

Machine Readable Synthetic Pathways in GSRS and KASA

Tyler Peryea

Chemist, Global Substance Registration System Product Lead

US FDA

Office of the Commissioner/ODT/ODAR/Health Informatics Staff

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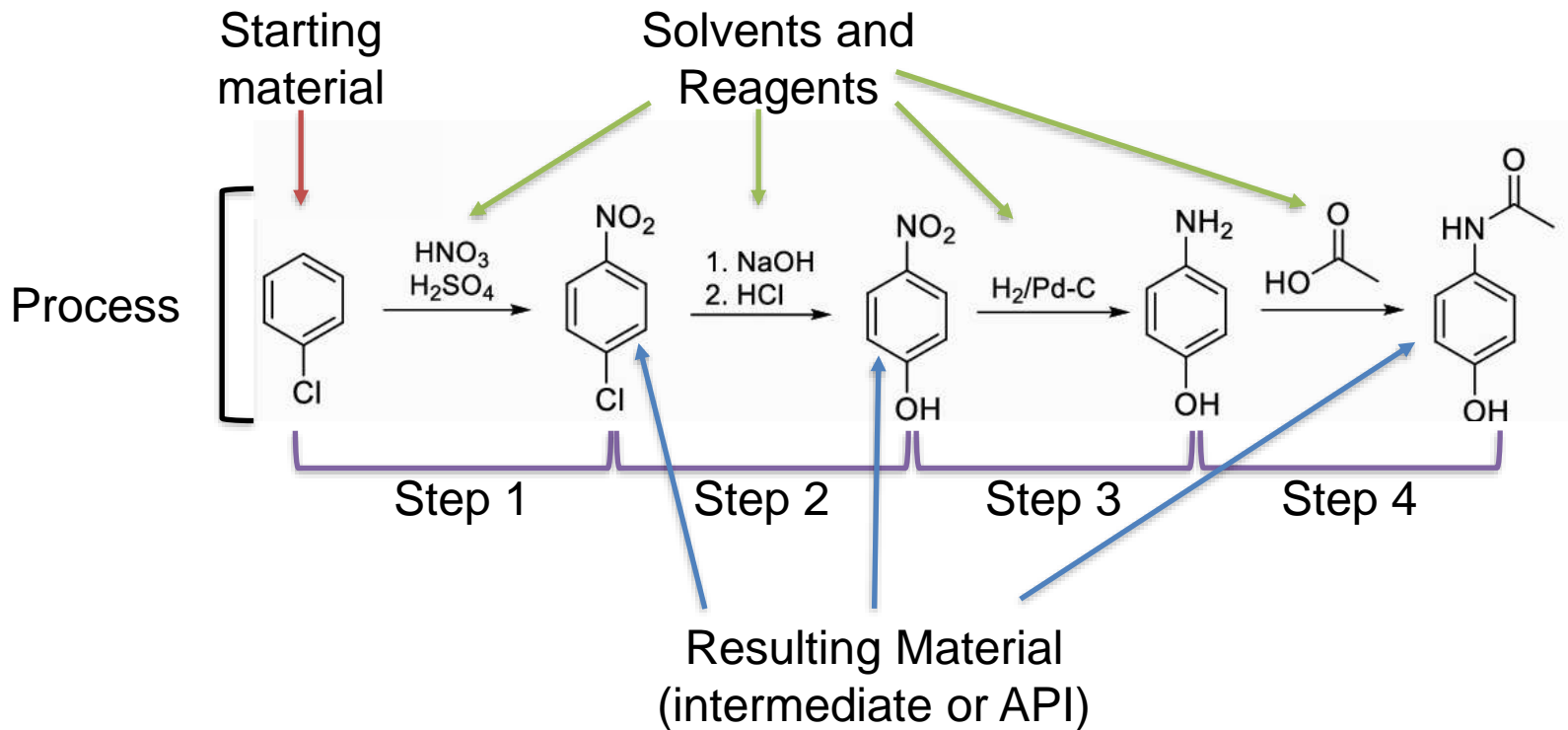
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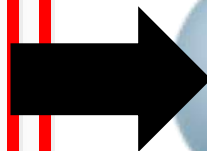
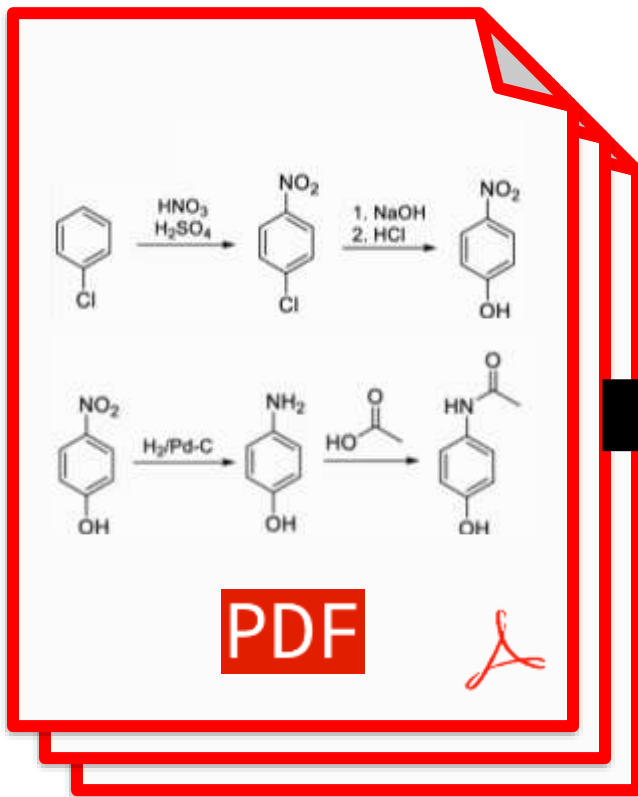
FDA's Global Substance Registration System (GSRS) group 4 specified substance manufacturing (G4SSM) form

