

FORMULATION, FILL AND KIT ASSEMBLY FOR CHEMICAL COMPOUNDS

GOAL: Design a kit to allow an unstable formulation containing 3 components to be delivered to patients at bedside.

CHALLENGE: To create the entire process and delivery system from scratch.

OUTCOME: Successfully developed, produced and shipped multi-component patient infusion kits with detailed instructions.

PROCESS DEVELOPMENT STEPS:

- Sourced all raw materials
- Developed and optimized filtration process for liquid component
- Set up sterilization process for dry components
- Conducted solubility studies and developed mixing protocol, while keeping total solution volume minimized
- Sourced and designed a multi-component sterile delivery system
- Wrote instructions to ensure proper mixing of kit components and delivery to patients

cGMP ACTIVITIES:

- Prepared the kit components
 - Aseptically filled the liquid component into bottles and tested for sterility
 - Filled both of the chemical compounds into bottles and terminally sterilized
 - Aseptically assembled multi-component delivery system
- Packaged and labeled the kit
- Quality control release tested and Quality Assurance reviewed documentation
- Designed and executed stability program

MANUFACTURE OF A CELL-BASED BIOLOGIC FOR THE CLINIC

GOAL: Take a research concept and develop all processes and assays in order to manufacture a cell-culture based biopharmaceutical for a phase I clinical trial

CHALLENGE: develop 6 new QC assays, optimize the yield and stability of the final product

OUTCOME: Our scientific team helped the client refine and scale-up their research process to develop manufacturing and purification processes to optimize product yield and stability. The team developed all new analytical tests and successfully manufactured, tested, released and shipped the material to multiple sites by the required deadline.

PROCESS DEVELOPMENT STEPS:

- Sourced all raw materials
- Converted a bench process to a cGMP-compliant process
- Cloned cells, selected and characterized the optimal clone for project
- Scaled-up and refined client manufacturing process
- Optimized chromatographic and filtration steps for purification
- Conducted filtration studies for post-purification bulk filtration
- Developed product-specific analytical methods
- Identified unknown impurity in bulk drug substance using mass spec and altered release specifications appropriately
- Developed all relevant supporting documentation

cGMP ACTIVITIES:

- Produced and characterized cell banks (Master and Working)
- Qualified all assays needed for product testing
- Conducted Engineering and production runs for bulk substance production
 - Set up and validated processes specific to client's requirements
 - Produced multiple batches of product
 - Purified the harvest material
 - Formulated final product, aseptically vialled, labeled and stored purified bulk
- QC release tested the vialled product and QA reviewed process documentation
- Designed and executed 2 year stability studies
- Shipped to multiple sites using validated shipping procedures
- Prepared regulatory documentation and delivered executed documents to client

Final Result: Successful Phase I trial. This client has now brought a new, completely different 2-3 year project to Florida Biologix for their Phase II study.

DEVELOPING RE-PURIFICATION STRATEGY FOR CLINICAL MATERIAL

GOAL: Fortune 500 company client urgently needed to re-purify 25g of protein biologic (made at another CMO) headed for the clinic that was unusable, as it did not meet a predetermined purity specification.

CHALLENGE: Client and original CMO had already made several unsuccessful attempts to develop conditions to allow identification of and removal an impurity closely related to the size of the active protein, and they needed it done quickly. Then, client realized the sample also contained excessive endotoxin levels.

OUTCOME: In only a few weeks, the experienced team at Florida Biologix had scouted multiple column chemistries and buffer conditions, developed HPLC test methodology and determined best method to re-purify protein. We provided a scalable solution to remove endotoxin and reduce impurity levels.

PROCESS DEVELOPMENT STEPS:

- Sourced all raw materials, including multiple types of column chromatography platforms and buffers
- FB purification scientists suggested plan of action and tested a variety of column (PPA, HEA, MEP, Capto Adhere, Capto MMC) and buffer (pH, acetate, citrate, MES, urea) conditions
- Analysis of samples was done both at FB and at offsite testing lab in Europe
- Continual, clear client communication and results sharing allowed rapid development of strategy
- Time and materials contract allowed flexibility
- Client took the process back for the final cGMP purification, although Florida Biologix was fully capable of this activity

FORMULATION, FILL FOR A VACCINE WITH ALUM ADJUVANT

GOAL: Develop a cGMP formulation and fill process for a vaccine combined with an alum adjuvant from a small-scale research process

CHALLENGE: To engineer a scaled-up process suitable for GMP manufacturing and fill, ensuring homogeneity of the suspension during the filling process. A key formulation challenge was that the two solutions to be mixed had similar densities (vaccine and alum adjuvant), and the solutions had to be mixed and separated several times during the process.

OUTCOME: FB scientists successfully developed a complex multi-day formulation process with a novel flotation device for washing steps and stirring methodology for filling suspension. Process was successfully conducted both in an engineering run and at 2,500 vial scale which were shipped to the clinical trial on time.

PROCESS DEVELOPMENT STEPS:

- Sourced all raw materials
- Developed wash and mixing protocol, while keeping product recovery rate high
- Experimented to determine optimal way to separate the vaccine (or wash) from the alum solution at GMP scale after mixing, holding and wash steps
- Solution was to engineer a custom cap for the vessel that had 3 tubes, a sterile filter and a flotation device to allow removal of the top layer of liquid only
- Determined optimal configuration and stir bar for use during filling of the suspension

cGMP ACTIVITIES:

- Engineering run of the 4 day formulation process and 1 day fill (20% scale)
- Final drug product manufacturing and fill of 2,500 vials
- Conducted all in-process tests and sampled for release testing
- Labeled and packaged vials
- Quality Control release testing completed; Quality Assurance reviewed all documents
- Product released and shipped for trial
- Designed and executed stability program concurrent with trial