Modernizing Quality Assessment of New Drugs

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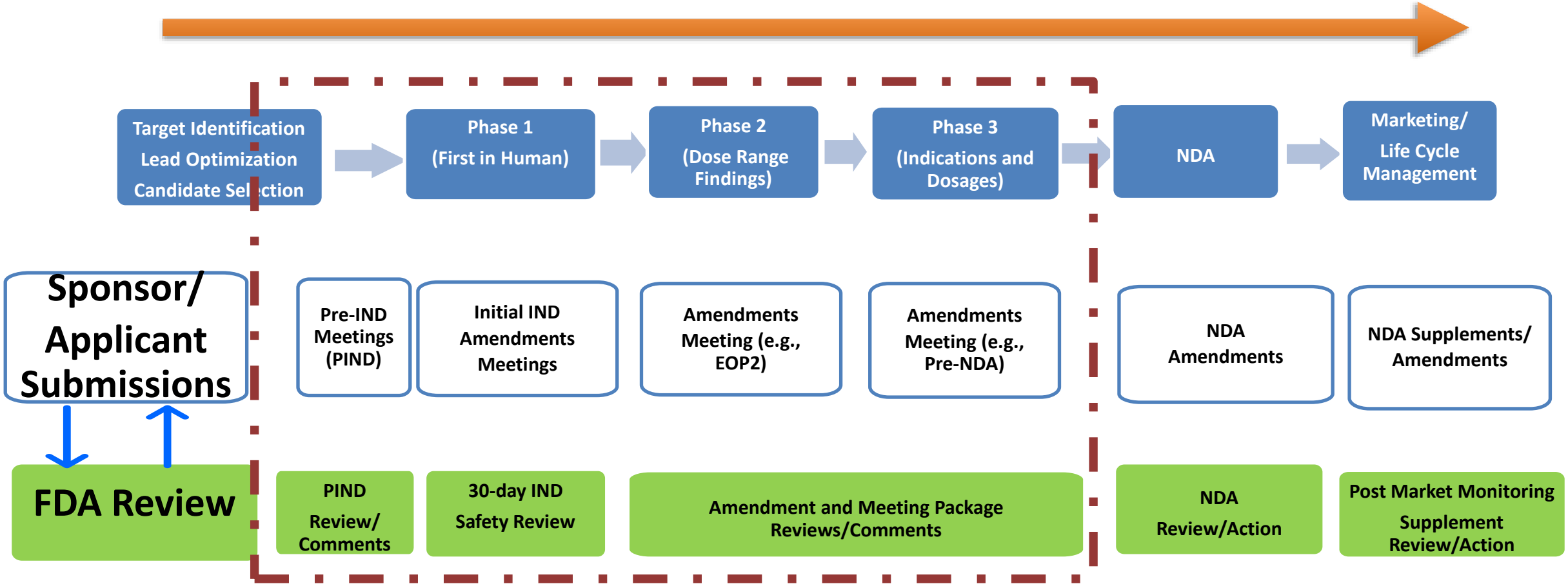
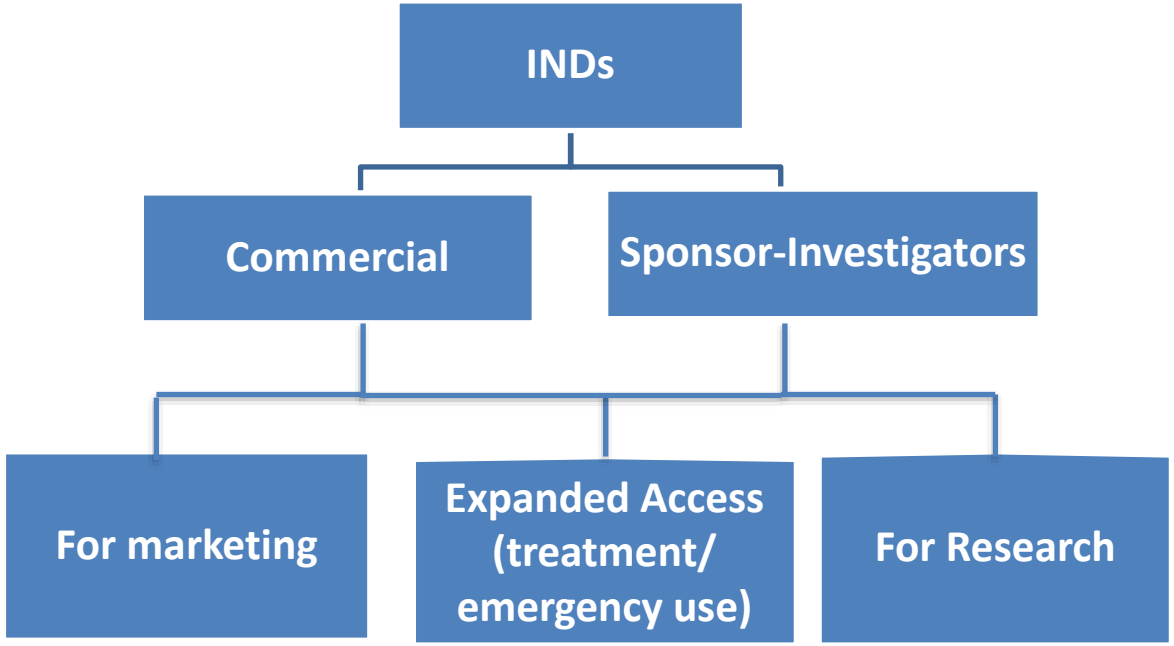
Outline

