

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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Disclaimer

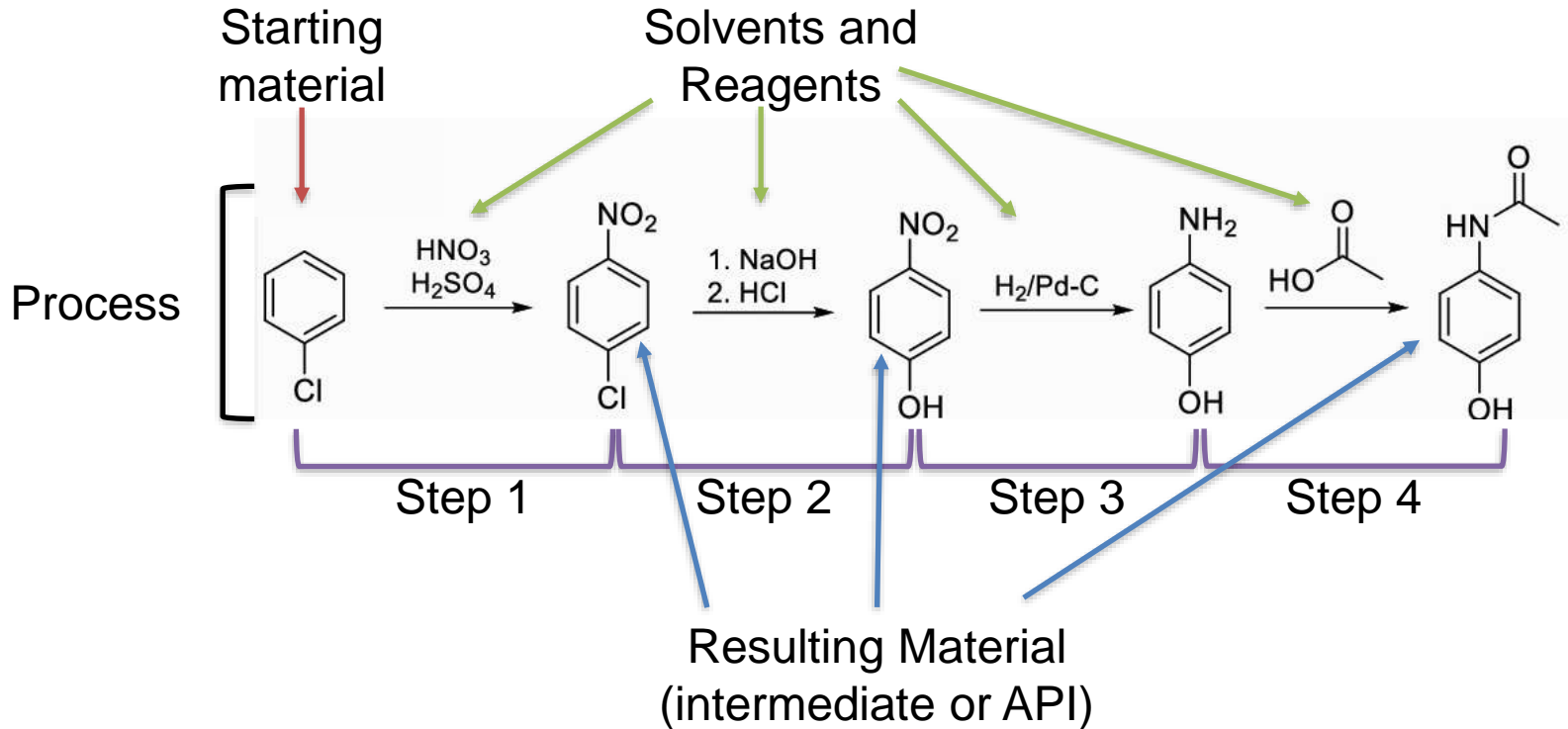
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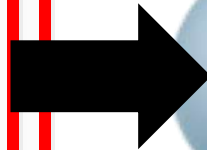
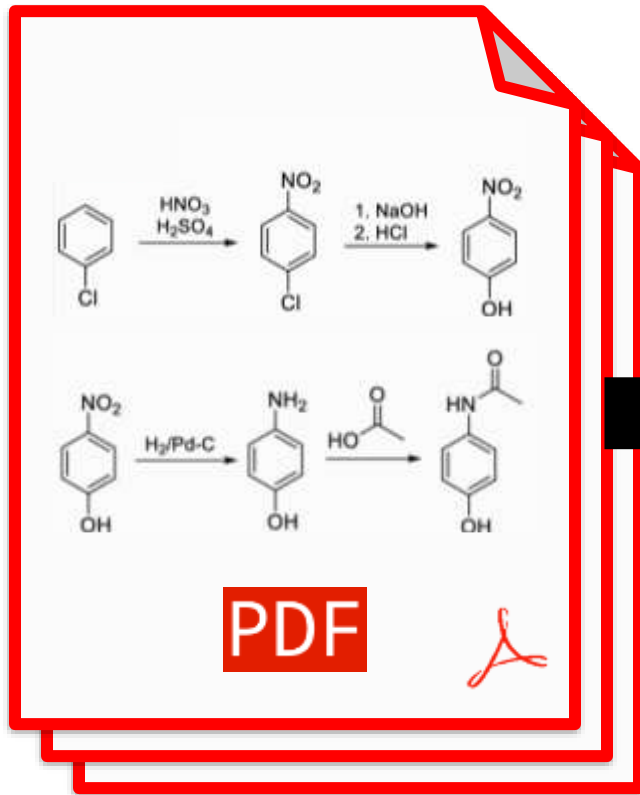
FDA's Global Substance Registration System (GSRS) group 4 specified substance manufacturing (G4SSM) form

