AURIGENE
PHARMACEUTICAL SERVICES

Case Study

Advancing a target molecule from *in vitro* studies to clinical supply:

An innovative scientific solution

Background:

A biotech firm based in the USA contacted us to assist with the development and rapid supply of a non-GMP drug substance. This drug substance has been identified as a promising candidate for an anti-viral treatment. The synthesis of this drug substance involved various complexities, including process requirements, safety considerations, purification challenges and polymorph issues. Additionally, there timely clinical supply was crucial.

Study design:

The first generation process of drug substance synthesis had following limitations:

- It involved multiple chiral centers and complex synthetic transformations requiring 11 linear steps
- The chiral Key Starting Material (KSM) was not available
- The high-temperature Diels-Alder reaction at 150 degrees had the risk of triggering a potential polymerization reaction
- There were challenges associated with the crystallization of the drug substance
- Agglomeration and higher residual solvents were also challenging

Aurigene solution:

- Developed a Route of Synthesis (ROS) and performed the column chromatography for the key starting material which had multiple chiral centers and same was enabled on large scale
- Identified the root cause for runaway reaction during Diels-Alder reaction and evaluated the flow process on small scale to mitigate the process associated challenges
- Solvent crystallization was developed to get drug substance meeting the acceptance criterial of residual solvents and >95.0% purity.
- Enabled the 3.0kg Drug substance for toxicology supply in the stipulated timeline.

While the generation-1 process has been successfully designed for toxicology testing, it presented limitations in terms of scalability and quality challenges for clinical supplies. To overcome these challenges and ensure molecule's viability for larger-scale, a generation- 2 process was developed.

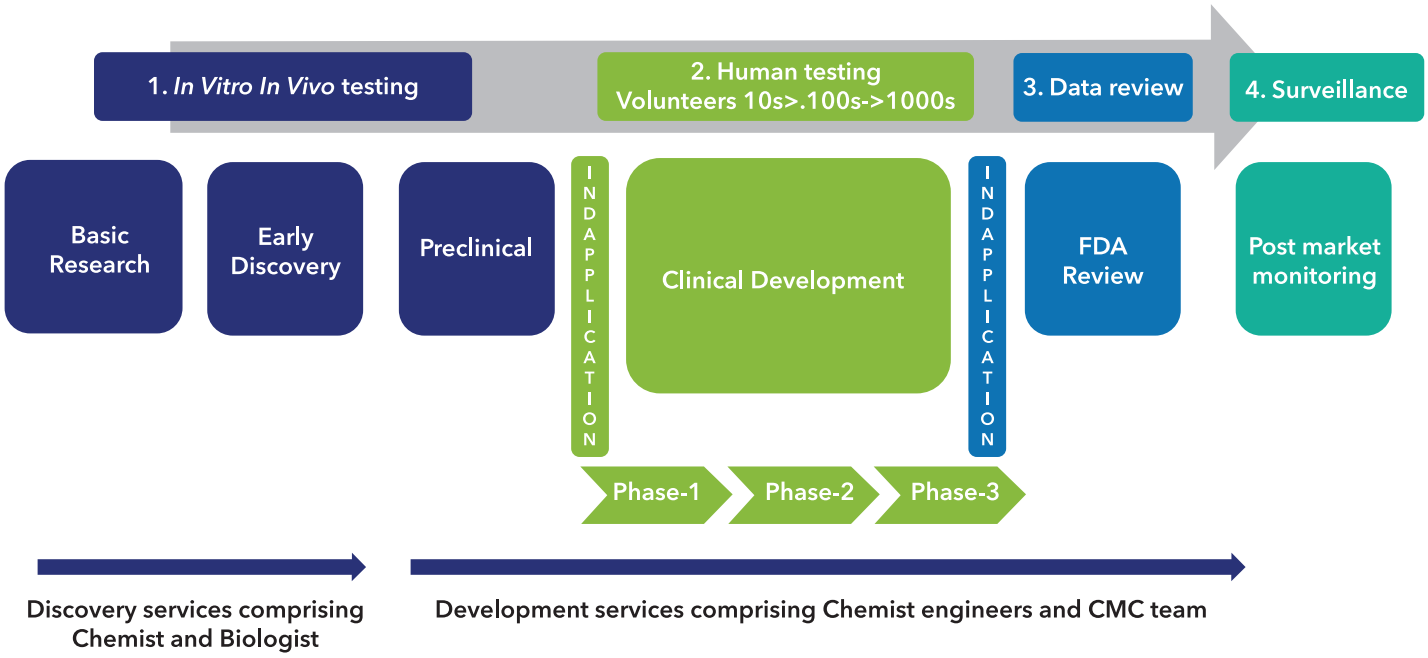
The following improvement were done in the generation-2 process:

- A robust method was developed for synthesizing the chiral Key Starting Material (KSM), involving seven synthetic transformations that yielded high quantities and improved throughput.
- The time-consuming and laborious chromatography process was eliminated by implementing simple crystallization and acid-base purification techniques for intermediates.
- Purification techniques and process conditions were optimized to effectively control the presence of genotoxic impurities in the drug substance intended for clinical supplies.
- Through extensive screening of the crystallization process, a suitable purification method was developed to achieve the Active Pharmaceutical Ingredient (API) with stringent purity specifications, reaching 98% while also meeting the residual solvent content requirements.

Outcome:

- A synergistic manufacturing strategy was implemented, wherein the first 6 stages of manufacturing were carried out followed by next 5 stages under GMP conditions. This approach facilitated the production of approximately 5 Kg of the API within a short timeframe.
- Our expertise in developing a fractional distillation process enabled us to purify the key raw material and effectively control impurities to a level of less than 30 parts per million (ppm).
- An alternative and safe route was devised, eliminating the need for column chromatography. This modification allowed for an increased batch size in the second production campaign.
- An innovative methodology was developed to prevent the formation of genotoxic impurities (GTI) during the final stage of the manufacturing process
- By adopting a fit-for-purpose process development strategy and considering the associated safety risks, we were able to manufacture the API for the toxicology study within the specified stringent timelines.

Development continuum:



Thank You

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