Machine Readable Synthetic Pathways in GSRS and KASA

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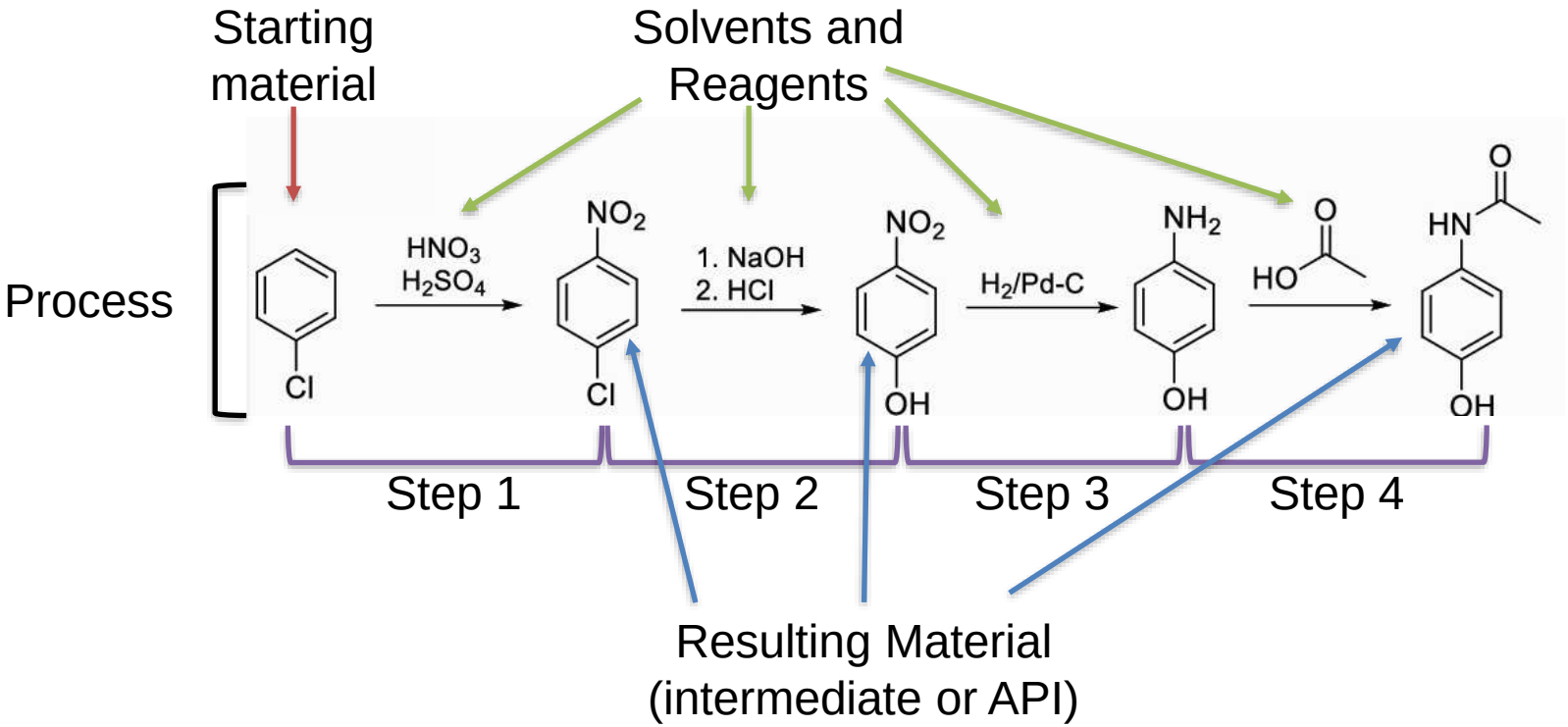
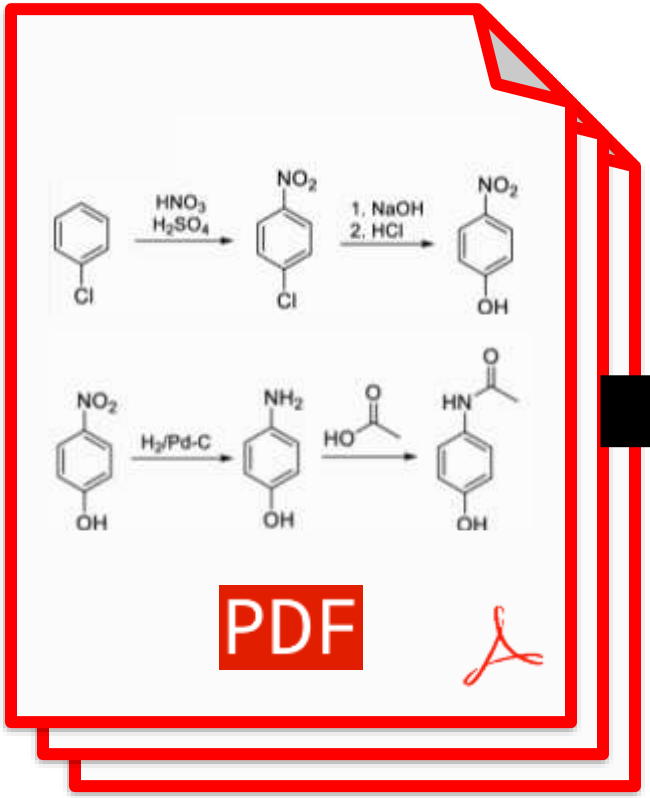
FDA's Global Substance Registration System (GSRS) group 4 specified substance manufacturing (G4SSM) form

