SBIA DMF Workshop: GDUFA III Enhancements and Structured Data Submissions

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U.S. FOOD & DRUG ADMINISTRATION

Modernization of Regulatory Submission

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Advancing Forward

Annually, OPQ reviews ~ 3,000 INDs, ~240 NDAs/BLAs, ~900 ANDAs, ~10,000 supplements, submitted in unstructured PDF format.

We recognize the need to modernize

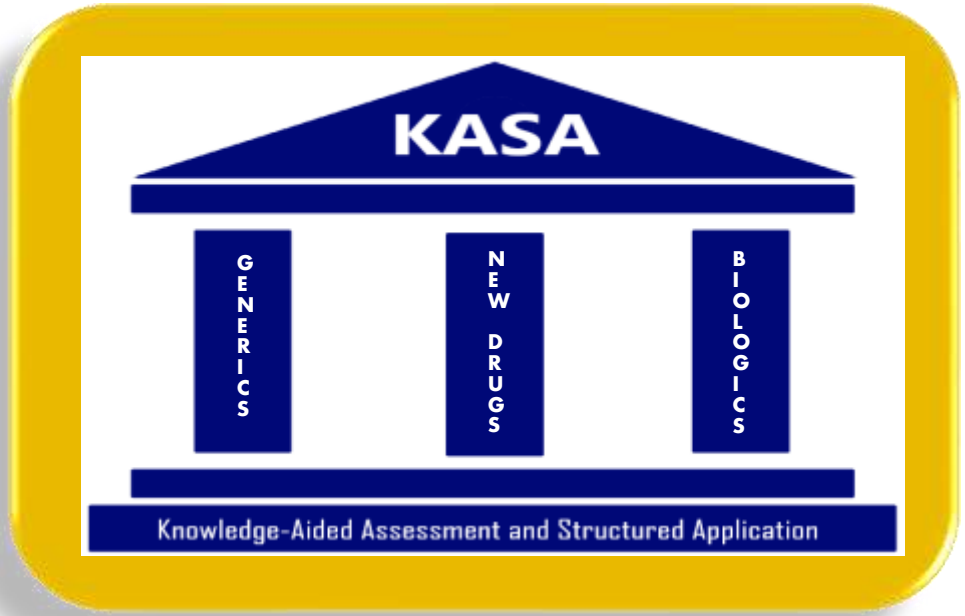
($20^{th} \rightarrow 21^{st}$ century technology)

Move from narrative information to **structured data*** in order to best capture/manage knowledge

* **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

The KASA System

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



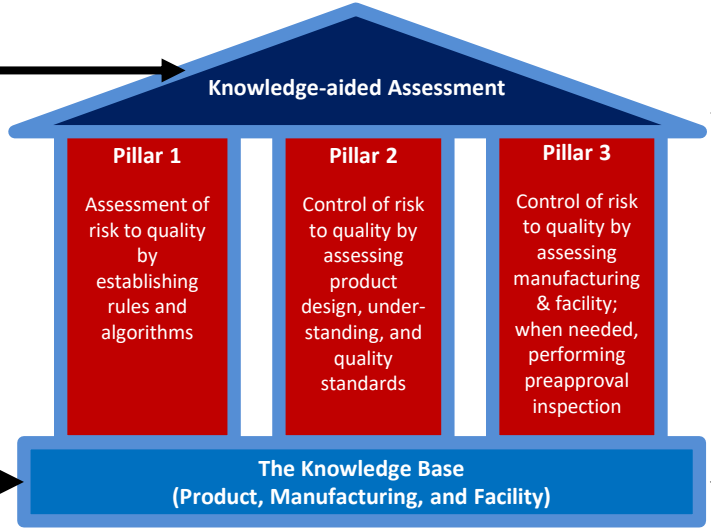
The KASA System:
A data-based platform for structured quality assessments and applications that supports knowledge management

KASA for DS applicable to assessment of API information submitted in NDAs, ANDAs, and DMFs will be released in CDER IT platform in February 2023.