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

What is in a synthetic pathway?



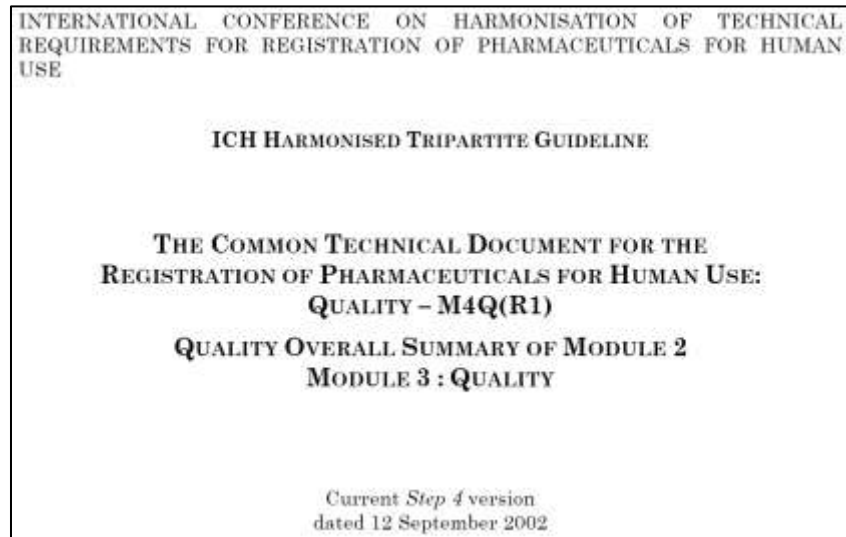
How does FDA get synthetic pathways?



electronic Common Technical Document (eCTD)

How does FDA use synthetic pathways?

