Challenges of Transferring Products into Manufacturing

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Types of Transfers

- **What Is Transfer**
  - **Knowledge**
  - **Processes**
  - **Documentation**
- **Types of Transfers -**
  - **New Products : R&D to MFG Site**
  - **Marketed Products**
    - **Internal Transfers : Site-to-Site**
    - **Outsourcing : Site-to-TPM**

Keys to a Successful Transfer

- A focused, committed team
- Select good receiving site / TPM
- Robust processes
- Manufacturing capabilities
- Proactive quality assurance
- Documentation
- Effective communications
- Relationship management
- Conflict resolution mechanisms
- A good contract & quality agreement

Supplier Qualification

- Project strategy & master plan reviewed
- Technical dossier prepared / CDA issued
- Form a project team
- Vendor Qualification
  - Capability assessment
  - Quality audit
  - Business contract negotiation
  - Quality agreement

Supplier Qualification

- **Quality Agreement**
  - **Responsibilities of both parties**
  - **Managing changes**
  - **Product / material release**
  - **Batch record retention**
  - **Retain samples & storage**
  - **Stability**
  - **Management of investigations – OOS, complaints**
  - **Recall**
  - **Annual product review**

Supplier Qualification

- **Quality Agreement (Cont'd)**
  - **Audits**
  - **Vendor qualification**
  - **Microbiological monitoring**
  - **Qualification / Validation**
  - **Regulatory & Compliance**
  - **Training**

Technology Transfer

- TT Team meeting at manufacturing site
- Identify excipients, intermediates, sourcing strategies and order materials
- Begin analytical method transfer, including cleaning, decontamination methods
- Identify EHS, regulatory, packaging, cleaning requirements
- Determine processes/analytical criteria, batch sizes, and tentative specs
- Develop master batch records
- Cleaning SOPs & detergents

Technology Transfer (Cont'd)

- Perform placebo and pilot studies
- Review stability protocols and study plans
- Manufacture registrational batches
- Initiate stability studies & review results
- Issue process and analytical tech transfer reports
- Review validation and manufacturing launch plan
- File NDA/sNDA/aNDA/MAA
- Receive regulatory approval
- Launch

Common Examples of Issues Faced in Industries

Example #1 – Processing Time

- **Product/Process - A viscous bulk solution is aseptically filtered and filled into vials to be lyophilized.**
- **Problem - Product was successfully transferred via continuous filtration upon filling. When the 1st production batch was made, filter clogged and only part of batch filtered.**
- **Investigations – During batching, filtration and filling takes long period of time with filling being the rate limiting process. A viscous gel-like substance forms with time. It disappears with slightly elevated temperature. No filtration problem occurs if entire batch is immediately filtered. TPM did not have SIP to support large glass-lined holding tank for batch filtration.**
- **Solutions – Use of jacketed filter housing with temperature control. Qualify stainless steel holding tank and filter complete batch before filling.**
- **Lesson Learned – Time can be an important element in sterile viscous product filtration and TPM needs to have proper equipment.**

Example #2 – Packaging Component

- **Product / Process – A sterile liquid filled into 5cc tubing vials with 20 mm finish.**
- **Problem – Vials tipped on the conveyor line which did not occur during line trials using smaller number of vials.**
- **Investigations – It was found that the seal diameter is slightly greater than vial diameter which causes vials to be unbalanced and tip over.**
- **Solutions – Change to flush button seal which has smaller diameter to eliminate domino effect.**
- **Lesson Learned - Increase number of vials during machine trials; Consult Packaging Technology for input.**

Example #3 – Process Handling

- **Product/Process – Wet granulation 50% containing API + extragranular 50% in an extended release product.**
- **Problem – During transfer, product made at 25% production scale was successful in tableting and uniformity across the batch. During scaleup in larger, like equipment, tablets compression was fine but rich in drug at the end of compression, greater than 105% release limit.**
- **Investigations – At small scale, granulation was immediately transferred to the drum and hand scooped to the hopper for compression. At full scale, granulation stayed in the bin and percolation *sometimes* occurred before compression leaving more of the larger, API-rich particles at the top of the bin.**
- **Solutions – Modify milling of wet granulated portion to better match the size of extragranule to reduce segregation.**
- **Lesson Learned – It is necessary to scale up a process before filing to assure that process is ready for commercialization.**