Current KASA System

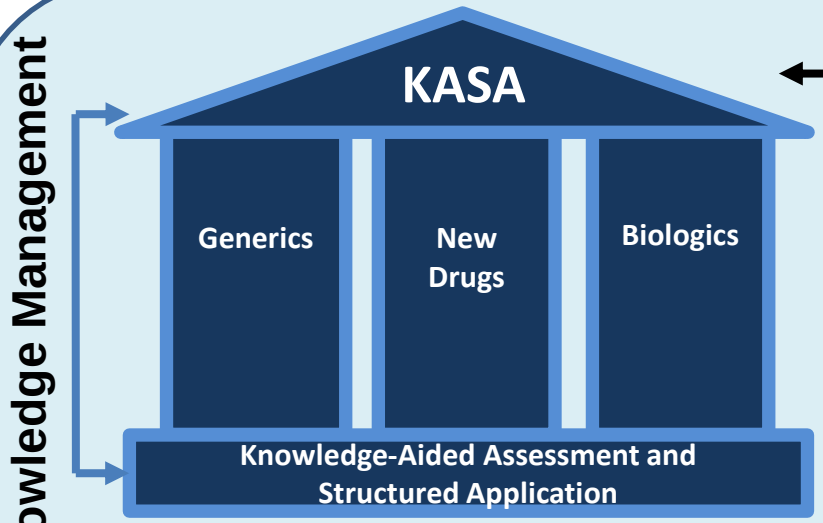
FDA internal driver for submission modernization

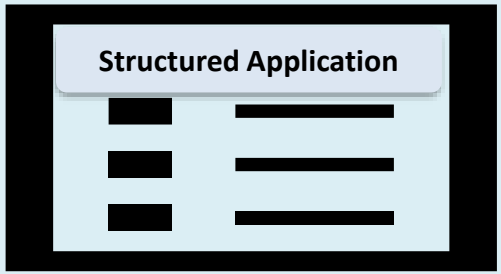
Assessors need to manually transpose information from unstructured submissions to KASA interface



Knowledge Management during lifecycle of a drug product

The KASA System





What information is submitted?

How is information organized?

ICH M4Q revision

Electronic data standards

PQ-CMC

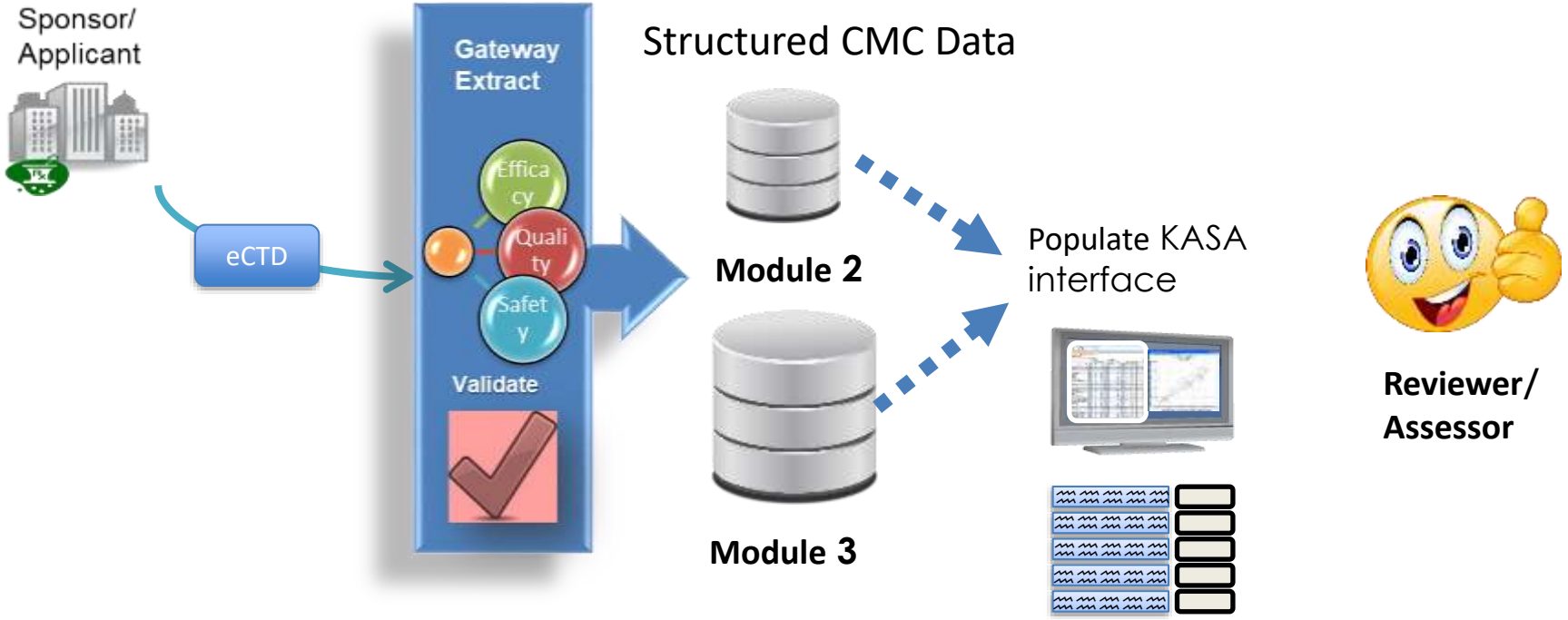
"KA"