- Challenges in quality assessment for Investigational New Drugs (INDs) and New Drug Applications (NDAs)
- Modernizing new drug quality review with Knowledge-aided Assessment and Structured Application (KASA)
  - KASA for INDs
  - KASA for Drug Substance Enhancement (NDAs, DMFs and ANDAs)
- Summary

INDs/NDAs Contain Drug Development History



IND/NDA Submissions



Historical CDER IND Receipts and Activities

Calendar Year	New IND*	INDs w/ Activity*
2022	1865	14268
2021	2068	13810
2020	2182	12935
2019	1678	12328
2018	1594	11223

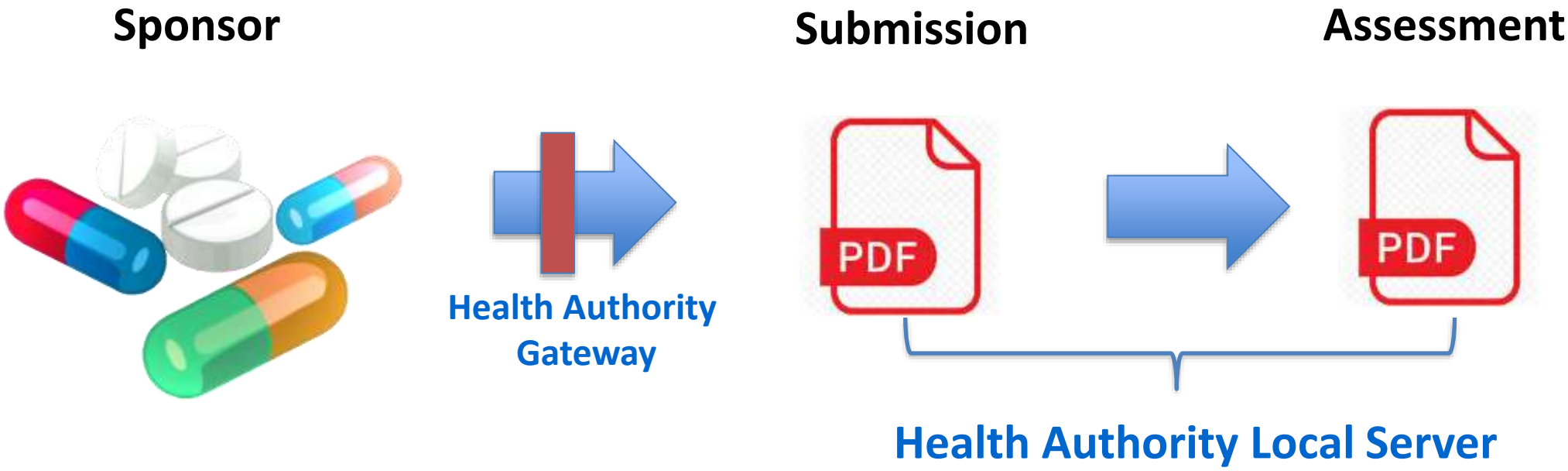
Fiscal Year	Expanded Access IND**
2020	2824
2019	1558
2018	1304
2017	1608
2016	1509

* Excludes Biosimilar Biologic INDs, Expanded Access INDs, and Unknown INDs. Unknown refers to those INDs where the designation of Commercial or Research had not been made at the end of the calendar year.
** Excludes Expanded Access Protocols

Sources:
https://www.fda.gov/drugs/how-drugs-are-developed-and-approved/drug-and-biologic-approval-and-ind-activity-reports

~200 NDAs (original and resubmission) per year for review

Current NDA/IND Submissions and Assessment



Assessment characteristics:

- **Lengthy unstructured text narrative with dispersed information**
- **Lack of efficient information sharing, knowledge management, and data analytics**

Challenges of IND/NDA Quality Assessment

Submission Characteristics	Review Challenges
• INDs often have long histories (>10 years) • Numerous types of IND with various objectives • May not be in eCTD format (e.g., research INDs) • Increasing technical complexity (e.g., novel dosage forms, emerging technologies) • Accelerated timelines (e.g., orphan drugs, expedited reviews) • Increasing number of submissions	• Large amounts of information/data but often dispersed in multiple places of an IND/NDA assessments • Difficult knowledge management hampering holistic review • Low efficiency, potential redundant work and inconsistency • Hinders the effort to produce high-quality reviews for stakeholders

