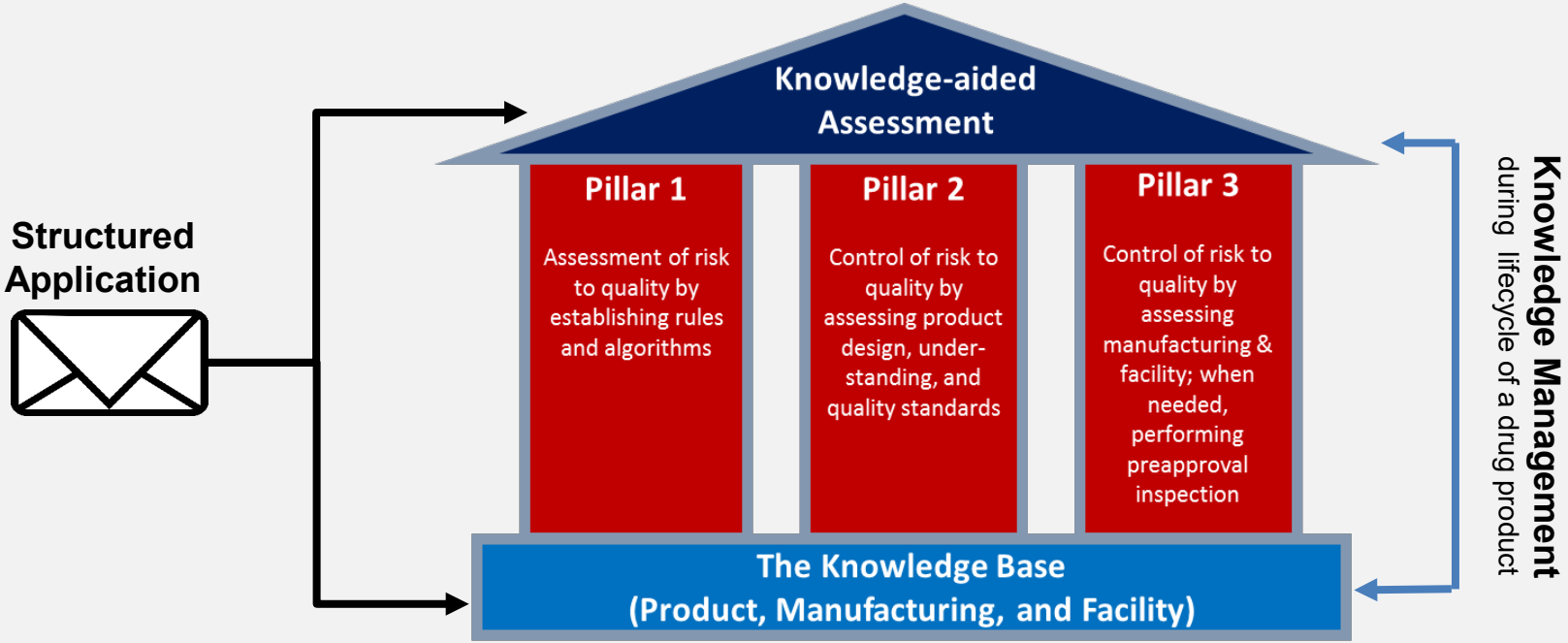
Encumbers best practices for:

- Knowledge sharing
- Management of knowledge across product lifecycle
- Overall modernization

Knowledge-Aided Assessment and Structure Application (KASA) is part of CDER's effort in modernizing regulatory assessment.

The KASA System

KASA – Knowledge-aided Assessment and Structured Application



A very important initiative to CDER and FDA!