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

What is in a synthetic pathway?



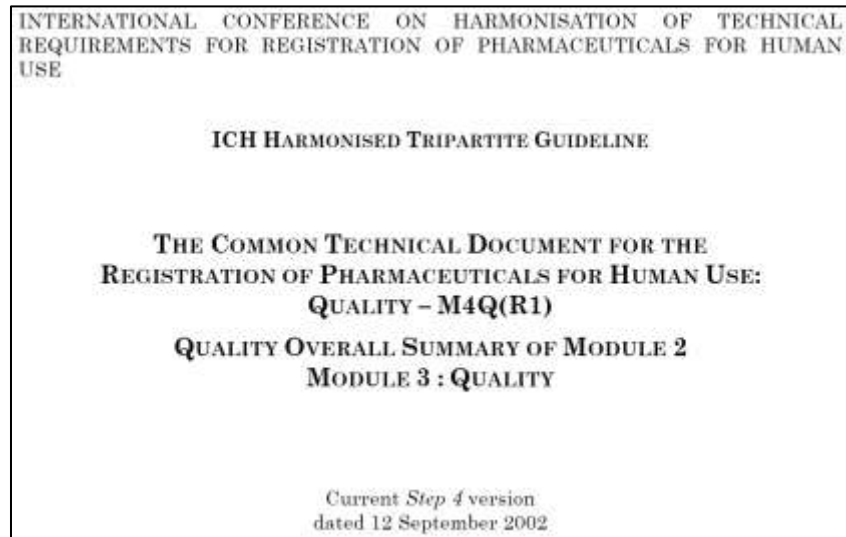
How does FDA get synthetic pathways?



electronic Common Technical Document (eCTD)

How does FDA use synthetic pathways?

