AURIGENE
PHARMACEUTICAL SERVICES

Case Study

Familiarization, process optimization and non-GMP manufacturing & supply of 3.0 kg of HPAPI product.

Background:

A biopharmaceutical company based in US approached Aurigene Pharmaceutical Services for the familiarization, process development and non-GMP manufacturing and supply of 3.0 kg HPAPI product (Steroidal) for their pre-clinical study. The synthesis of the desired product involves four stages (3 linear stages and 1 side chain), and which starts with reaction of 5-pregnen-3b-ol-20-one with primary amine to give the oxime intermediate, which on Oppenauer oxidation afford the keto intermediate. Keto intermediate upon reaction with phosphoric acid followed salt formation with appropriate base yield the desired product.

Challenges:

- Establishing appropriate reaction conditions for all the stages by optimizing mole equivalents of reagents and isolation procedure to improve yield and quality.
- Identifying a suitable crystallization procedure for all the stages to achieve the desired quality.
- Major challenge associated with API stage as acid intermediate is highly unstable.
- Identification of impurities and its control is very challenging.

Aurigene solution:

- Replaced the base pyridine with NaOAc and to reduce the time for process operations and better scalability of the process in plant, avoided the distillation and simplified the product isolation in stage-1.
- Screening of ketone for Oppenaur oxidation, identified 2-butanone for reaction which is preferred over other ketone due to homogeneous nature of the reaction mass.
- Sequence of reagents were optimized for API stage to get stable reaction conditions and product isolation process was simplified for robust scalable process.
- Adapting a fit-for-purpose process development strategy helped to deliver the API quickly for pre-clinical study.
- Crystallization procedure were established and optimized to attain constant yield and quality.
- Process controls were well defined to monitor the reactions in all stages.

Outcome:

- Robust and cost-effective process was developed for the quick non-GMP supply of targeted HPAPI product.
- Suitable process controls were established in the process for pilot plant suitability enable the smooth execution.
- Consistent yield and quality were obtained with the optimized process.
- Achieved all the pre-defined product specifications with the optimized process.
- Manufactured 3.0 kg of final product in HPAPI facility and delivered to customer.

Thank You

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