- Structuring synthetic pathways
- International Organization for Standardization (ISO) 11238
- GSRS G4SSM form and features

What is in a synthetic pathway?



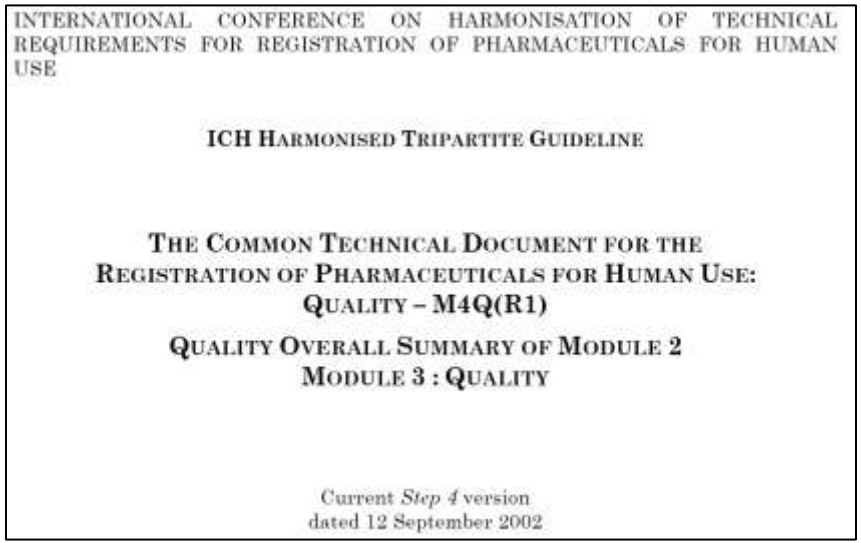
How does FDA get synthetic pathways?



electronic Common Technical Document (eCTD)

How does FDA use synthetic pathways?

- ICH M4Q(R1)
- 3.2.S.2.2 Verifies that the synthetic pathway described matches the data found in the executed batch record
- 3.2.S.2.3 and 2.4 Identifies raw materials used and intermediates generated in the synthetic pathway