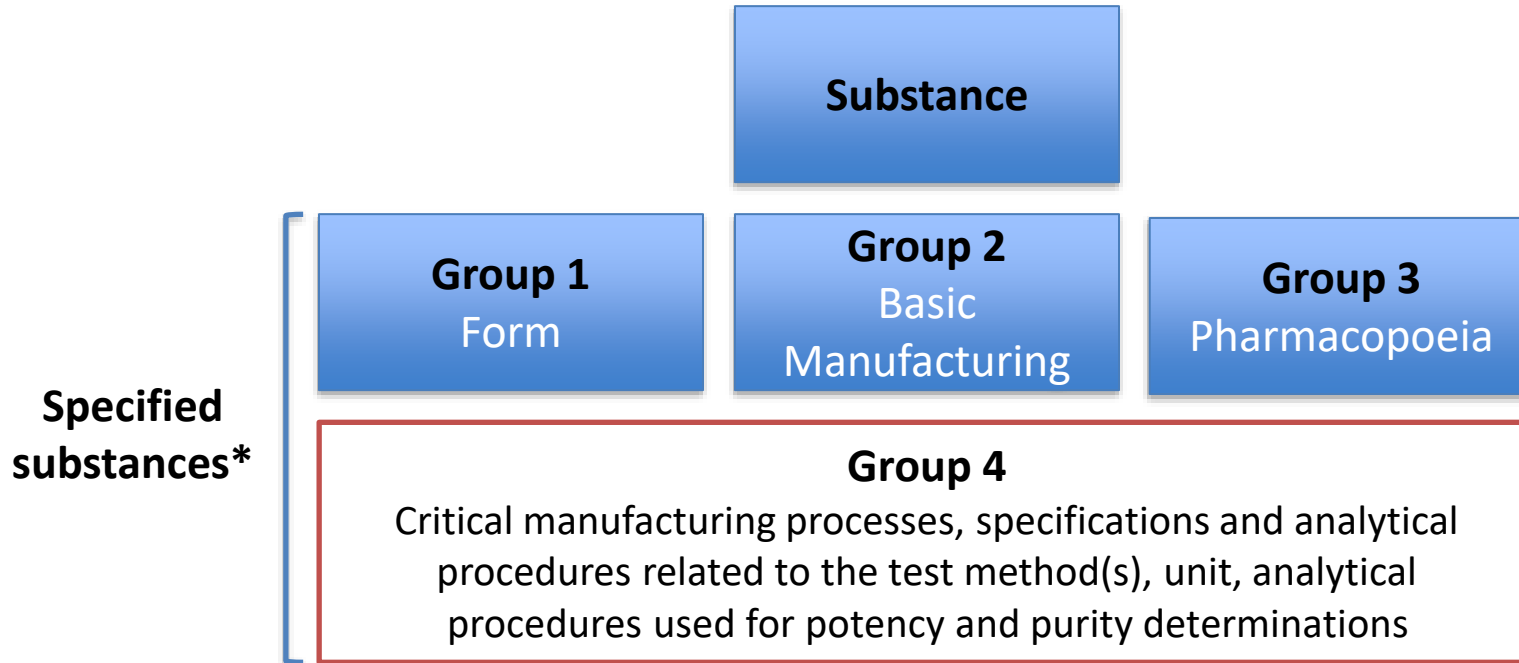
- [ICH M4Q\(R1\)](#)
- 3.2.S.2.2 Verifies that the synthetic pathway described matches the data found in the executed batch record
- 3.2.S.2.3 and 2.4 Identifies raw materials used and intermediates generated in the synthetic pathway