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;

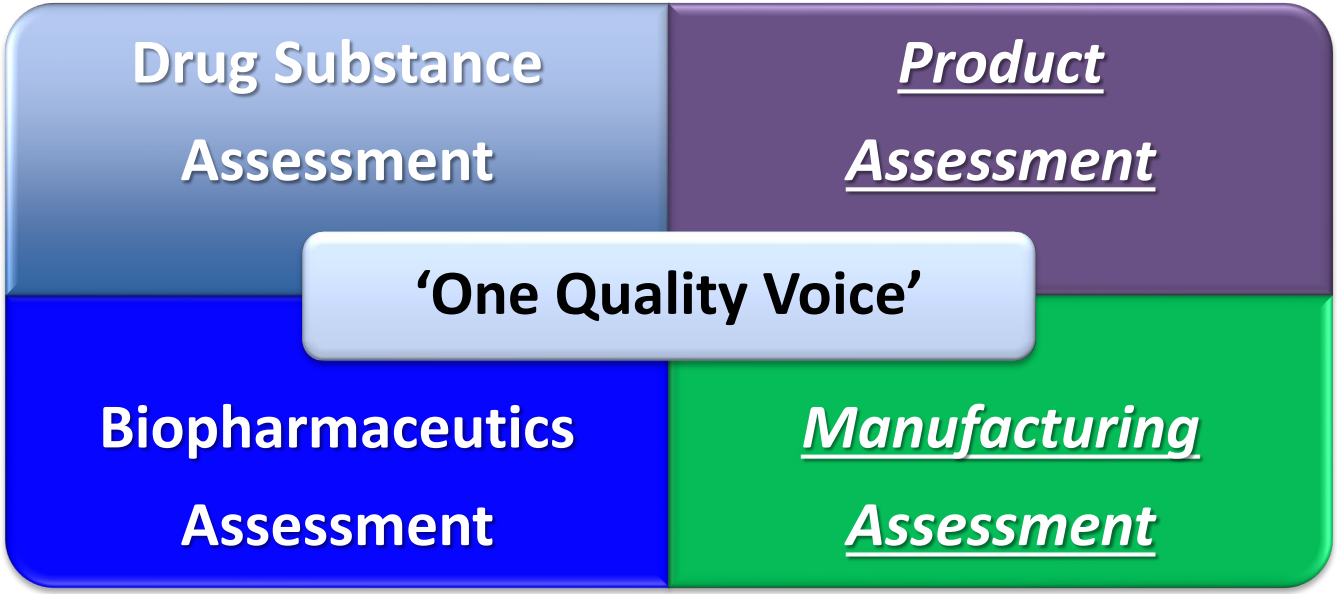
Objectives of KASA System

KASA is designed to:

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.

