Addressing Loss of Yield and Increased Impurity Levels in Clinical Manufacture

Challenge

During the manufacture of a product in AstraZeneca's Large Scale Lab (LSL) a negative trend in yield was spotted, coupled with an increase in impurities. Three batches had been manufactured with yields of 60%, 54% and 49%, whilst all user trials in the lab were passing with a yield of 80%. The externally manufactured starting materials had passed a use test, so what was going wrong?

Approach

With many possible causes for the issue and a very limited amount of time and resource to resolve the issue, the team chose a Britest Study to structure their root cause analysis and prioritise experimentation to establish the true cause.

The three hour session brought together a mixture of skills sets and perspectives: how the product had been developed and how it was being manufacturing, plus a "cold eyes" view from a chemist working on the next manufacture who was new to Britest.

The study used Britest Initial Screening Analysis, Process Definition Diagram, Transformation Map and Rich Picture tools combined with analytical data on impurities and an understanding of mass transfer effects in the reaction.

Benefits

- Shared high level understanding of the problem, clarifying time and resources constraint and (since the problem area was part of a reaction telescope) consideration of the downstream effect of any process changes.
- Potential process differences between user trial and LSL scales highlighted. Potential failure modes due to side reactions identified and evaluated.
- 14 possible actions identified covering chemistry, engineering and analysis. By systematic testing and process of elimination, oxygen ingress due to suck back during vessel cooling identified as the root cause.
- With an improved nitrogen purge rate during cooling, impurity was reduced to 2% and yield increased from 50% to 70%. Manufacture was completed successfully, with a corresponding cost deferral of $250K.

Key Features:

Client - AstraZeneca

Industry - Application Area

Pharmaceuticals - Process problem solving, Scale-up

Challenge

Product manufacture in AZ's Large Scale Lab encountered a significant negative trend in yield and increased impurity. Starting materials had passed a use test and small lab scale yields were fine, so what was going wrong?

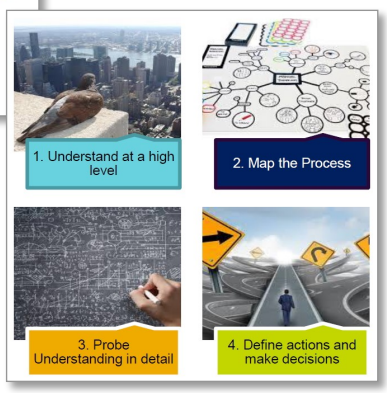
Solution

A three-hour Britest session involving a mixture of skills sets and perspectives on product development and manufacture identified 14 potential actions covering chemistry, engineering and analysis.

Outcomes

Systematically testing each possibility, oxygen ingress was identified as the root cause. Improved purging reduced impurity to 2% and increased the yield from 50% to 70%. Successful manufacture corresponded to $250K of cost deferred.

Encouraging input from multiple perspectives and a structured four-step approach were key to the success of this study



> ***"The Britest tools enabled us to 'follow the science' – the outcome of this study saved costs, improved process robustness, and secured future supply of the active pharmaceutical ingredient."***

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