International Organization for Standardization (ISO) 11238



Outlines models for defining four specified substance groups

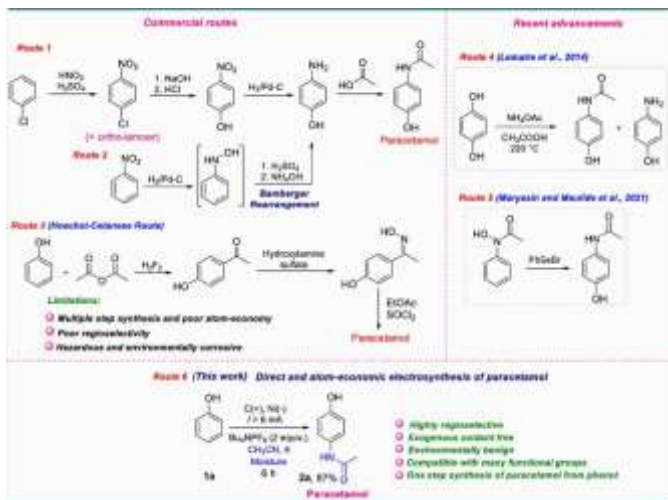


KASA and GSRS

- 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

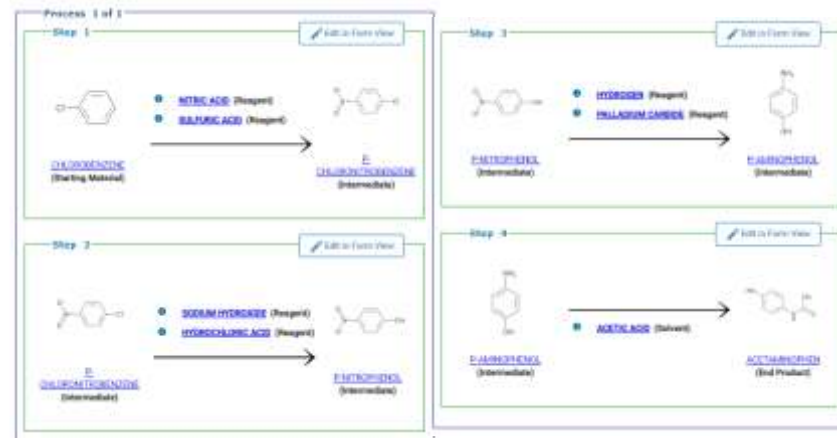
Non-machine-readable



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

Form View
Step View
Scheme View

☐ Show All Parameters

Process 1 of 1

Delete Process 1

Process Name
 Process 1

Step 1 of 1

Step View

Delete Step 1

Step Number
 1

Comments

Starting Materials

Add Starting Material

Solvents and Reagents

Add Solvents and Reagents

Resulting Materials

Add Resulting Material

Process Controls

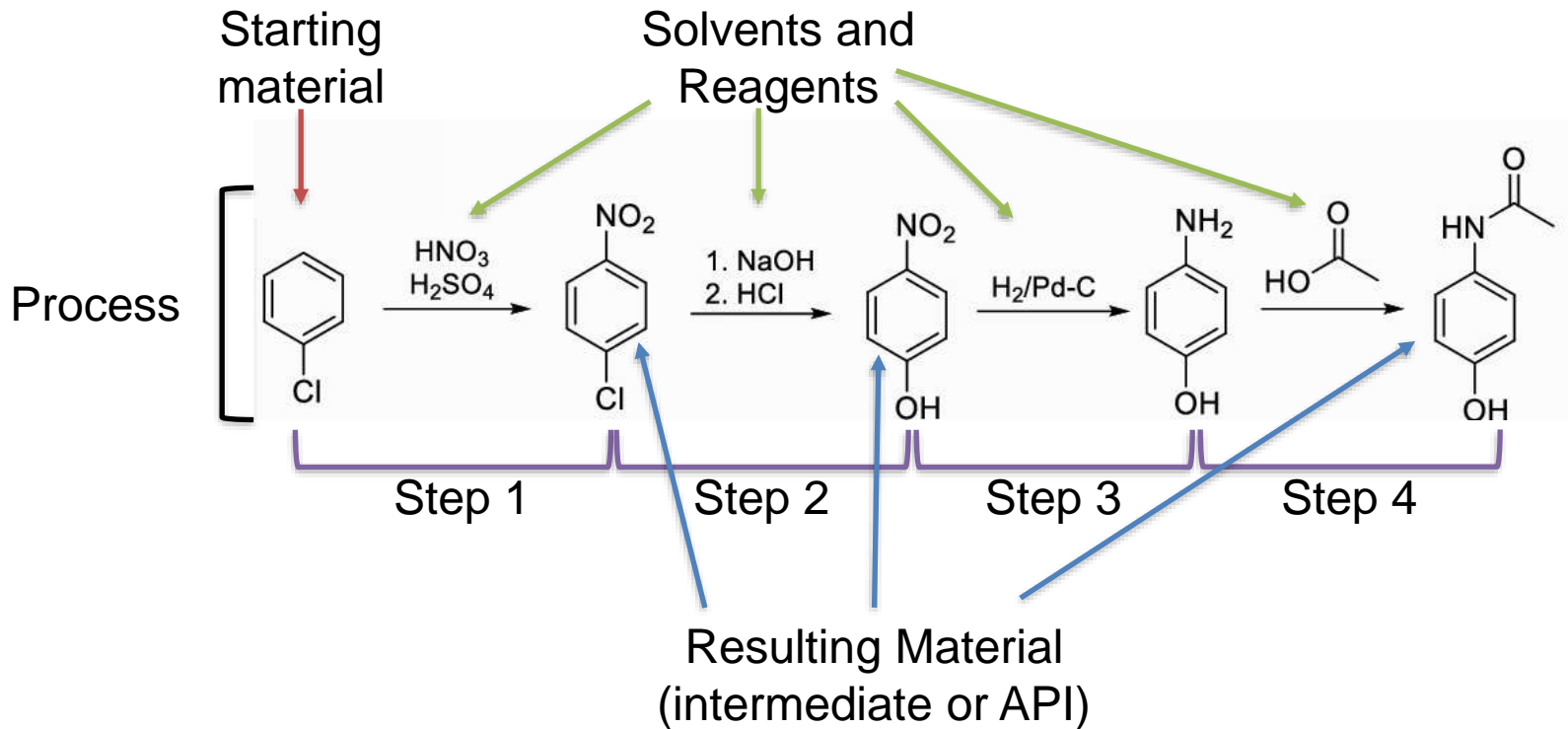
Add Process Control

Add Step

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?