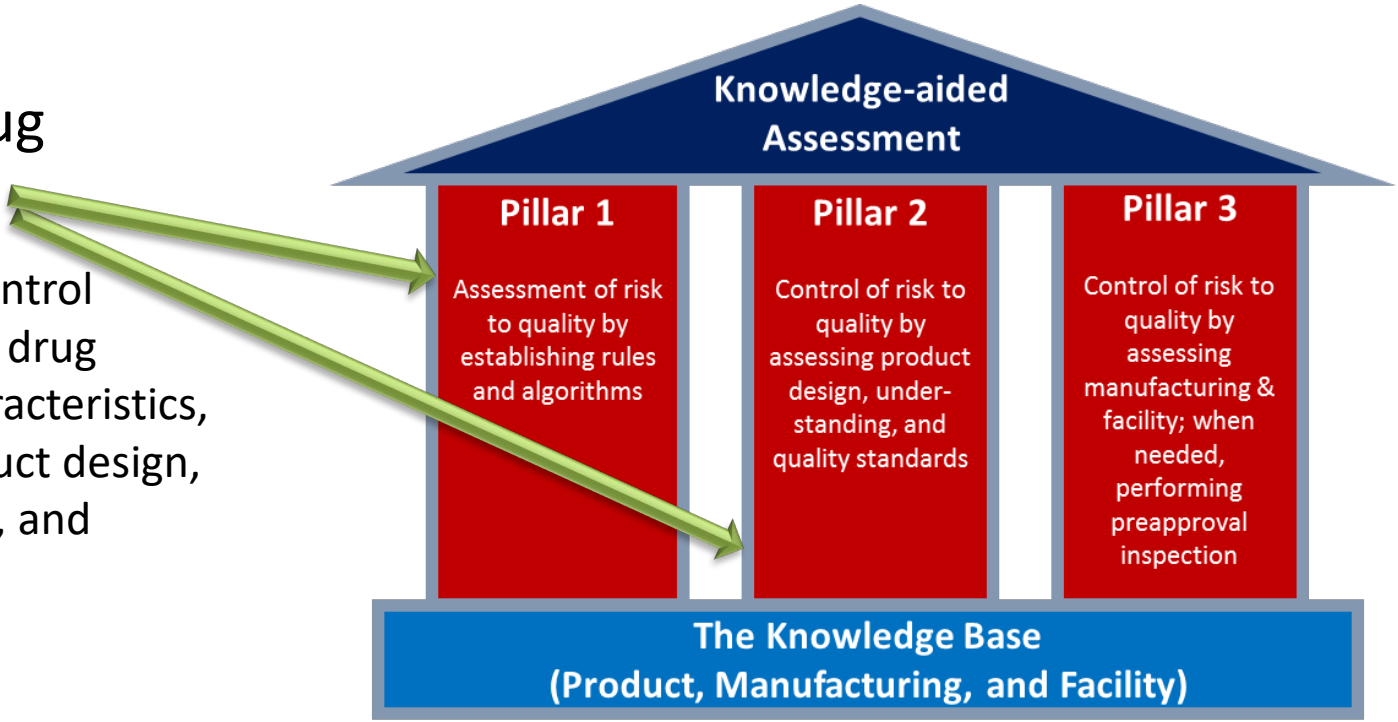
Team-based Integrated Quality Assessment (IQA)

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



Pillar 1 & 2 – Drug Product

- Control of drug product risk:
  - Product risk control focuses on the drug substance characteristics, and drug product design, understanding, and control



Initial Risk Assessment Algorithm

- The Algorithm objectively and quantitatively captures initial inherent risk of CQA
- The overall risk is considered low, medium or high based on *predefined* ranges
- KASA calculates the initial risk based on drug product characteristics

