Development, Scale-up & Manufacture of API Using 15 Step Process

INTRODUCTION & BACKGROUND

The first multi-kilogram lot (API development candidate for cognitive disorders) had been prepared by another CRO at the 20-gallon scale of operation. The processing was difficult and several scale-up problems were encountered. Expedited work-arounds were identified and implemented. The API output from the preparation was below the required amount.

CHALLENGE

The client retained Ricerca to:

- Resolve process scale-up problems
- Produce a minimum of 10 kilograms of API as a single lot using cGMP controls
- Deliver the API lot in 6-7 months
- Manage all components of the project

The process provided to Ricerca as the technical input to the project consisted of 15 chemical steps. The process chemistry included the following challenges:

- Creation of two chiral centers using chiral auxiliaries
- Use of pyrophoric raw materials
- Processing temperatures below – 50 °C
- Unstable intermediates
- Flash chromatography
- Low yields
- Awkward, tedious isolations
- Low process productivities

APPROACH & EXECUTION

Ricerca used the following approach to execute the project:

- The existing process was analyzed taking into account both chemistry and engineering considerations – a list of required process changes was developed and used as the basis for the focused process research component of the project.
- The custom raw materials were specified and procured – in some cases validated off-shore suppliers were used in order to minimize costs.
- A mass contingency of 50% was chosen for planning the production component based on the status of the technology. The target output was set at 15 kilograms.
- The process chemistry evaluation was started.
- In parallel, the upfront engineering needed to ready the pilot plant was started.
- The scale-up/production component of the project was started in the pilot plant after completion of the process chemistry work on Step 4. This parallel approach was used to compress the project timeline.
- The in-process and API release testing methods were transferred, upgraded, and qualified for use on the project.

RESULTS

The project was successfully executed with the following outcome:

- Overall project duration was 9 months with the production component taking 6.5 months
- The process was scaled to the nominal 200-gallon scale of operation – a scale-up factor of 10.
- The overall process yield was increased from 9.7 to 13.1%
- As a result, the actual in-specification API produced was 25.1 kilograms – 2.5X the minimum requirement and 1.7X the target output.
- The following significant process improvements were identified and demonstrated:
  1. By developing crystallization purification for the API precursor, q full-scale chromatography at Step 15 was eliminated with a single API recrystallization was required to reach 99.5% API purity.
  2. By process optimization and use of Ricerca's –50 °C processing capabilities, the stereo-selectivity of both chiral auxiliary-controlled alkyations was very high - (99:1 or better selectivity).

3. The yield of Step 11 was improved from 40 to 74% by improved reaction conditions, an optimized extractive workup, and use of silica gel filtration rather than full-scale chromatography for purification.
4. Five processing steps were drastically modified to accommodate intermediates unstable to the time/temperature exposure expected at pilot plant scale. In two steps alternative reagents and improved reaction conditions were developed. In all five steps new reaction quenches and product purifications were implemented. No degradation was encountered during the scale-ups.
5. Process operations not amenable to plant equipment (such as stripping to dryness, non-agitatable slurries, and poor phase separations) were eliminated.

- The process technology provides a basis to economic analysis and possibly a commercial manufacturing process.