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Analytical method development & validation of a parenteral grade API involving carryover of a toxic cyanide compound.

OVERVIEW

The customer involved in following case study is amongst the most awarded generic drug manufacturers in the US. They are engaged in process research and early-stage development as well as commercial production of new chemical entities (NCEs), generic API's and other specialty chemical products with a GMP approved facility.

ExSyn supplies several critical intermediates to customer and has a relationship spanning almost two decades. One of their API's for parentral formulation under ANDA application and US-FDA review, had received a deficiency notification from the authorities, which required filing clarifications. Customer was required to qualify their API and its raw materials based on method development, validation, and standardization of specification. Due to multiple ongoing product developments within its inhouse quality control laboratories and time constraint in responding to authorities, the customer approached ExSyn to assist them in outsourcing these activities to a competent CRO offering comprehensive analytical solutions including method development and validation.

Based on ExSyn's recommendation of an Indian CRO offering robust quality services, the customer was able to complete method development activity and submit appropriate response to the authorities within stipulated time frame.

The development involved qualifying their API with respect to complex carryover of a cyanide compound, which was monitored, validated, and established by ion exchange chromatography and the control of elemental impurities by ICP-OES.

THE CHALLENGE

- The task for CRO was to develop an Ion Exchange Chromatographic (IEC) method for determination of cyanide compound and ICP-OES method for analyzing elemental impurities.
- It required Exsyn to scout several Indian Contract Research Laboratories based on their competence, scientific expertise, infrastructure, instrumentation capabilities and timely delivery of protocols and reports.

THE SOLUTION

Exsyn carefully shortlisted and recommended two CROs from India who met all the requirements to handle and analyse cyanides. Consequently, a CRO was approved based on feasibility audit by the customer.

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IEC Development

Since manufacturing of the API involved cyanide producing key starting material, it was imperative to control the cyanide carryover in the final drug substance. To monitor the cyanide carryover in the drug substance within acceptable limit, a simple and reliable method of high-performance ion-exchange chromatography (IEC) was developed.

- A selective and sensitive method of chromatographic separation of free cyanide ions was accomplished with an anion-exchange column. NaCN and KCN peaks were successfully resolved and analyzed.
- Developed method exhibited a linear response.
- Multiple batch analyses were performed to demonstrate the level of cyanide.
- All electronic data management systems compliance were as per 21CFR, Part 11.
- The obtained results were statistically analyzed with ANOVA. All statistical analyses were performed using the Statistical Analysis System.
- The final closure of the project was a risk assessment audit by the customer based on quality systems, operational compliance to internal procedures, documentation review and quality based on the applicable regulatory requirements for analytical testing services under cGMP.

ICP-OES Development

As several raw materials were involved in manufacturing of API, the authorities notified that it was imperative to control the elemental impurities in the final product and its raw materials.

- The analytical method development using the ICP-OES system was adopted as a suitable choice due high sensitivity and precision as well as relative freedom from interference it afforded.
- This method was also stipulated in USP <232> and <233>, along with ICH Q3D for the determination of metals in raw materials and the final product.
- The elemental impurities were analyzed and reported in the API (first time ever) as well in the raw materials.
- It was found that elemental impurities in the API and raw materials were within acceptable limits.
- Multiple batch analyses were performed to demonstrate the levels of elemental impurities.

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EXSYN'S ROLE

- Carefully scouting various cGMP laboratories and recommending two most suitable laboratories offering custom-made solutions for standalone project.
- Ensuring documentation conformity as per global regulatory requirements of ICH and USP at several stages of project.
- Conducting monthly site visits for project updates and manging weekly conference calls between the CRO and customer for technical discussions.
- Offering logistical support in custom clearance of several samples of API, raw materials and reference standards required for this project.
- Procuring suitable columns, working standards required in method development activity.

> *"ExSyn conducted an intense due diligence of several laboratories to find out the right potential partner to cater to our analytical development activities. With a rationale justification based on the scientific conclusion our customer was able to successfully respond to the deficiencies notified by the US-FDA authorities within the required time frame."*
>
> ExSyn Corp

> *"Right from finding the suitable CRO and diligently managing the project through weekly teleconferences by ExSyn, we were able to meet the submission timelines on a suitable method development activity and respond to US-FDA authorities for an API utilized in parenteral formulation which involved carryover of a highly toxic cyanide compound."*
>
> US API manufacturer