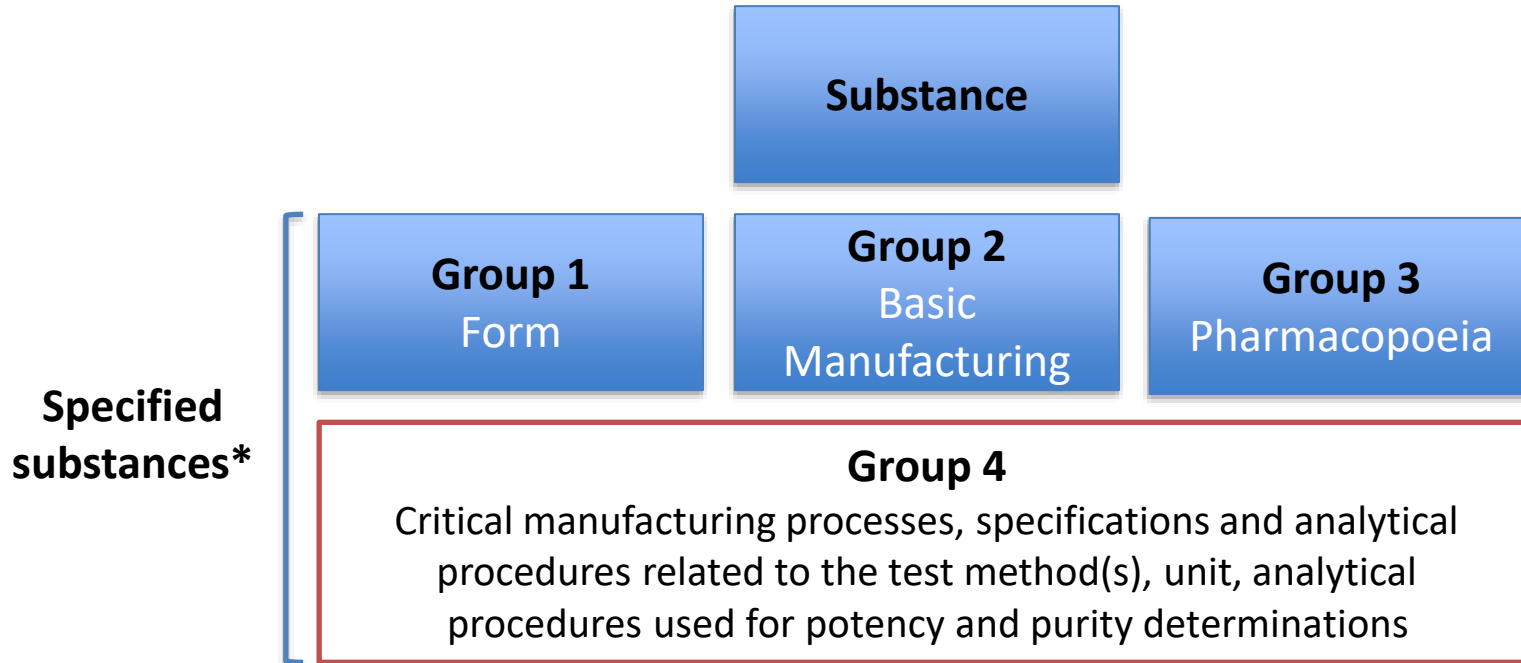
- [ICH M4Q\(R1\)](#)
- 3.2.S.2.2 Verifies that the synthetic pathway described matches the data found in the executed batch record
- 3.2.S.2.3 and 2.4 Identifies raw materials used and intermediates generated in the synthetic pathway