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

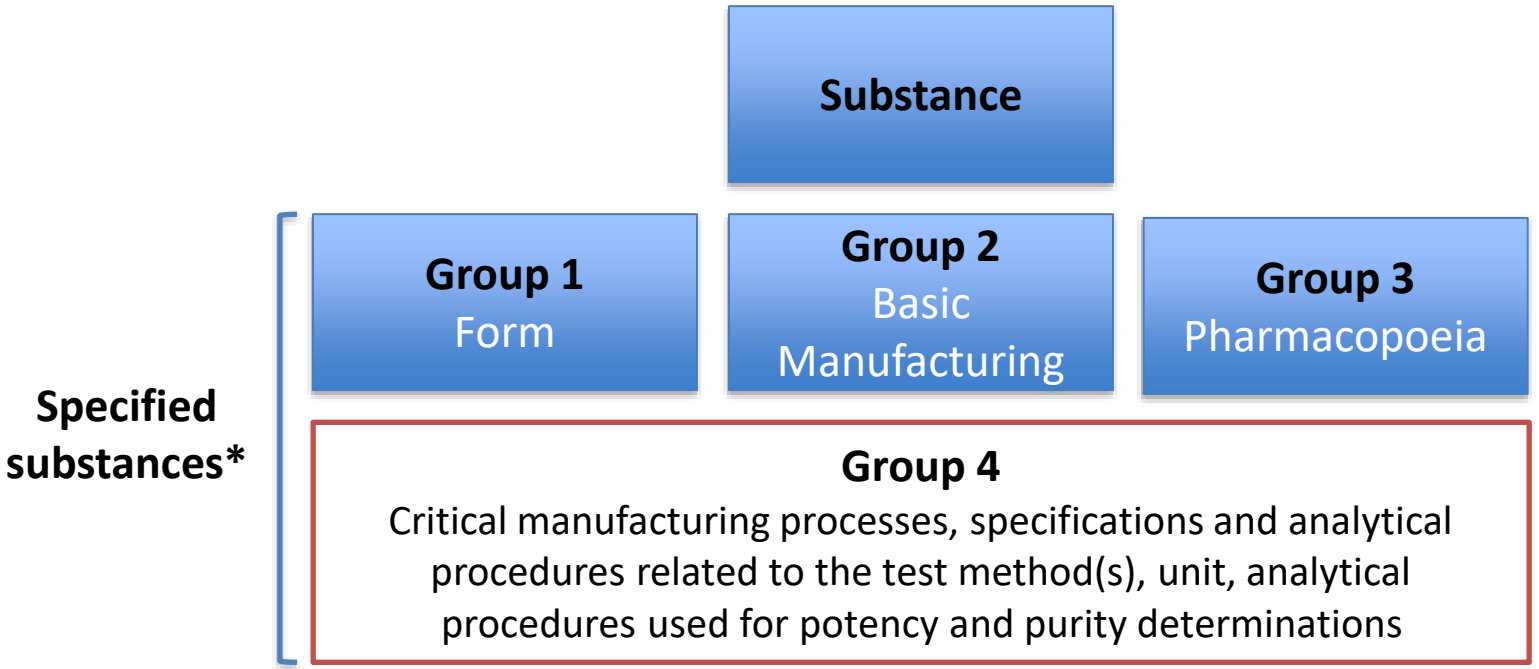
THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY – M4Q(R1)

QUALITY OVERALL SUMMARY OF MODULE 2
MODULE 3 : QUALITY

Current *Step 4* version
dated 12 September 2002

International Organization for Standardization (ISO) 11238

Outlines models for defining four specified substance groups

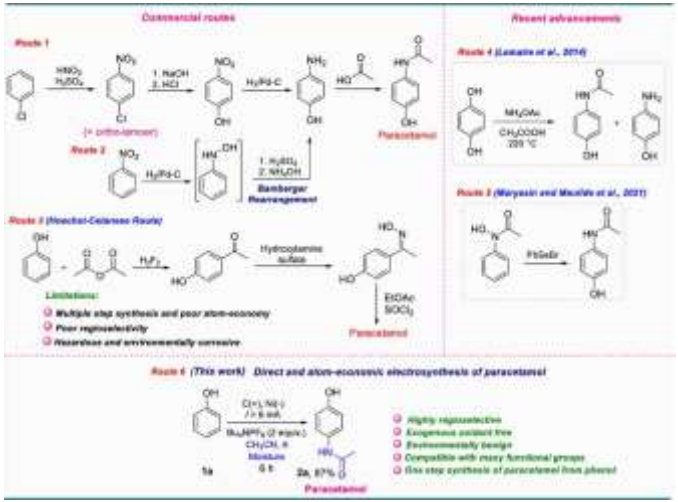


KASA and GSRS

- GSRS and KASA teams collaborated to capture synthetic pathway details in the KASA platform by developing a G4SSM form
  - Enables the Assessor to capture the synthetic pathway and process details in a structured format
  - Form will be used in KASA for drug substance assessments for ANDA, NDA and DMF submissions