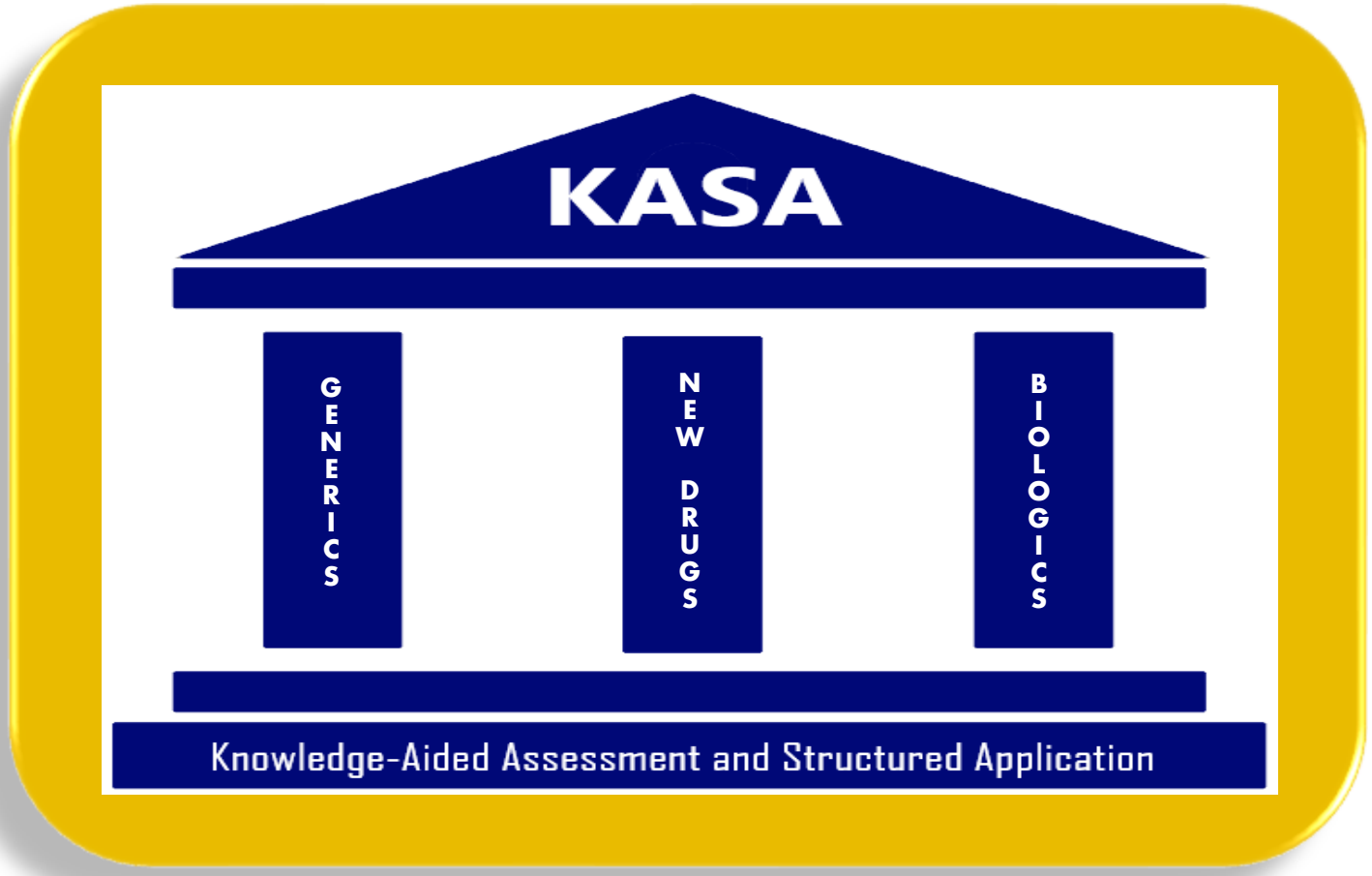
Quality Assessment Modernization: KASA System

Quality Assessment:
$20^{th} \rightarrow 21^{st}$ century technology

In 2016, FDA's KASA system was envisioned as a means of modernizing FDA's assessment (or review) by utilizing:

- Structured data (as opposed to narrative information)
- Advanced analytics; and
- Knowledge management

What is KASA?



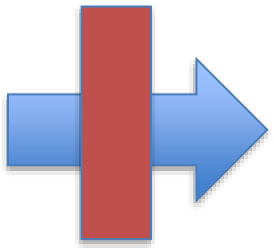
FDA's KASA System: A data-based platform for structured quality assessments and applications that supports knowledge management