International Organization for Standardization (ISO) 11238



Outlines models for defining four specified substance groups

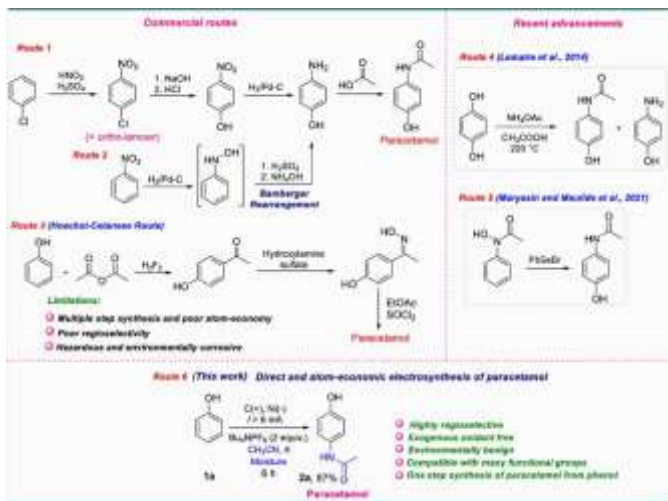


KASA and GSRS

- 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

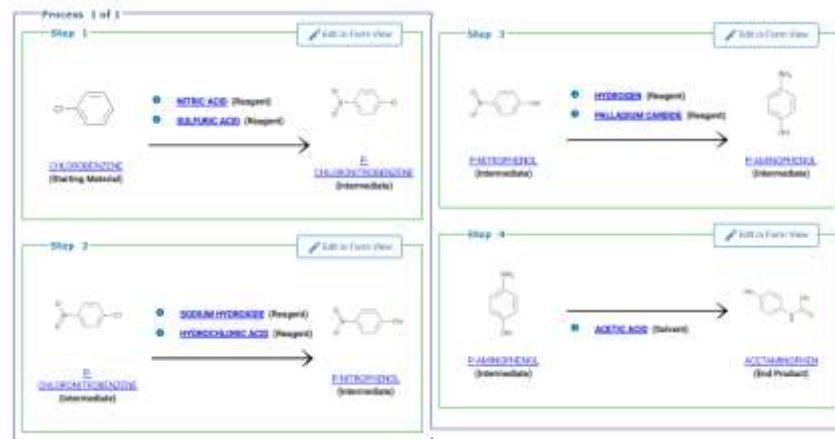
Non-machine-readable



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

The screenshot displays the GSRS G4SSM form interface. At the top right, there are buttons for "Import and Export" and "Save". Below these are tabs for "Form View", "Step View", and "Scheme View". A checkbox labeled "Show All Parameters" is located in the upper right area of the form.

The main content area is titled "Process 1 of 1" and includes a "Process Name" field with the value "Process 1". It features three management buttons: "↑ Insert Process Before", "↓ Insert Process After", and "Delete Process 1".

Below the process level, the "Step 1 of 1" section is visible. It includes a "Step View" button and three management buttons: "↑ Insert Step Before", "↓ Insert Step After", and "Delete Step 1".

The step details section contains several input fields, each with an "Add" button:

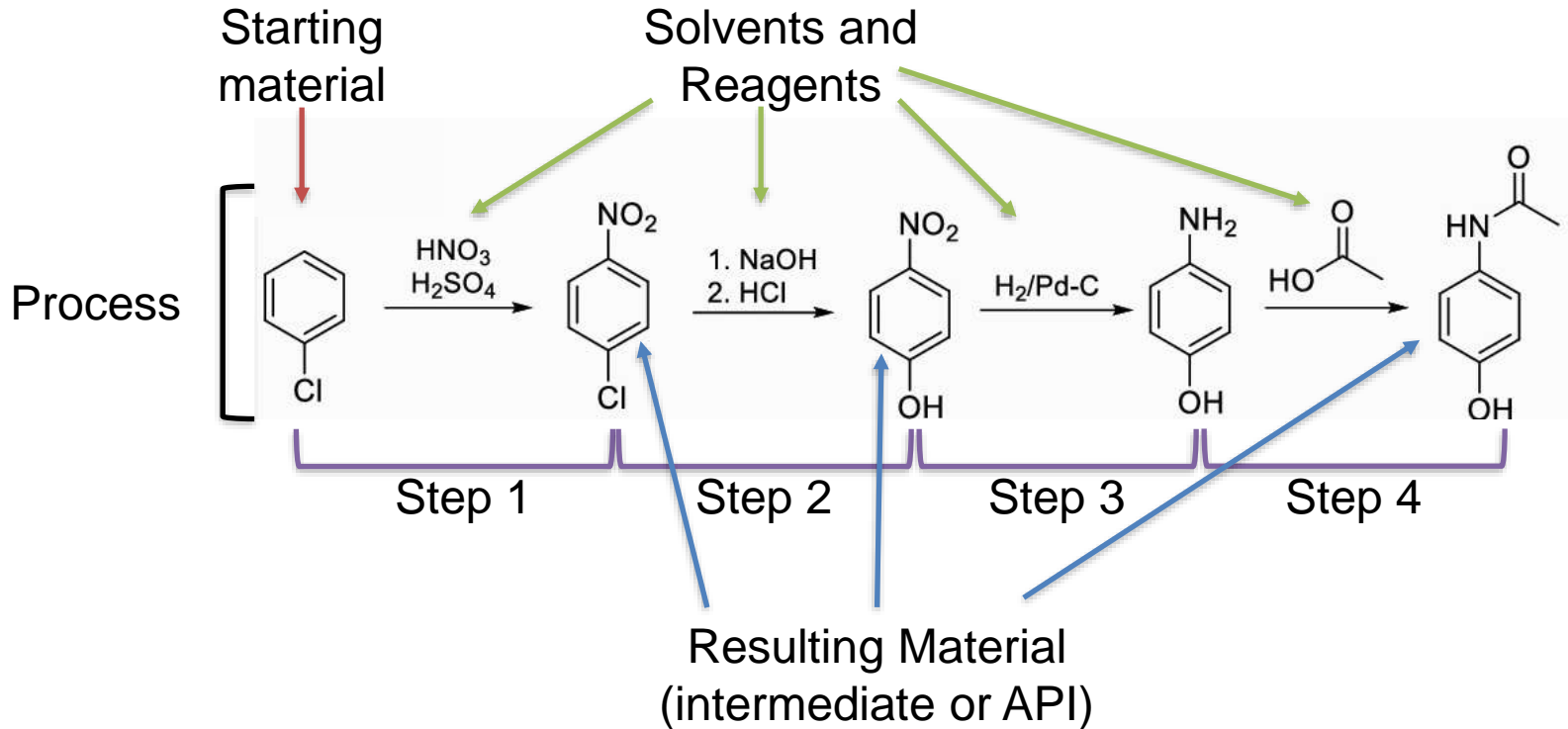
- Step Number:** A text field containing the number "1".
- Comments:** A text area for notes.
- Starting Materials:** A text area with an "Add Starting Material" button.
- Solvents and Reagents:** A text area with an "Add Solvents and Reagents" button.
- Resulting Materials:** A text area with an "Add Resulting Material" button.
- Process Controls:** A text area with an "Add Process Control" button.

At the bottom right of the step section, there is an "Add Step" button.