Synthetic pathways

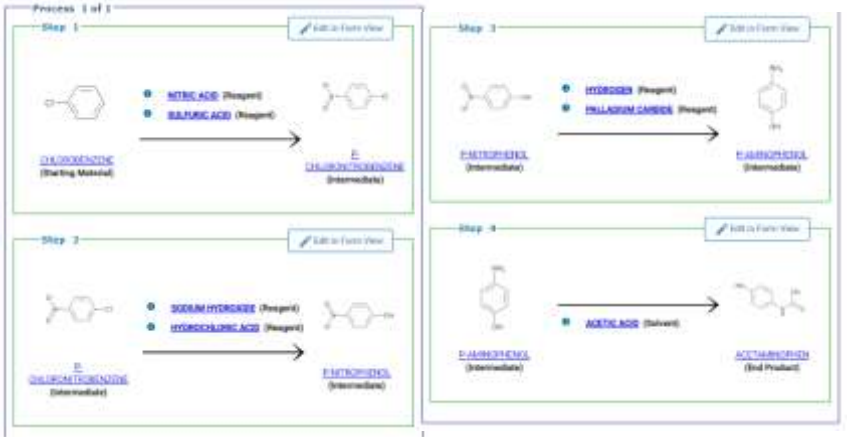
Non-machine-readable



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

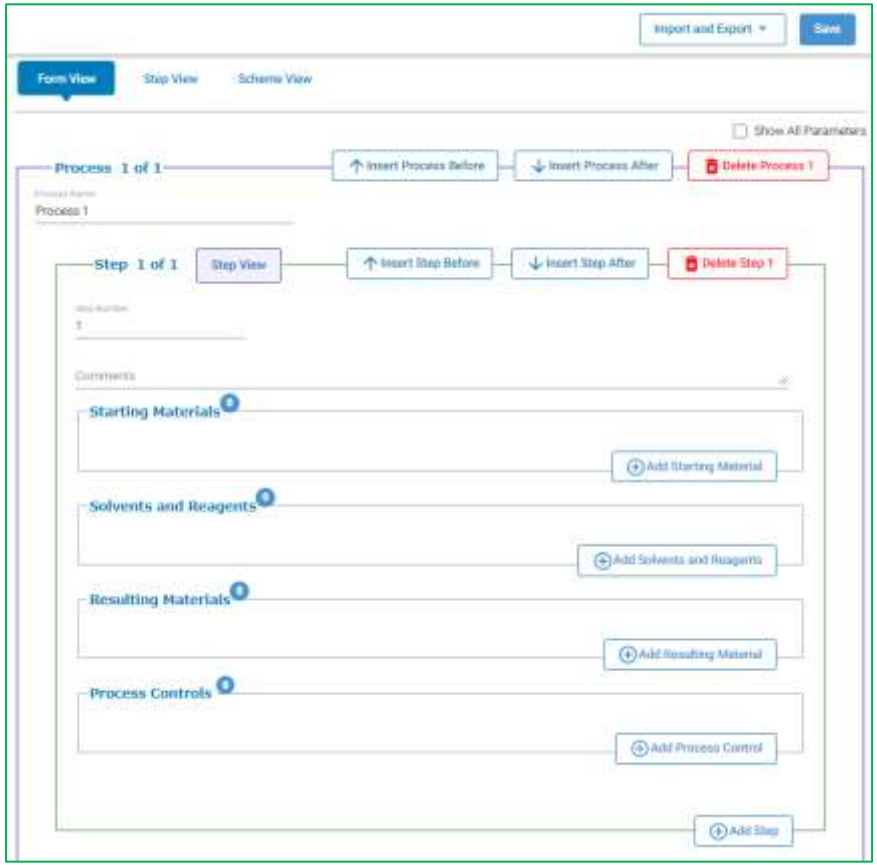
Picture or PDF

Machine-readable GSRS form