integrated set of tools and framework to aid regulatory assessment and knowledge management

"SA"

content and organization of submission and electronic data standards

Future KASA System with Structured Application



How to Get There?

- Regulatory Assessment Transformation
  - KASA
- Regulatory Submission Transformation
  - Revision of ICH M4Q
  - Structured Pharmaceutical Quality Standards

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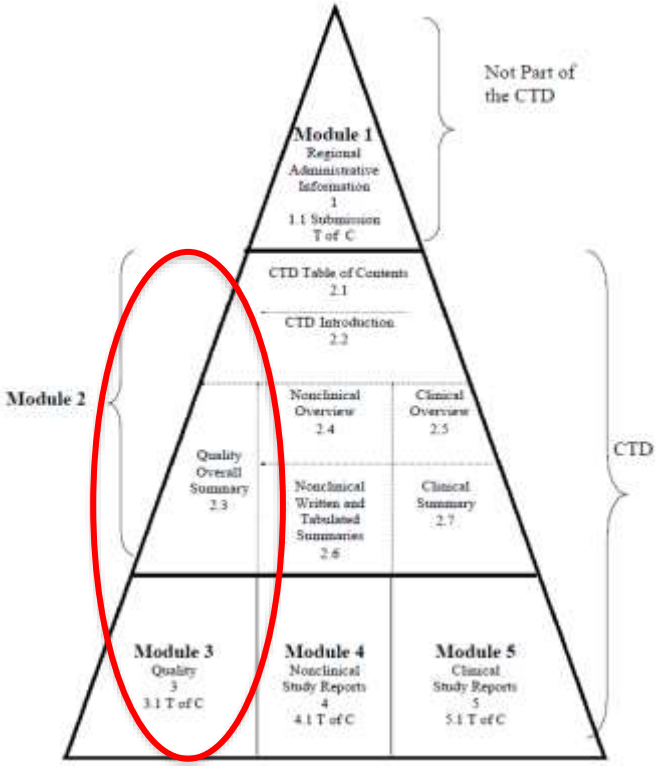
Ongoing efforts related to structured applications:

- **Revision of ICH Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1)**

What is M4Q 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) 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).

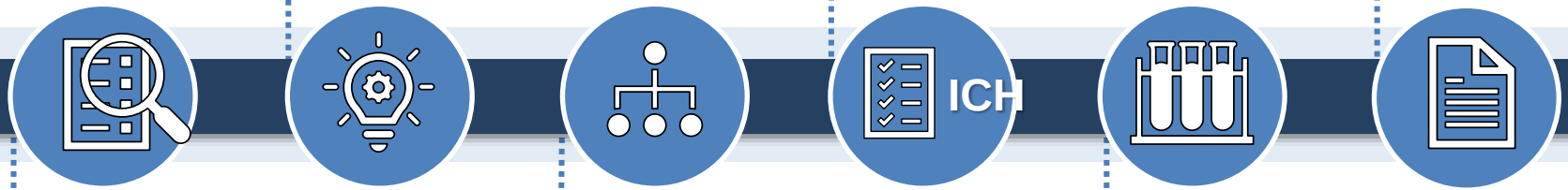
For your expanded interest see *Concept Paper M4Q(R2) Common Technical Document on Quality Guideline Endorsed by the Management Committee on 15 November 2021* ICH Official web site : ICH

What Are Perceived Problems (Cont.)?