Structured Product Risk Control

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

Enhanced Risk Management

Application 1

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

Application 2

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

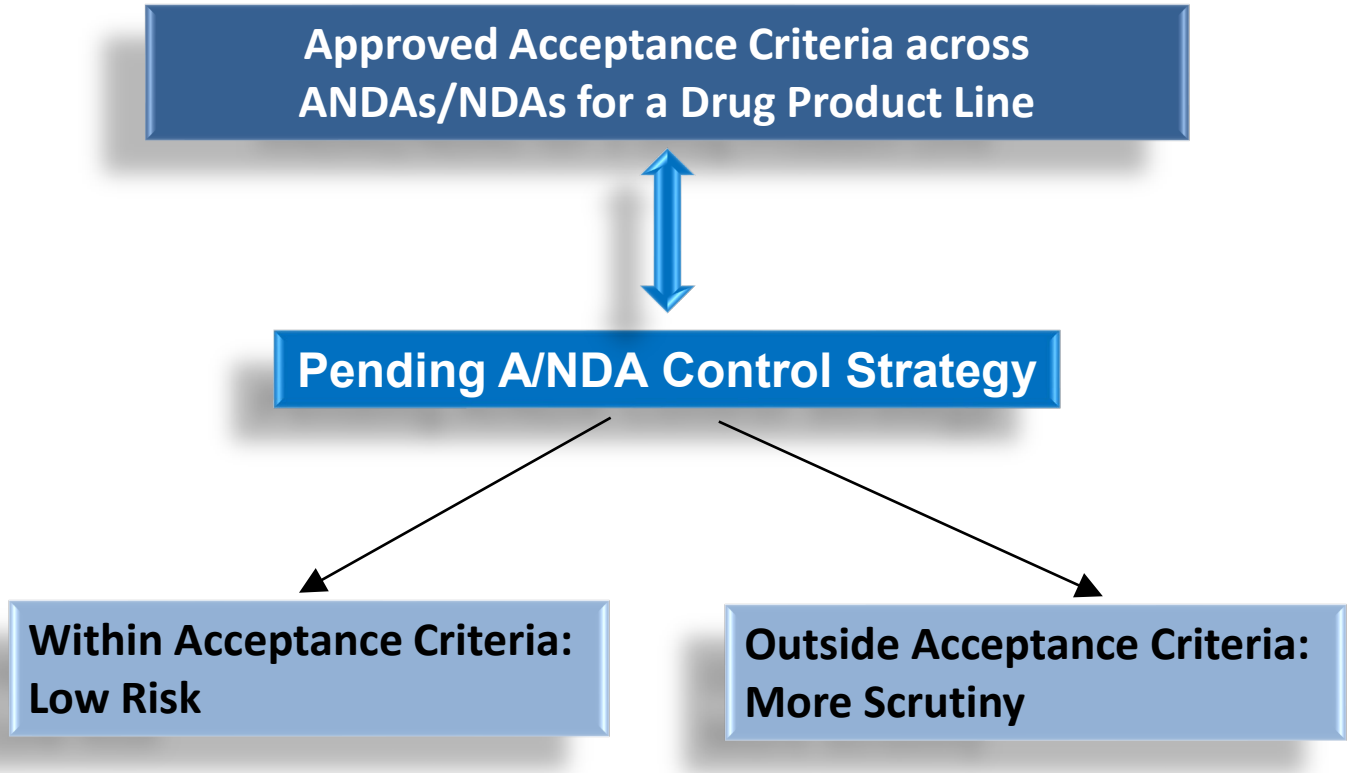
Application 3

	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

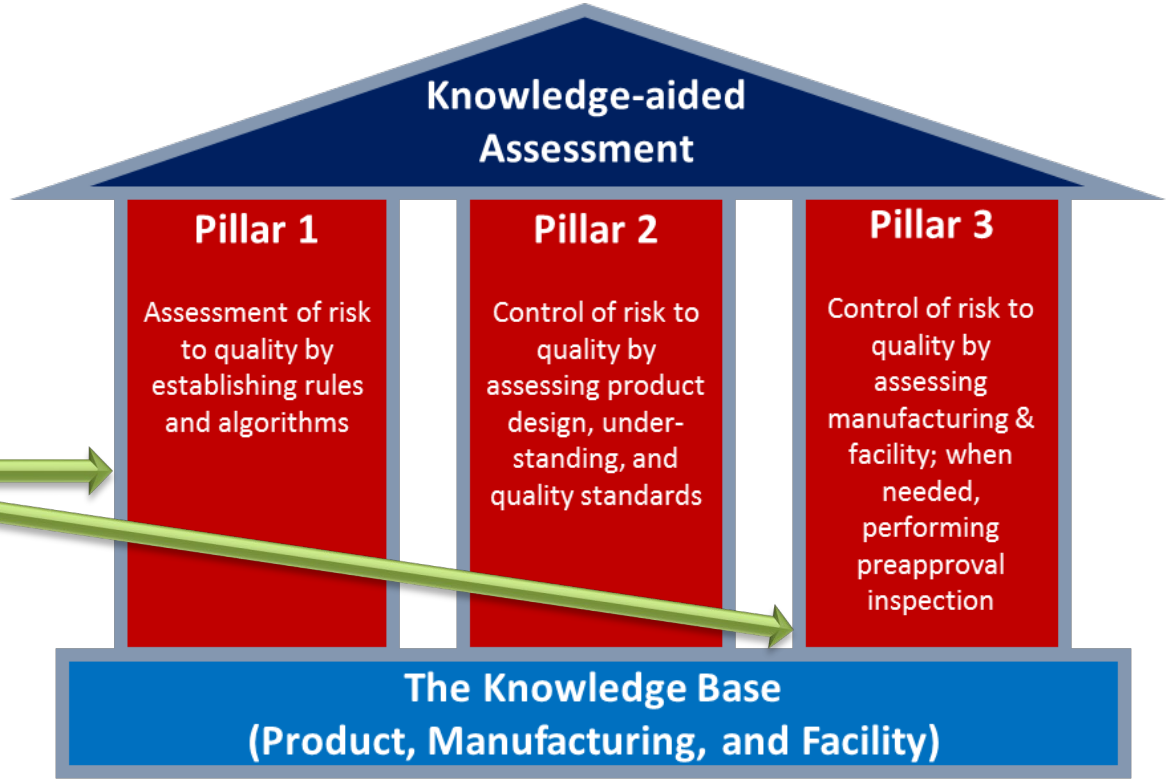
Increasing Level of Risk Control

KASA informatics

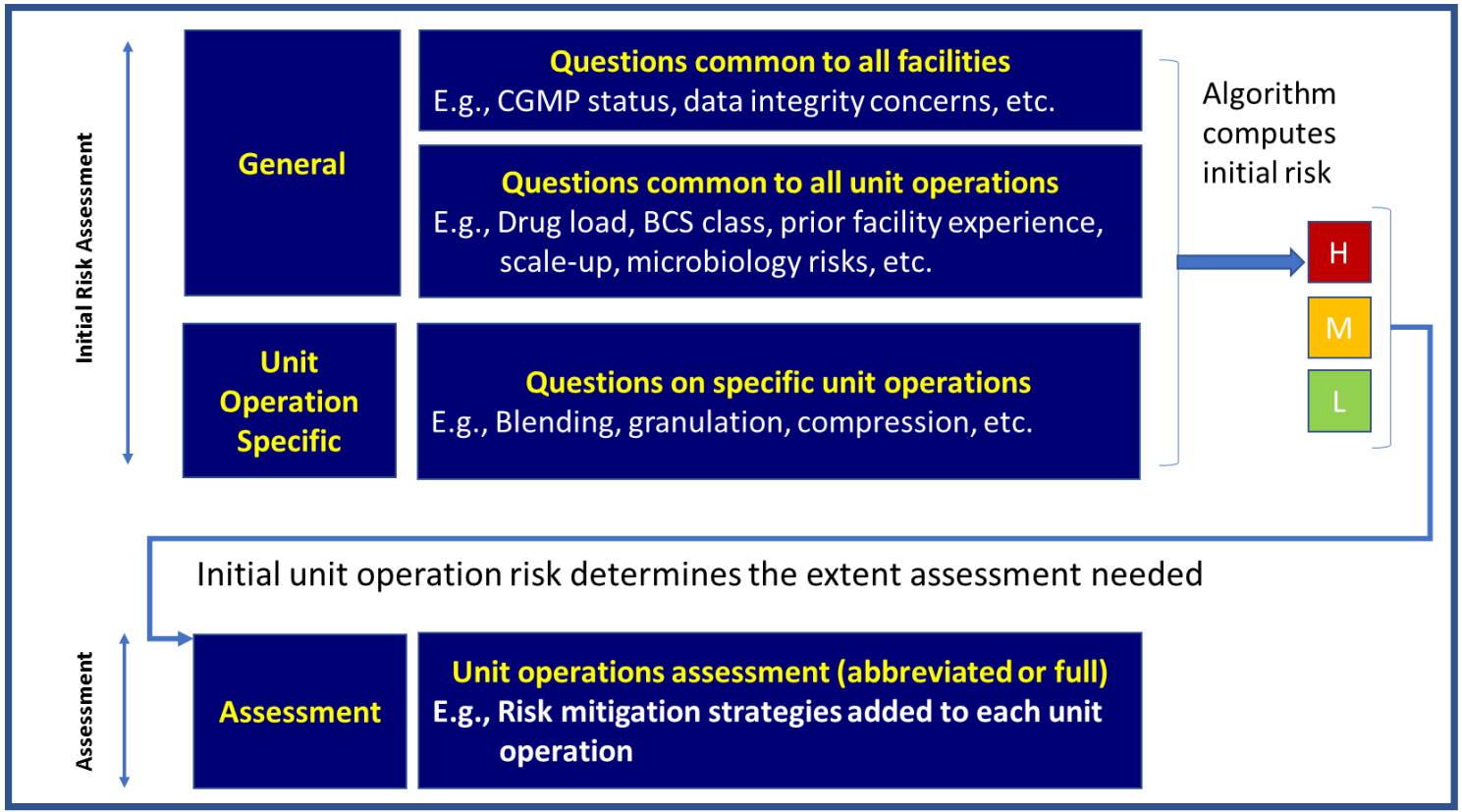


Pillar 1 & 3 – Manufacturing

- Control of drug manufacturing risk:
  - Focuses on the risk to each product CQA from a manufacturing process and facilities perspective and risk mitigation



Manufacturing Risk Assessment & Control



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	*Descriptors:* 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	*Descriptors:* Prior experience, Site History	