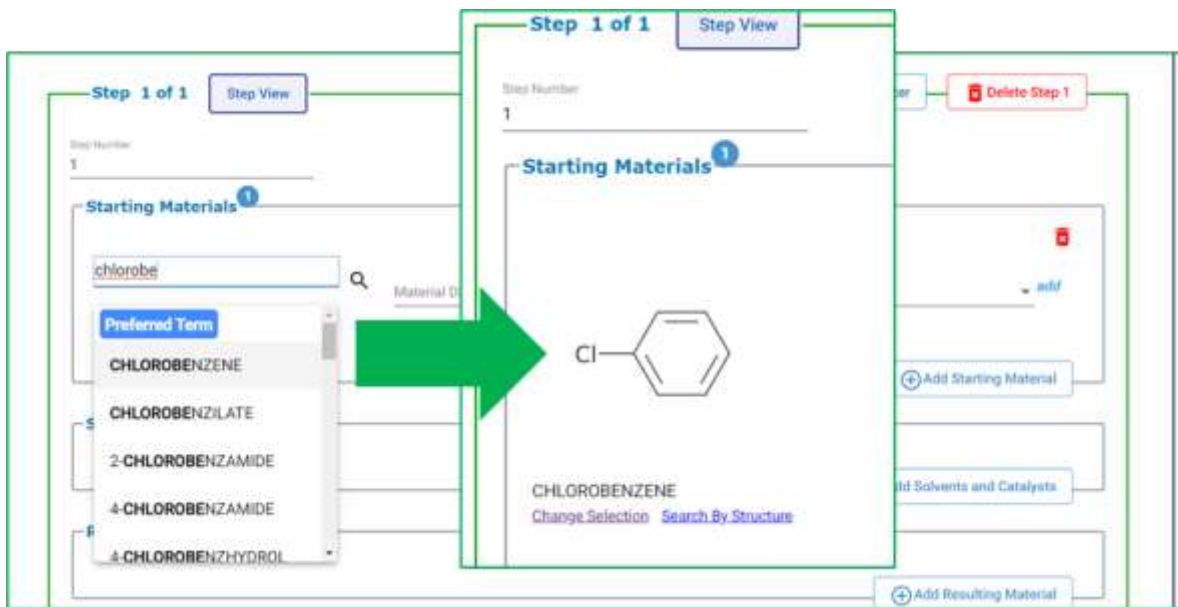


Form has fields that allow users to query GSRS for substances



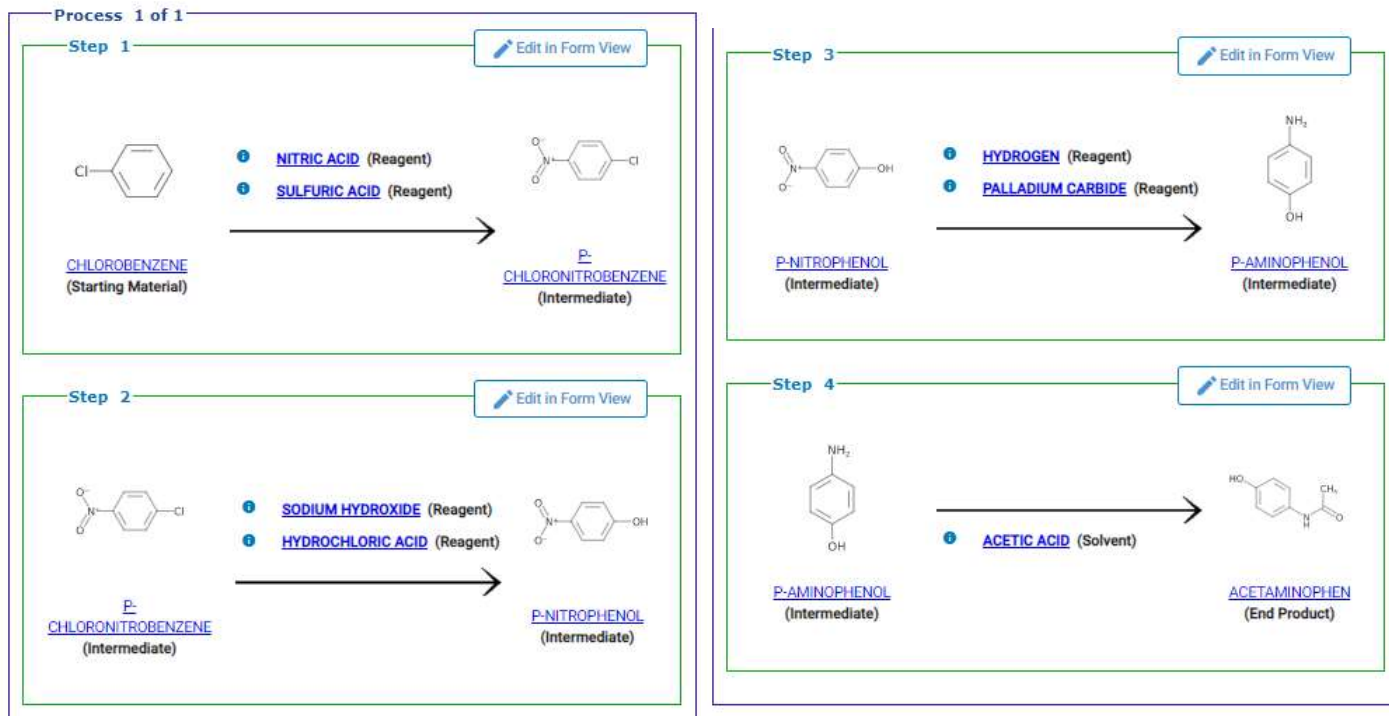
The screenshot shows a web form for managing steps in a process. At the top, it says "Step 1 of 1" and has a "Step View" button. To the right are buttons for "Insert Step Before", "Insert Step After", and "Delete Step 1". Below this is a section for "Starting Materials" with a count of 0. A green arrow points to a "+ Add Starting Material" button in this section, with the text "Click here" next to it. Below this is another "Starting Materials" section with a count of 1. A green arrow points to the search area of this section, with the text "Query here" next to it. The search area includes a text input field with the placeholder "Search by Name/CAS RN/UNII/BDNUM", a magnifying glass icon, a "Search By Structure" link, a "Material Display Name" input field, a "Substance Role" dropdown menu with "Starting Material (not in CV)" selected, and an "add" button. At the bottom right of this section is another "+ Add Starting Material" button.