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

FDA's Pharmaceutical Quality Assessment Is Moving into the Cloud

Sponsor

Submission



Health Authority Gateway

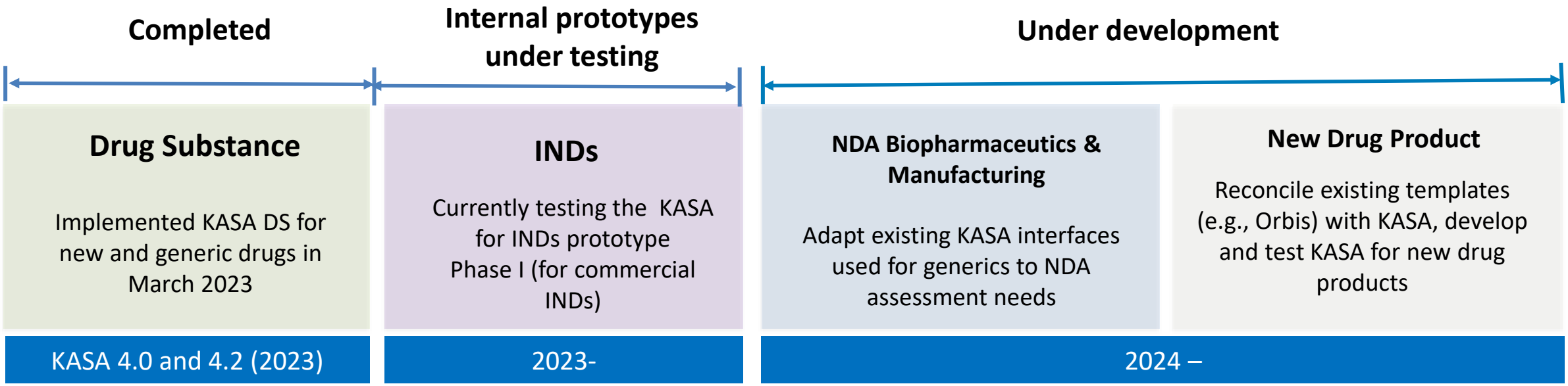
Health Authority Local Server

Assessment

Health Authority Cloud Server

KASA for New Drugs

- Build on the success of KASA for generics and expand to new drug quality assessment
- Add flexibility to meet various assessment needs for new drug development
- Facilitate risk-based assessment and promote innovation
- Involve the users (assessors) in all stages of development from prototype to production including testing, implementation and optimization



KASA IND Design Considerations

IND CMC Characteristics

- CMC changes are common for INDs
- Different INDs share the same API (same DMF)
- Same investigational drug product may be studied in multiple INDs
- Various development goals: research, expanded access and treatment in addition to marketing purpose

KASA IND Desired Features

KASA IND: Modular Design for Flexibility

Assessment Modules with Flexible Building Blocks

Overview
Submission Background
Executive Summary
Investigational Labeling , Environmental Assessment exclusion claim
Consult requests from other discipline or centers, etc.
Recommendations (safe to proceed, safe to proceed with non-hold comments; CMC hold)

Drug Substance
DS Overall Summary, LOAs
Structure and Properties
Manufacturing Process (e.g., SM, Intermediate)
Characterizations and References
Specifications, Batch Data and Analytical Methods
Impurities
Packaging and Stability
Others

Investigational Drug Product
DP overall Summary, LOAs
Components and Composition
Excipients
Manufacturers and Manufacturing Process
Specification, Batch Data, and Analytical Methods
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Placebo or Active Controls
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Others