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

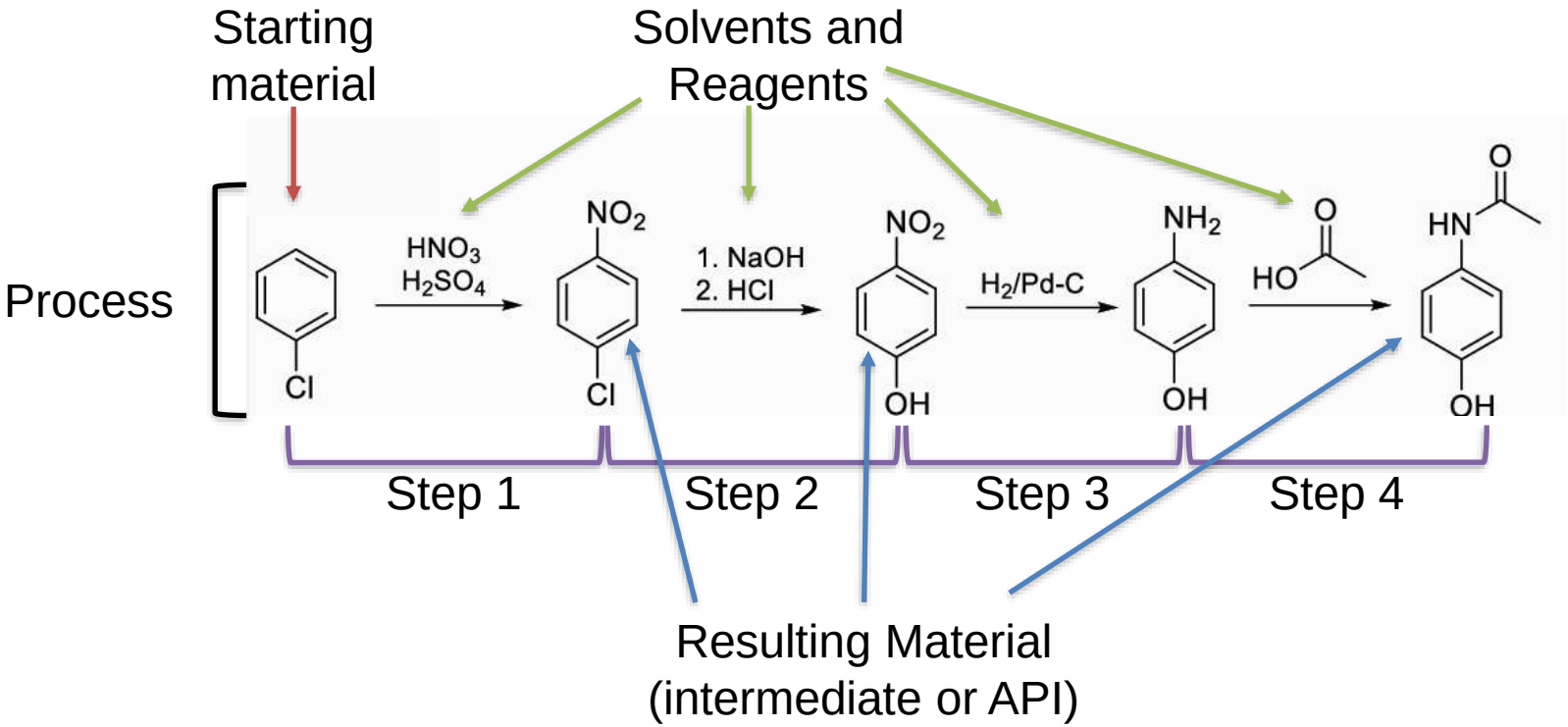
GSRS G4SSM form



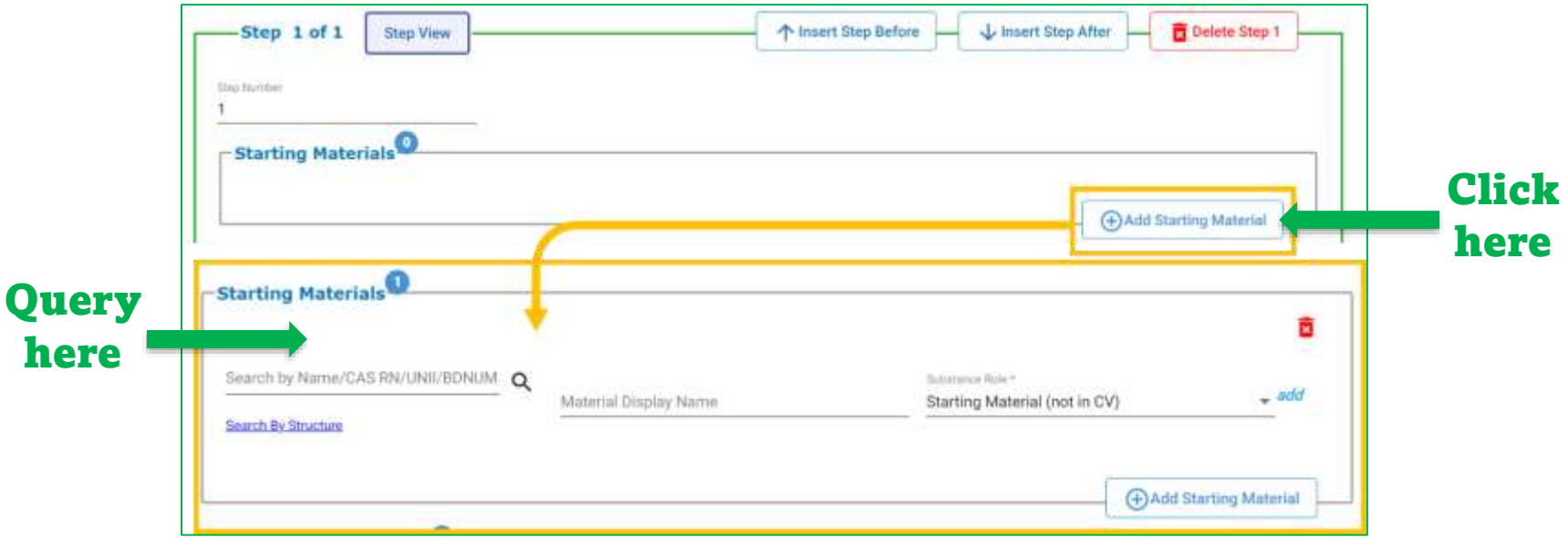
How the GSRS G4SSM form works

1. Obtain the synthetic pathway
2. Populate the form
   - Process(es)
