Chemical Development & Toxicology Studies Supporting IND

INTRODUCTION & BACKGROUND

The client contracted Ricerca to conduct a series of biological evaluations of their compound including a critical 28-day toxicology study in dogs. Completion of the dog study controlled the IND filing date. The compound needed for these studies had been prepared by another CRO. This lot of compound could not be properly formulated for use in the animal studies. In addition, there was a concern that the amount of compound available was too little to support the needed studies. As a consequence, the IND filing date was at risk.

CHALLENGE

The client asked Ricerca to resolve this problem as soon as possible so that the critical IND filing date could be met.

APPROACH & EXECUTION

Ricerca tackled the problem using the following approach:

- Conduct physical and chemical characterization of the API lot that formulated properly and compare to the problem lot
- Review the preparation process and its history to determine if the changes made could have caused the problem
- Reprocess the problem lot to allow it to be formulated
- Prepare additional compound to assure that all the IND studies could be completed

RESULTS

The project was successfully executed with the following outcome:

- The cause of the formulation problem was traced to a process change made by the other CRO that resulted in a dramatic change in the physical characteristics of the API.
- The analytical characterization of the problem lot which was conducted using an improved LC method, revealed the presence of new impurities that had not been observed in earlier lots used in animal studies.
- The new impurities were identified using LC/MS and the probable mechanisms for their generation were postulated.
- A reprocessing technique was developed and demonstrated then implemented at the kilo-lab scale in order to reprocess the problem lot so that it formulated properly and could be used in the animal studies.
- Several kilograms of the API were prepared and characterized at the kilo-lab scale in order to assure that all the necessary animal testing could be done.
- The ability to formulate the compound was periodically checked during the research phase of the project in order to guide the work.
- The reprocessed and newly prepared API lots were fully characterized in accordance with GLP.
- Scheduling of the animal studies was synchronized with the process work so that those critical studies could start as soon as suitable API was available.
- Suitable API was delivered in time to allow the critical animal studies to be completed on time.
- The client was able to meet the original IND filing date.

IMPACT

Ricerca subsequently scaled the process to the pilot plant and produced the cGMP grade API lot needed for the Phase I clinical trials.