Cross Referenced to a DMF via LOA

Investigational Drug Product
DP overall Summary, LOAs
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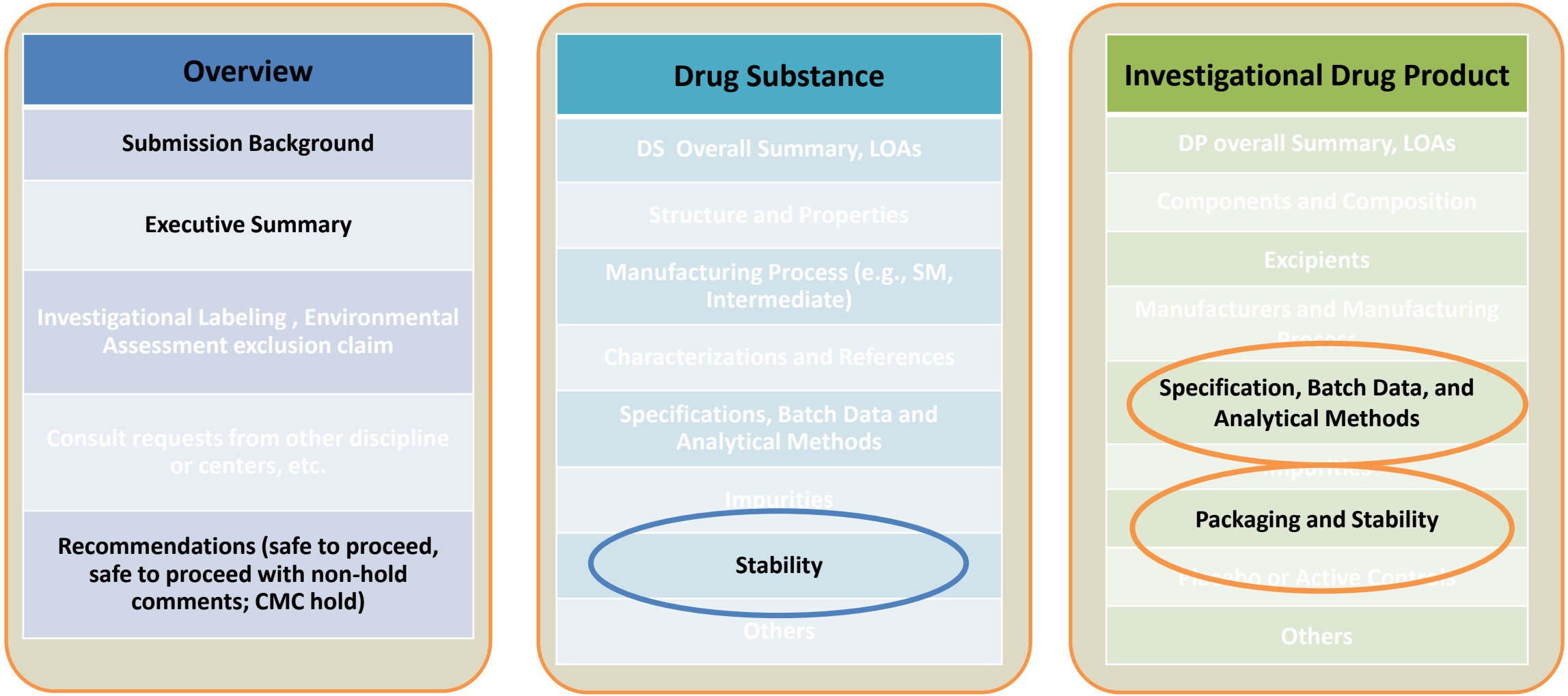
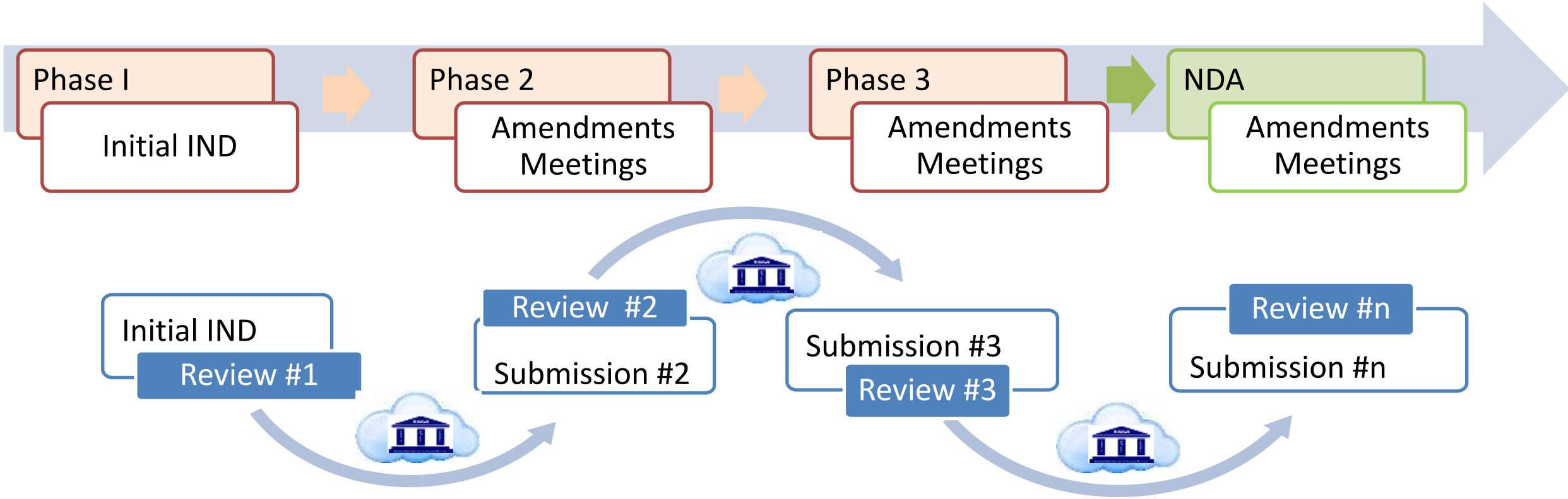
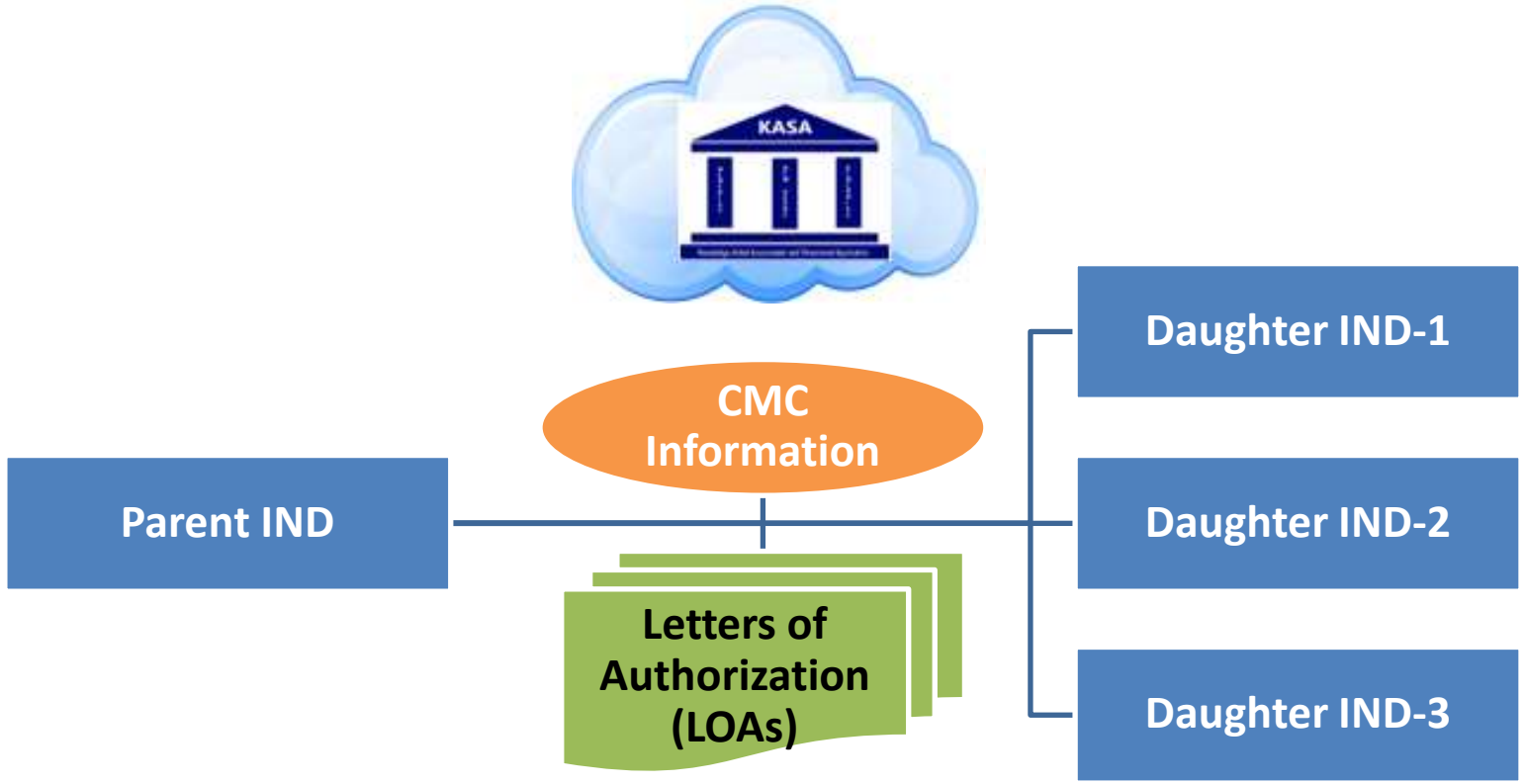


