Synthetic Chemistry

Impurity Preparation Capabilities – Example

A late-stage API isolated by a fermentation process required more than 10 impurities to be used as standards / markers. Six of them required synthesis and purification using reverse phase flash chromatography and preparative HPLC.

In one case the impurity initially required eight chemical steps and three preparative HPLC purifications.

- We developed a process that telescoped the individual purifications of the first four steps into a single reverse phase purification.
- The next three steps were telescoped to a single preparative HPLC purification that afforded the penultimate intermediate of such purity that final step required no purification.
- This process was used to deliver multiple lots of > 20 grams.

Another of the impurities was a N-Hydroxymethyl analog of the API which was unstable at room temperature. Following the once synthetic step, we purified this compound using preparative HPLC where the purified product was maintained at 0 – 5 ºC from the time it came off the column until it was isolated by freeze drying.

- Buffered HPLC fractions were collected in an ice bath container.
- Organic solvent was removed b y rotary evaporation over an ice bath
- The buffered eluent was desalted over hydrophobic resin using a jacketed column @ 0 ºC
- The aqueous eluent was freeze dried @ -5 ºC to afford the dry product
- This process was used in multiple campaigns of > 20 grams

All six impurities were successfully prepared at Olon USA. The API was approved by FDA and is currently in the market. We have been supplying the impurities to the client for the continued support of their commercial API production.