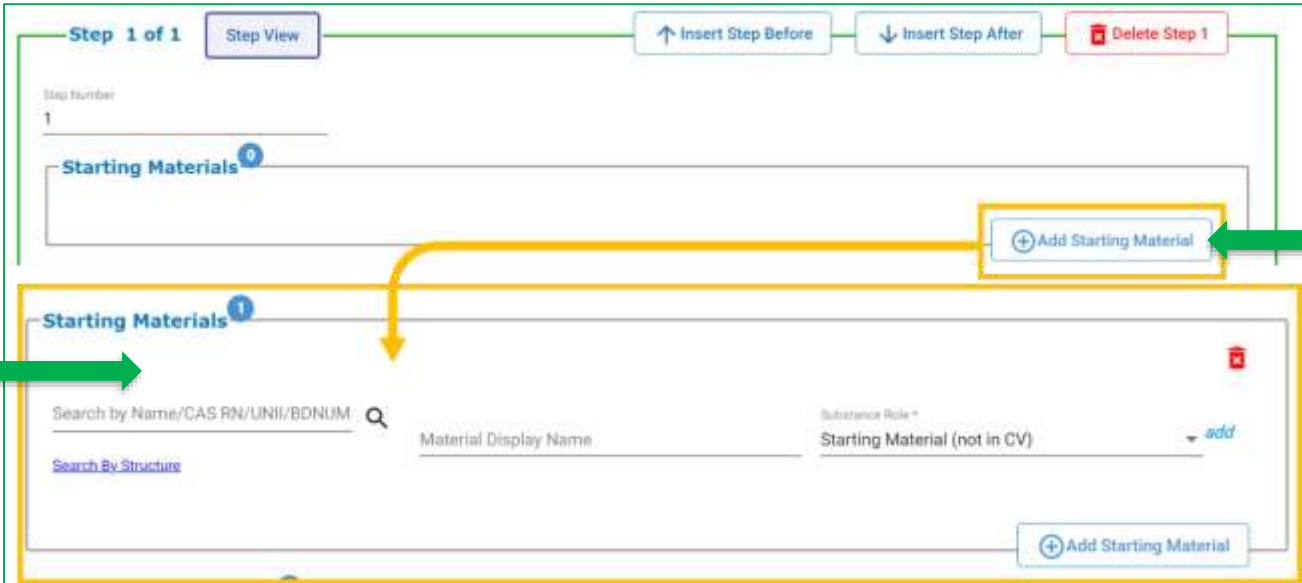
How the GSRS G4SSM form works

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 displays a software interface for managing a process step. At the top, it indicates 'Step 1 of 1' and provides navigation options: 'Step View', 'Insert Step Before', 'Insert Step After', and 'Delete Step 1'. Below this, there are two 'Starting Materials' sections. The upper section is currently empty. The lower section contains a search interface with the following elements:

- A search bar labeled 'Search by Name/CAS RN/UNII/BDNUM' with a magnifying glass icon.
- A link for 'Search By Structure'.
- Fields for 'Material Display Name' and 'Starting Material (not in CV)'.
- A dropdown menu for 'Substance Role' with an 'add' button.
- An 'Add Starting Material' button at the bottom right of the section.

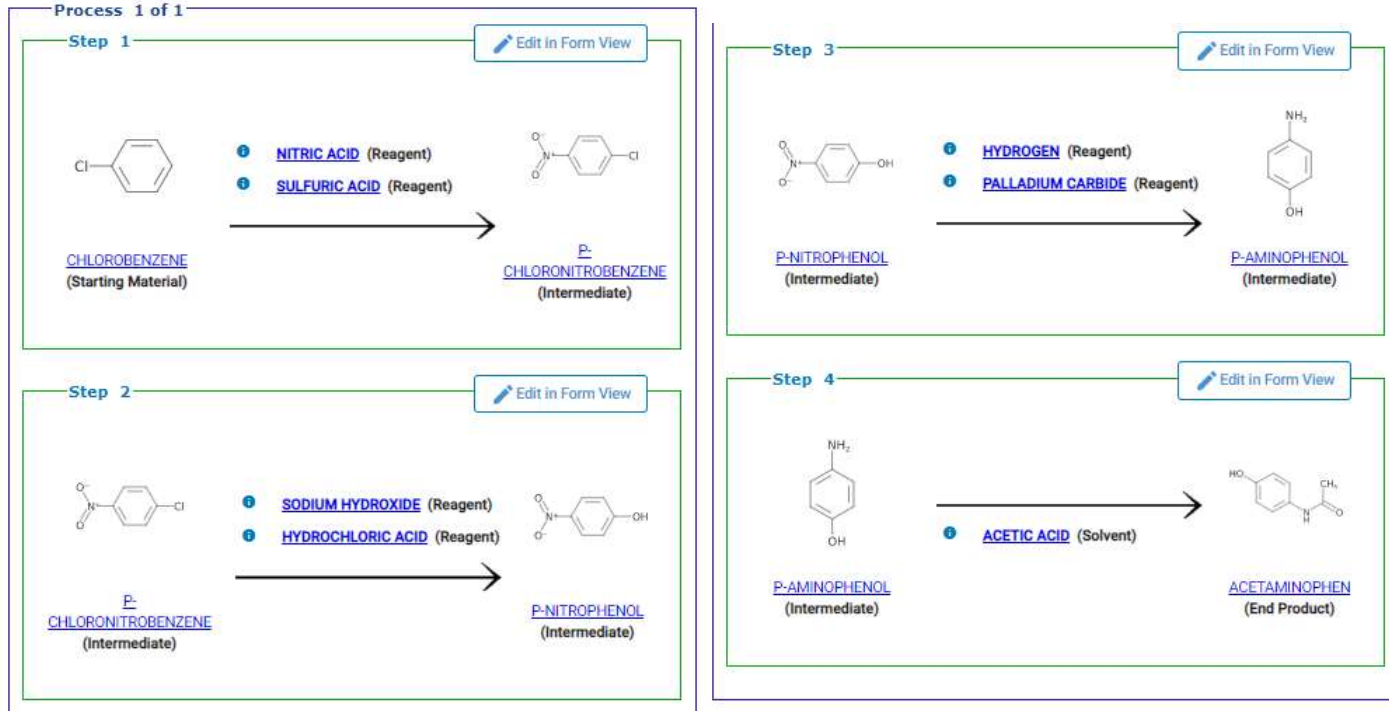
Two green arrows point to specific features:

- An arrow labeled 'Query here' points to the search bar.
- An arrow labeled 'Click here' points to the 'Add Starting Material' button in the upper section.

Select substance from drop-down window

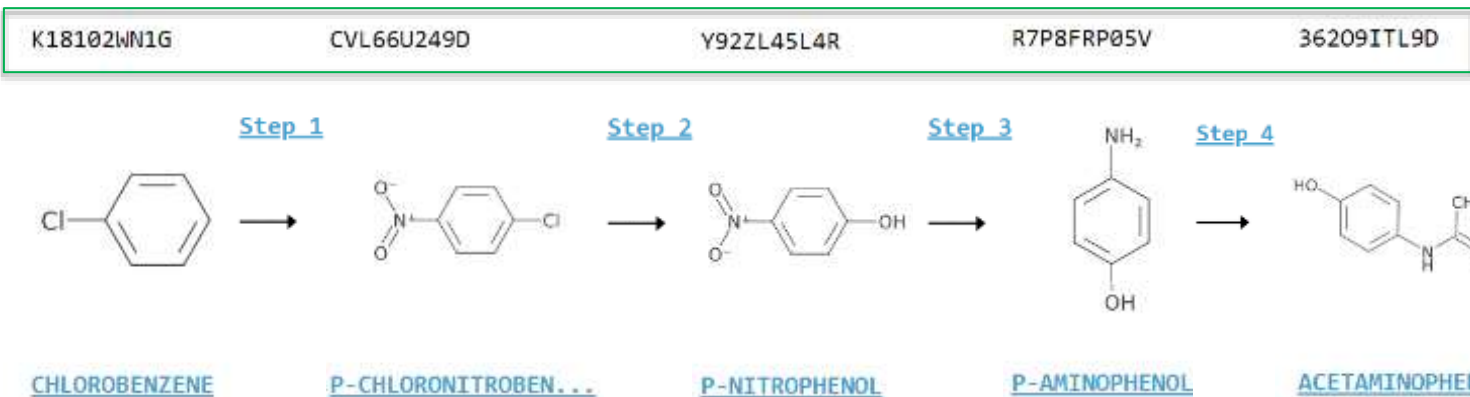
The image shows a software interface for defining a chemical step. On the left, a search box contains the text "chlorobe". Below it, a dropdown menu displays a list of "Preferred Term" suggestions: "CHLOROBENZENE", "CHLOROBENZILATE", "2-CHLOROBENZAMIDE", "4-CHLOROBENZAMIDE", and "4-CHLOROBENZHYDROL". A large green arrow points from the "CHLOROBENZENE" option to the main step view on the right. The main view, titled "Step 1 of 1", shows the "Starting Materials" section with the chemical structure of chlorobenzene (a benzene ring with a chlorine atom) and the text "CHLOROBENZENE". Below the structure 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



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

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?