   - Steps
     - Starting materials
     - Solvents and reagents
     - Resulting Material (e.g., intermediate or drug substance/API)
     - Process controls

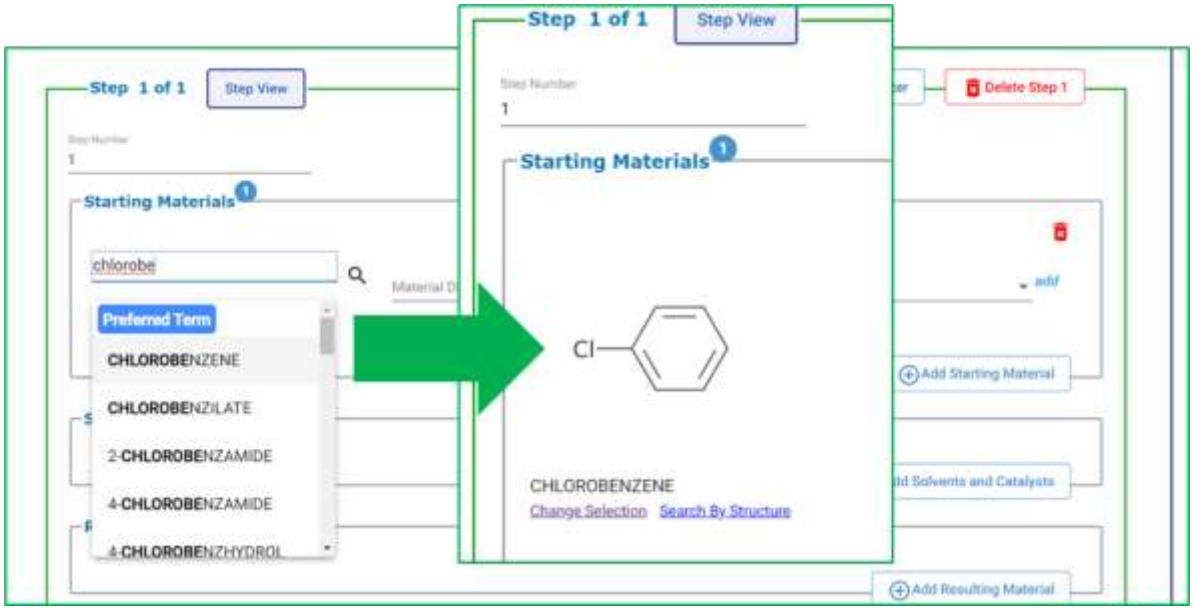
What is in a synthetic pathway?