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, 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.

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

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.

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

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

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

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Ongoing efforts related to structured applications

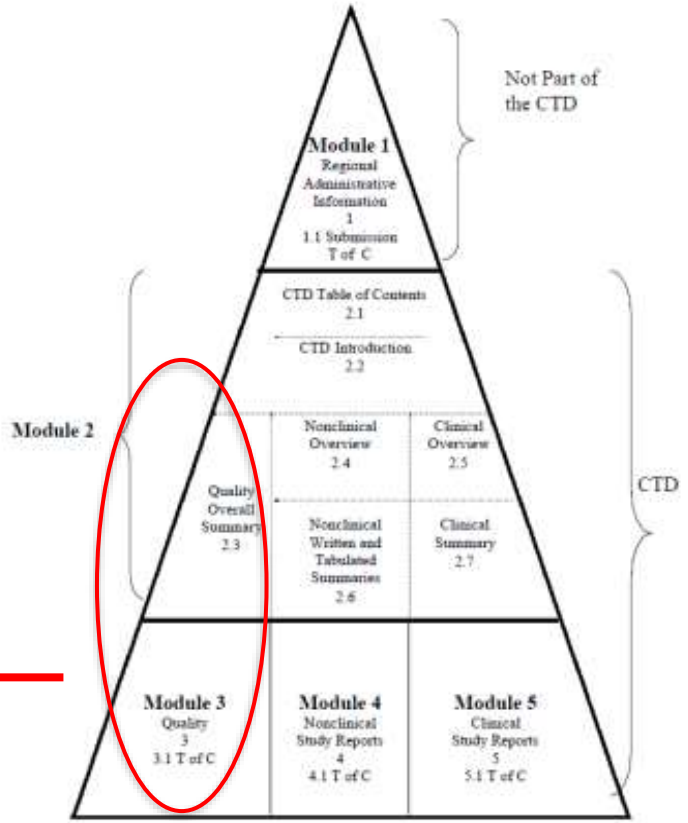
- **Structured Pharmaceutical Quality Standards**

Pharmaceutical Quality Electronic Data Standards

- Module 3 body of data
  - Currently submitted in PDF format with unstructured pharmaceutical quality data.
  - Significantly hinders the efficiency of data exchange, quality assessment, and lifecycle knowledge management.

FDA initiated an effort to establish content standards and electronic exchange standards for submitting PQ/CMC data.

eCTD submissions with unstructured PQ/CMC data



Data Standards Development at FDA

- FDA PQ/CMC structuring and standardization is intended to be accomplished in multiple phases.
  - **Phase 1** covers the following topics: Drug Product, Drug Substance, Quality Specification, Batch Formula, Batch Analysis and Stability
    - Substantially completed by end of 2020; ~ 33% of Module 3 data
  - **Phase 2** data standards are under development, and will cover the following topics: Drug Product Manufacturing, Drug Substance Manufacturing, etc.
    - Initiated in January 2021

For your expanded interest see *Pharmaceutical Quality/Chemistry, Manufacturing & Controls (PQ/CMC)* Pharmaceutical Quality/Chemistry, Manufacturing & Controls (PQ/CMC) | FDA

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Structured Application for Drug Substance

Current efforts

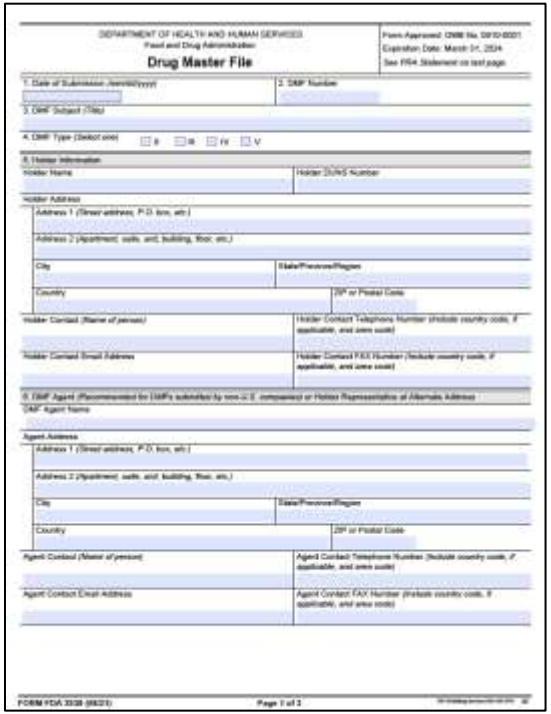
- Form 3938 for DMFs
- SD files for chemical structures