Select substance from drop-down window



The screenshot displays a chemical synthesis software interface. On the left, a search bar contains the text "chlorobe". Below it, a drop-down menu lists several chemical names: "CHLOROBENZENE", "CHLOROBENZILATE", "2-CHLOROBENZAMIDE", "4-CHLOROBENZAMIDE", and "4-CHLOROBENZHYDROL". A large green arrow points from the "CHLOROBENZENE" option in the drop-down menu to the "Starting Materials" section of the main workspace. The main workspace, titled "Step 1 of 1", shows the chemical structure of chlorobenzene (a benzene ring with a chlorine atom) and the text "CHLOROBENZENE". Below the structure, there are links for "Change Selection" and "Search By Structure". The interface also includes buttons for "Step View", "Delete Step 1", "Add Starting Material", "Add Solvents and Catalysts", and "Add Resulting Material".

Step View



Scheme View

UNII

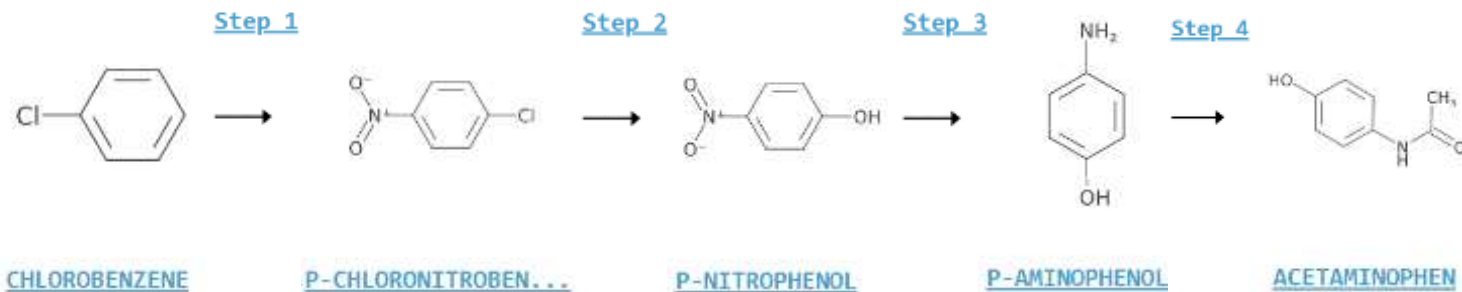
K18102WN1G

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/GSRSEnterprise/tree/development_3.0/src/app/core/substance-ssg4m

Thank you!



GSRS Scientists

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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?



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