CMC Drug Substance Development

1 DEVELOPMENT

1.1 Chemical Development and Optimization

We can offer complete assistance in the development of chemical processes and optimization trials to produce new chemical entities and generic pharmaceuticals, beginning with publicly available information, existing processes, and novel concepts. The design of the development and optimization activities will take regulatory consequences, such as regulatory starting materials (RSMs) into account ICH guidelines shall be considered in the context of development.

1.2 Control Strategy

Methods of analysis are crucial for the production and release of all medications. For the objective of control strategy, we can assist our clients in establishing a program to develop new ways or optimize existing ones. We collaborate with our clients to determine the optimal approach for establishing processes for starting materials, IPCs, intermediates, and APIs, contingent upon the clinical phase. Method validation will also be determined in accordance with the clinical phase. Chemical trials will be utilized to determine the capability of a process to eliminate impurities and produce a conforming product to establish specifications.

1.3 PAR/NOR/IF

As per ICH Q11, the process must be robust and yield a product that regularly satisfies its specifications. To accomplish this objective, DOE (Design Of Experiments) and OFAT (One Factor At A Time) experiments may be implemented to ascertain CQAs (Critical Quality Attributes), NOR (Normal Operative Ranges), and PAR (Proven Acceptable Ranges).
Using the relevant information and the FMEA (Failure Mode Effect Analysis) methodology, the parameters to be investigated are determined.
It is possible to develop IF (Impurity Fate) trials to determine the robustness of a procedure in removing impurities. This part will aid in determining the optimal drug control plan.

1.4 Analytical Development/Optimization

A gap analysis of existing methods can be performed to understand their status (stability indicating, robustness, reproducibility). We have the expertise to understand method performances and help in defining an optimization strategy to arrive at a final method ready for validation. QbD approaches can be used for analytical development too.

2 SCALE-UP

Once ready, we can support our clients in defining the best strategy to scale up the process and help also in finding the right partner based on the category (API potency) and quantities to be produced (e.g. kg vs. metric tons).
Partners might be selected based also on the commercial forecast, preventing the need for future technology transfers.

3 PROCESS AND CLEANING VALIDATION

Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes (ICH Q7).
We have expertise in preparing VMPs (Validation Master Plans) as well as PVPs (Process Validation Protocols). This will be accompanied by a specific global RA (Risk Assessment) to avoid potential risks during manufacturing and to assess the robustness of the package.
The best cleaning validation approach will be chosen based on the stage of the product, helping in defining the right solvents, agents, and/or techniques to clean equipment and check its cleaning status.

4 STABILITY STUDIES, RETEST PERIOD, EXPIRY DATE

Stability protocols can be prepared upon request based on ICH Q1A (R2). In addition, special conditions can be set up based on the targeted commercial areas (e.g. Zone IVb).
Data analysis and trending can be performed to assess retest periods for API and expiry dates for Drug Products using Q1E as a guideline.

5 RISK ASSESSMENT (RA) REPORTS

We have expertise in preparing various RA reports using the FMEA tool. We can provide EI (Elemental Impurities), Nitrosamines, and global risk assessments for process validation purposes.
Other risk assessments can be defined together with our clients.

6 REGULATORY SUPPORT

We provide expertise in drafting, filing, and managing regulatory files regarding the CMC sections (2.3.S, 3.2.S, 2.3.P, 3.2.P).
We can also support the Client with the preparation of meetings with regulatory authorities.

7 PROJECT MANAGEMENT

Project management is part of our services to follow activities from the supply of starting materials to the production of the final drug.

CMC Drug Product Development

1 PROJECT MANAGEMENT

- Management of CMC projects from discovery up to life cycle management of commercial products already distributed to multiple markets.
- CMC integration with clinical and preclinical development
- Scouting and selection of external CDMOs for development, production, and analysis, depending on the different status of the projects.
- Direct supervision of the external CDMOs for project management and any technical and quality aspect

2 REGULATORY COMPLIANCE

- Authoring and reviewing documents and regulatory packages.
- eCTD module 3 aligned with pharmacopeias and CMC international guidelines (e.g. FDA, EMA, PMDA, ANVISA, PIC/S, WHO, ICH)
- Manufacturing of Investigational Medicinal Products (IMPs) for the different clinical phases.
- Interactions with the regulatory authorities on CMC topics: CMC meetings, pre-submission meetings, deficiencies, requests during eCTD review, post-approval meetings

3 TECHNICAL DEVELOPMENT

The drug product development and the post-approval strategy are driven by considering the molecule characteristics, the drug target, and the final regulatory objectives. We offer oversight and management of:

- Due Diligence and project evaluations
- Analytical and manufacturing technical transfers, validations, and continuous improvements.
- Analytical development (phase appropriate), troubleshooting, validation and transfer activities, stability strategy and oversight
- Aseptic manufacturing, lyophilization, Quality Control, in-vitro correlation, oral and topical manufacturing, fermentations
- Intellectual Property support, especially for Patents
- CMC team coaching and training.

4 GMP COMPLIANCE

- External expert review to improve the efficiency and robustness of the internal processes.
- Person In Plant (PIP) service, representing the clients at the site during core events such as scale-up productions, registration, or validation campaigns.