Future KASA IND with Knowledge Management Enhancement



- Subsequent reviews automatically built on the previous one
- Refresh the assessors with regards to the application history
- Assists regulatory decision making and increase efficiency
- Benefit workload management and resource planning

Future KASA IND with Knowledge Management Enhancement



- Easy to manage and track INDs via LOAs with shared CMC information
- Enable to access previous quality assessments for parent and daughter INDs easily
- Optimize assessment knowledge management and improve efficiency

KASA for Drug Substance (DS) Enhancement

Machine Readable Structures: SD Files for Chemical Structures

Assessment Goals:

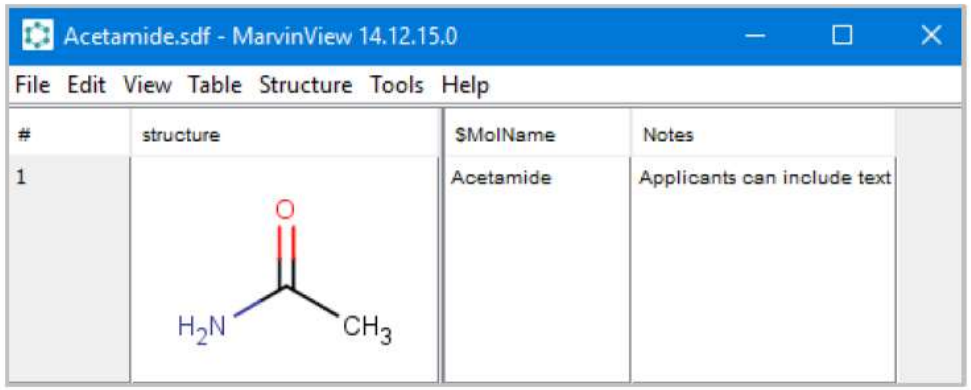
- Quickly identify potentially high-risk impurities
- Apply consistent standards for assessment of DS information in NDAs, ANDAs and DMFs
- Inform decision making and increase efficiency of assessment

SD Files for Chemical Structures

- 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.
- Errors are eliminated
- Easier to transmit structures to other offices or stakeholders within the Agency

