Isolating three unknown impurities from a Phase III manufacturing batch

A two-step SFC and HPLC strategy to isolate >10 mg of each impurity for HRMS and NMR characterisation

The challenge

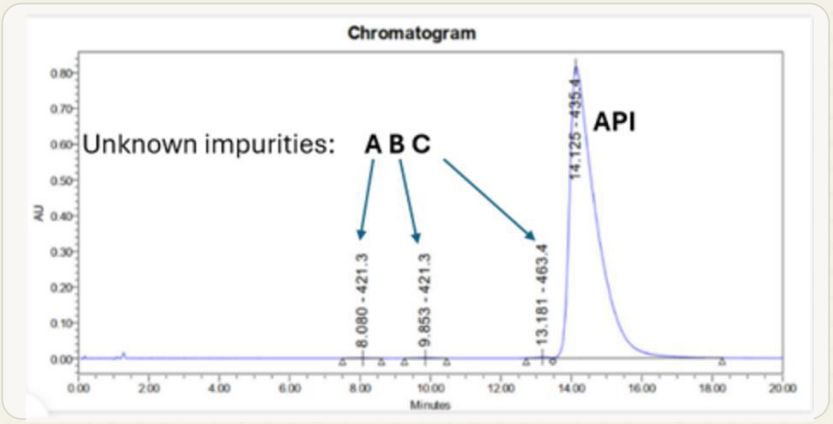
- A COPD drug was in Phase III trials.
- During manufacture of an intermediate, three previously unknown impurities were discovered.
- There was a risk they could carry through to the final API.

How?

- **Step 1 — Chiral SFC:** A 70 g batch was processed on a chiral stationary phase by SFC, efficiently removing the bulk of the main component and enriching the impurities.
- **Step 2 — Reverse-phase HPLC:** The enriched fractions were re-purified using this orthogonal technique, isolating each impurity to >90% purity.

The achievement

- >10 mg of each impurity was isolated to >90% purity and characterised by HRMS and NMR.
- With the structures confirmed, the process chemists redesigned the route to eliminate all three impurities from the final API.
- **This kept the Phase III clinical trials on track.**



Chromatogram of the intermediate — impurities A, B and C resolved ahead of the API peak.