Structured Assessment Approach

- On-line monitoring
- Enhanced Process understanding

- No-online monitoring
- Fixed process parameters

Application	CQA impacted	Unit Operation	Initial Manufacturing Risk Assessment	Manufacturing (Process & Facility) Control Approach	Facility CGMP Control Approach	Pre-Approval Inspection (PAI) Needed?	Updated Risk Assessment based on PAI outcome
A	Content uniformity	Wet Granulation	High	Approach A	Approach C	**YES**	**LOW**
B	Content uniformity	Wet Granulation	High	Approach B	Approach A	**NO**	**MEDIUM - Surveillance inspection considerations**
C	Content uniformity	Wet Granulation	High	Approach C	Approach C	**YES**	**HIGH – Potential withhold**

- Limited development data
- Inadequate controls

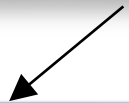
- Poor inspectional history, quality defect signals OR
- No experience with similar product type and/or process

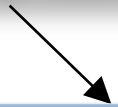
- No CGMP issues
- Sufficient experience with similar product type and process

KASA Informatics

- 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
- Access approved control strategy for a complex unit operation (e.g. laser drilling process) across multiple applications

Pending A/NDA Manufacturing Assessment





Proposed site has demonstrated capability and proposed process control strategy is in alignment with other approved applications: Low risk

Proposed site does not have demonstrated capability and/or proposed process control strategy is not in alignment with other approved applications : More Scrutiny