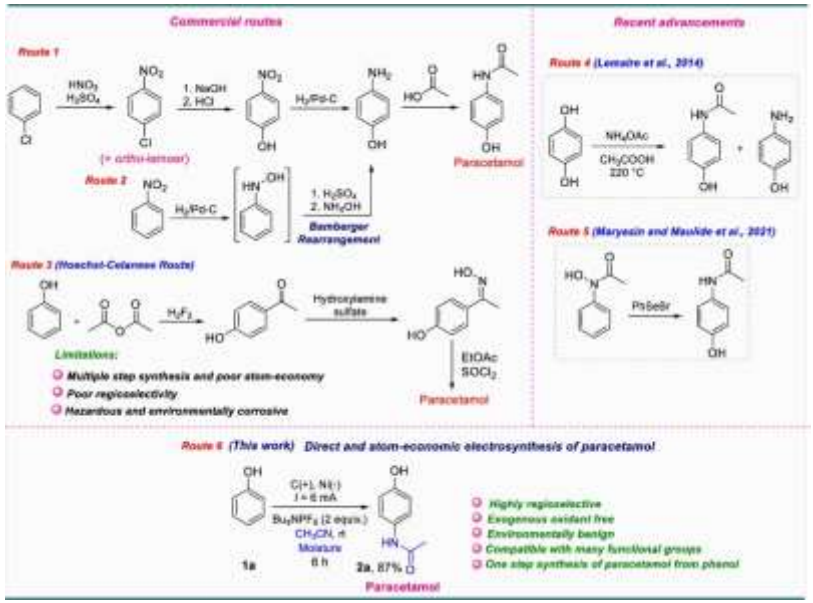
```
Acetamide


  4  3  0  0  0  0  0  0  0  0999 V2000
    0.0000   -0.2062    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.0000    0.6188    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   -0.7145   -0.6188    0.0000 N   0  0  0  0  0  0  0  0  0  0  0  0
    0.7145   -0.6188    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
  1  2  2  0  0  0  0
  1  3  1  0  0  0  0
  1  4  1  0  0  0  0
M  END
```



Structured Synthetic Pathways

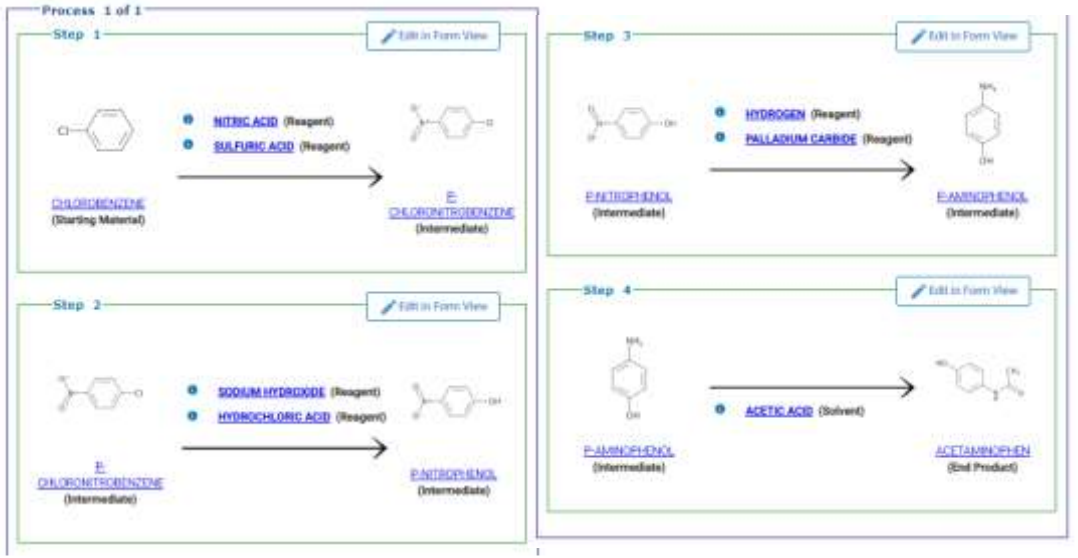
Non-machine-readable



Taily IM, et al. , Organic Letters. 2022 Mar 21;24(12):2310-4.