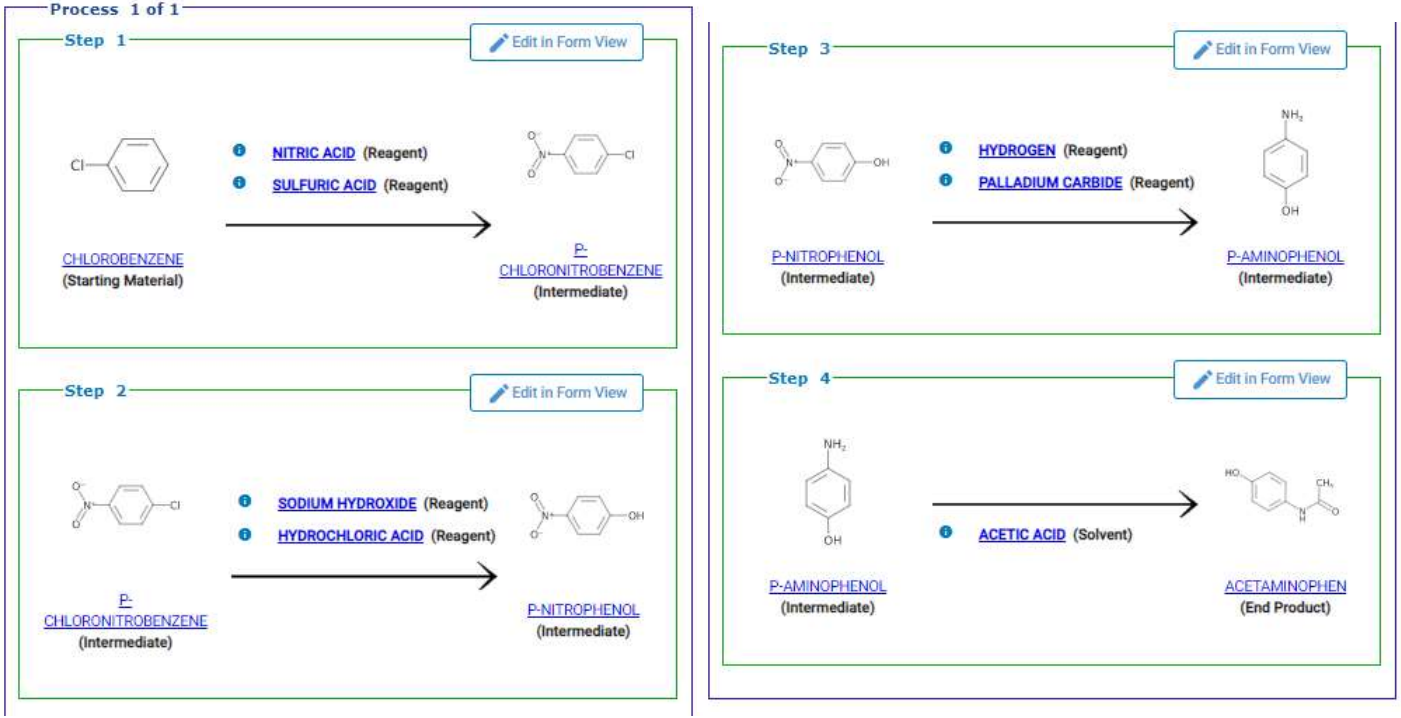
Form has fields that allow users to query GSRS for substances