Unanimous Support

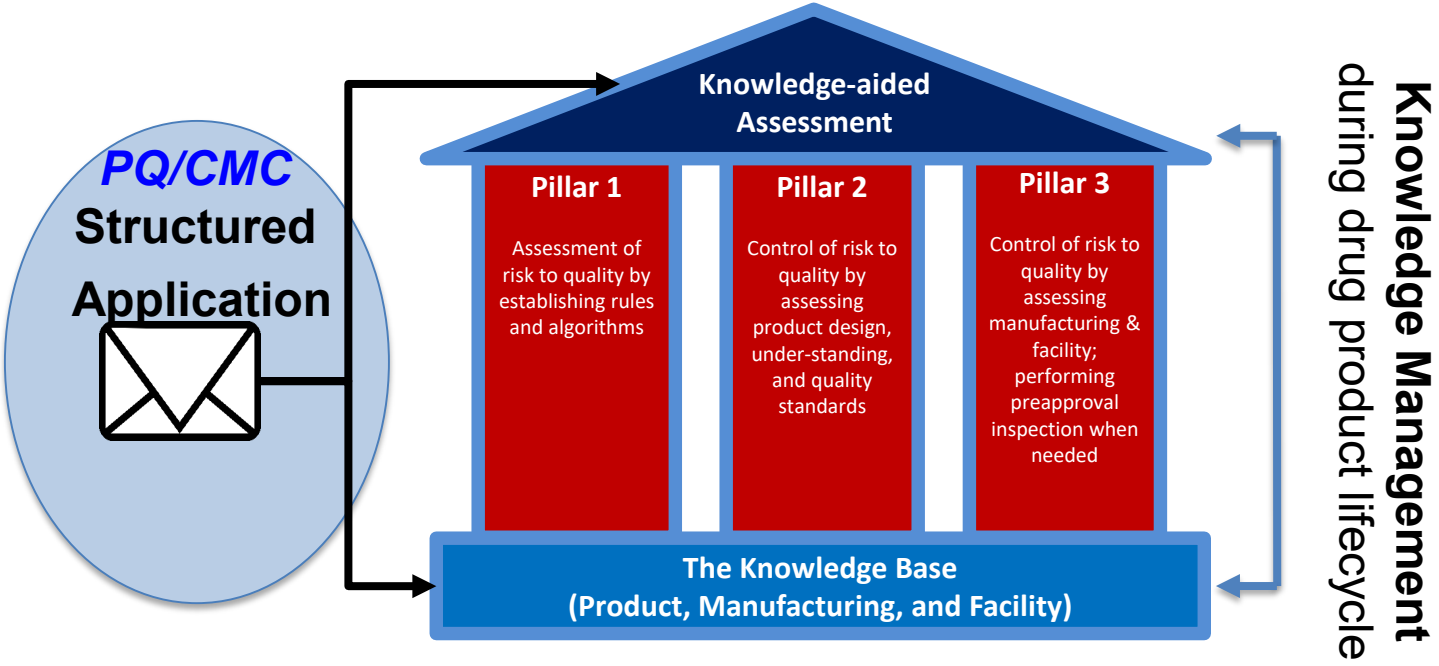
- FDA Advisory Committee Meeting - September 20, 2018
- Ten (10) members from Industry and Academia

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.*

Future State



PQ/CMC Project **– establishes electronic standards for submitting Pharmaceutical Quality (PQ) and Chemistry, Manufacturing and Controls (CMC) data.**

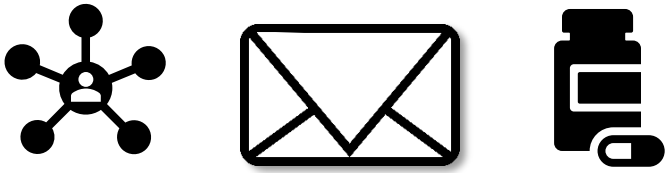
Benefits of KASA System

Benefits to FDA

- Enhances consistency and objectivity of regulatory assessment
- Enables knowledge management of product, manufacturing, and facility
- Excels regulatory action and decision-making

Benefits of KASA System

Benefits to Industry and Patients



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

Acknowledgement

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Paul Seo
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Bhagwant Rege
Bing Cai

Rakhi Shah
Ying Zhang
Ryan Nguyen
Micael Guillot
Brock Roughton

Norman Schmuff
Lawrence Callahan
Frank Switzer
Deborah Elliott
Michael Philips
IT contractors

Xiang (Shane) Yu
Rongzuo Xu
Zhouxi Wang

OPQ KASA Expo Booth

SMEs:

Micael Guillot (Drug Product)
Edwin Jao (Manufacturing)
Ryan Nguyen (Drug Product)
Brock Roughton (Drug Product)
Paul Seo (Biopharmaceutics)
Rakhi Shah (Manufacturing)
Norman Schmuff (PQ/CMC)
Larisa Wu (Manufacturing)

- **Date:** Nov. 5th, 2019
- **Time:** 3:30 pm -5:30 pm
- **Booth #:** 22-23


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