Picture or PDF

Machine-readable GSRS form



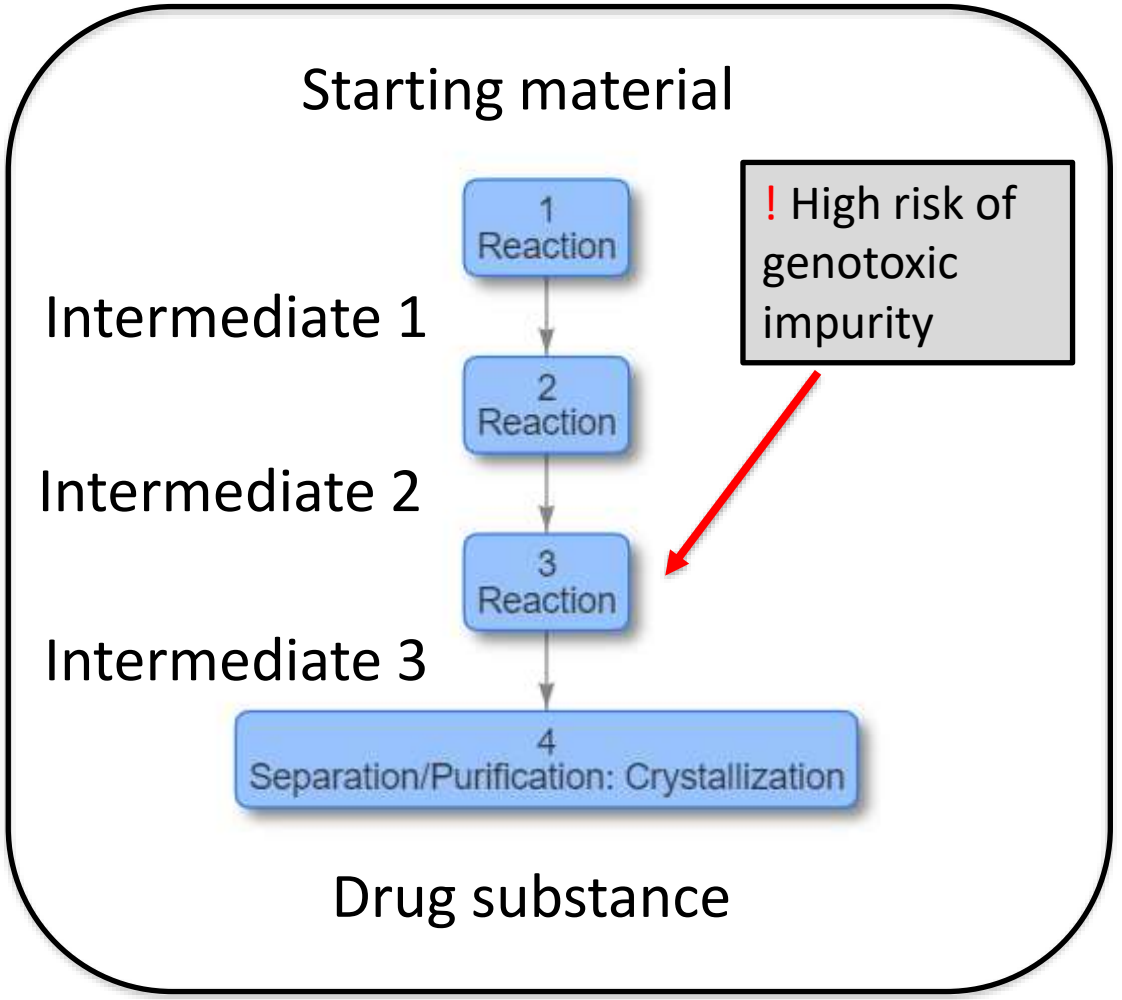
Attributes and data elements (e.g., name, role, structure) are databased

Desired State: Structured DS Synthetic Pathway in Submissions

- DS synthetic routes in KASA can be:
  - Searched
  - Analyzed

- Analytics tools will enable KASA to search based on DS, reagents, solvents, impurities and display synthetic pathways

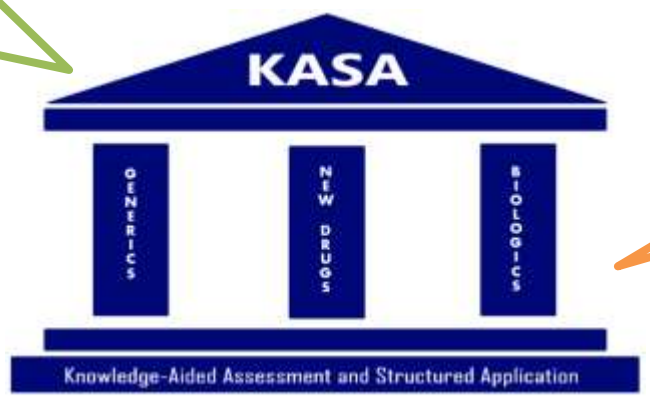
Goal:
- ✓ Identify reactions/combinations of chemicals that potentially generate high risk impurities
- ✓ Track global supply chain, identify supply chain vulnerabilities



KASA System

Built In Data Analytics (established rules and algorithms) to Improve Assessment Quality

Modernize Institutional Knowledge Management



Improve Assessment Efficiency and Consistency

Inform Decision-making and Facilitate Innovation

More affordable and accessible medicines for American patients

Summary

- KASA for new drugs are built using the same approach as KASA for generics, but include unique elements, e.g., flexibility, and analytics tools based on the needs of IND and NDA assessments
- KASA for IND prototype is undergoing pilot testing to optimize its modules for various assessment needs
- KASA for DS interface and enhancements (NDA, DMF and ANDA) have been released in CDER IT platform
- KASA for new drug enables knowledge management, critical thinking and promotes consistency and efficiency in regulatory assessment

Acknowledgements

- OPQ KASA for IND Working Groups
- OPQ KASA for DS Working Group
- OPQ KASA for DS NEXUS Implementation Group
- All developers, super-users, testers, and staff implementing KASA
- Our host CDER Small Business & Industry Assistance (SBIA) Team

Thank You!


FDA
U.S. FOOD & DRUG
ADMINISTRATION