Future efforts

- Structured DS synthetic pathway

Form 3938 for DMFs

- Provides the Agency contact and facility information in a structured format for easier use
- Improves efficiency and accuracy
- https://www.fda.gov/drugs/drug-master-files-dmfs/drug-master-file-dmf-submission-resources
- Contains
  - Current contact information
  - Facilities information
  - Cross-referenced DMFs
- Functional Goals
  - Pre-populate letters and communications
  - Cross-reference facility information to referencing applications
  - Flag secondary DMFs earlier in the process



Drug Master File

Form 3938

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.
- Other associated information is part of the structured data

```
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
>  <Notes>
Applicants can include text
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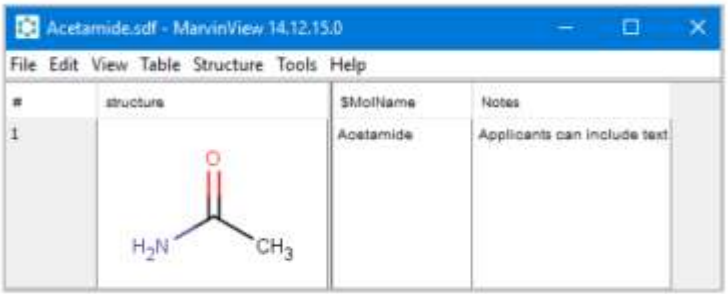
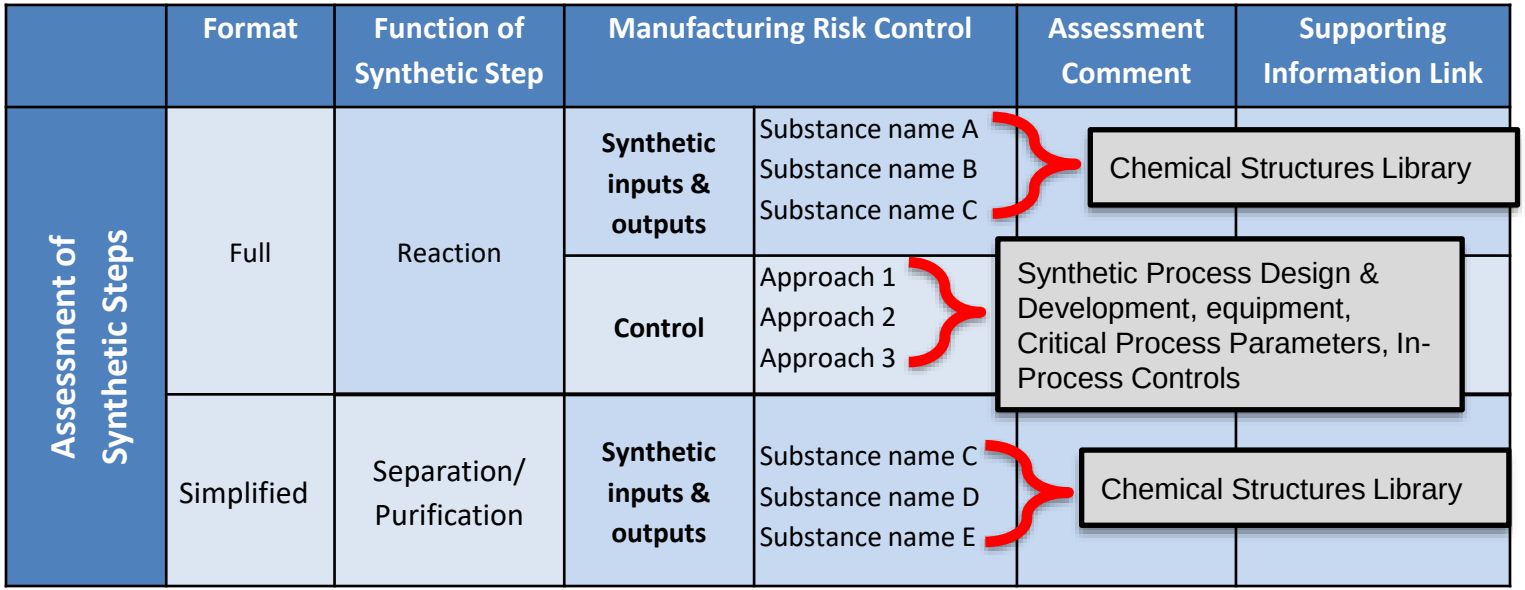


How SD Files help FDA?

- Errors are eliminated
- Easier to transmit structures to other regulatory bodies with the Agency
- Structures represent synthetic inputs, synthetic outputs, impurities from synthetic steps; they will receive a tag for immediate and subsequent review cycles.