Select substance from drop-down window

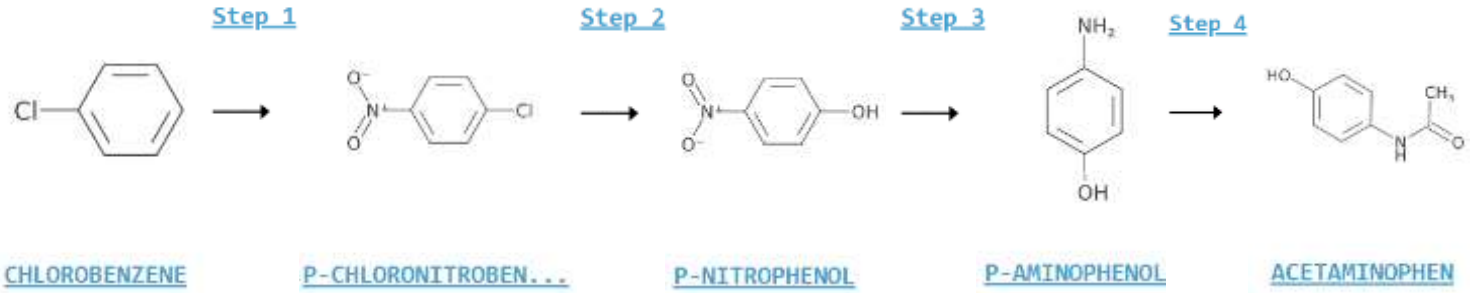


Step View


Process 1 of 1
Step 1
Edit in Form View
NITRIC ACID (Reagent)
SULFURIC ACID (Reagent)
CHLOROBENZENE
(Starting Material)
P-CHLORONITROBENZENE
(Intermediate)
Step 2
Edit in Form View
SODIUM HYDROXIDE (Reagent)
HYDROCHLORIC ACID (Reagent)
P-CHLORONITROBENZENE
(Intermediate)
P-NITROPHENOL
(Intermediate)
Step 3
Edit in Form View
HYDROGEN (Reagent)
PALLADIUM CARBIDE (Reagent)
P-NITROPHENOL
(Intermediate)
P-AMINOPHENOL
(Intermediate)
Step 4
Edit in Form View
ACETIC ACID (Solvent)
P-AMINOPHENOL
(Intermediate)
ACETAMINOPHEN
(End Product)

Scheme View

UNII				
K18102WN1G	CVL66U249D	Y92ZL45L4R	R7P8FRP05V	36209ITL9D



Machine-readable GSRS G4SSM form capabilities

- ☑ Find all routes that use a specific SOLVENT
- ☑ Find all routes that involve a specific STARTING MATERIAL or INTERMEDIATE
- ☑ Quickly compare similar pathways
- ☑ Find all routes involving substances with specific chemical motifs or SUBSTRUCTURES
- ☑ Accept structured synthetic pathways directly

Final thoughts

- KASA and GSRS collaborated to develop a structured, machine-readable G4SSM form
- Allows Assessors to create and visualize the manufacturing process
- Advanced search capabilities
- Enables rapid comparison of synthetic schemes
- GSRS G4SSM form will be made publicly available for download in 2023

https://github.com/ncats/GSRSFrontend/tree/development_3.0/src/app/core/substance-ssg4m

Thank you!

GSRS Scientists

Frank Switzer

Larry Callahan

Marlene Kim

Tyler Peryea

Dammika Amugoda

Marian Nkeng

Siba Bhattacharyya

GSRS Developers

Tyler Peryea

Archana Newatia

Ramez Ghazzaoui

Lihui Hu

Niko Anderson

Mitchell Miller

Alex Welch

KASA Team

Andre Raw

Archana Narayanaswamy

Larisa Wu

Sara Wu

Patrick McAuliffe

Tamanna Rajpal

Charles Robertson

QUESTIONS?


FDA
U.S. FOOD & DRUG
ADMINISTRATION