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

Current Structured DS Synthetic Pathway in KASA



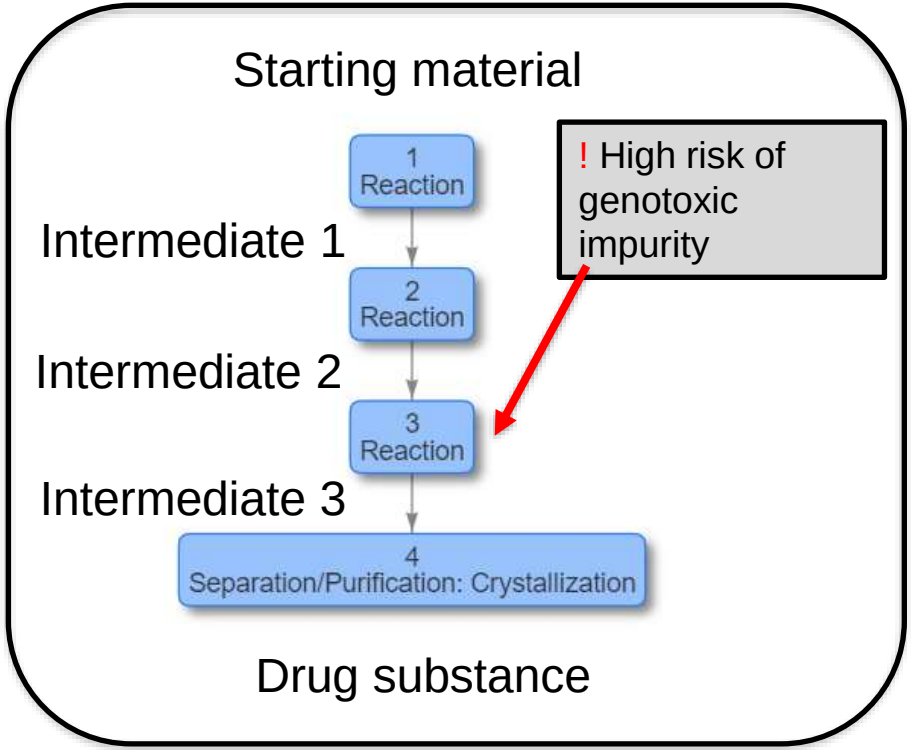
+ control of starting materials, control of intermediates, control of reagents

Desired State: Structured DS Synthetic Pathway in Submissions

DS synthetic routes in KASA can be:

- searched
- visualized
- analyzed

Having DS synthetic pathways submitted in structured format will increase assessment efficiency, avoid transcription mistakes, and improve DS knowledge management.



Conclusion

- KASA for DS interface will be released in February 2023 for assessment of DS information submitted in DMFs, ANDAs and NDAs. It presents opportunities for knowledge management, consistency in decision making, and improved assessment efficiency.
- Efforts are ongoing at ICH (ICH M4Q(R2)) and FDA (PQ-CMC) levels to structure quality information in submissions.
- DS information can be currently submitted in a structured format, in Form 3938 for DMFs and SD files for chemical structures. It eliminates potential transcription errors and further increase assessment efficiency.

Thank You

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