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Some Critical Aspects in the Scale up of Pharmaceutical Dosage Forms

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Agenda

- Basic definitions
- Key elements of success
- What is technology transfer strategy?
- Oral Solid scale up and technology transfer principles
- Scale up and technology transfer of Dermal Products
- Parenteral Scale up Principles
- Industry Academia Partnerships

Basic Definitions

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Definition

- **Scale up:** the process of increasing the batch size. The process wherein the product that is successfully developed in the lab is transferred to pilot scale and then to commercial scale.
- **Scale down?**
- **Technology Transfer**: The goal of technology transfer activities is to transfer **product and process knowledge** between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement. *(Ref.: ICH Q10 [1], paragraph 3.1.2)*

WHO goes one step further to define as follows

- Transfer of technology is defined as "a **logical procedure** that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites".
- It is a **systematic** procedure that is followed in order to pass the **documented knowledge** and **experience** gained during development and or commercialization to an appropriate, responsible and authorized party. Technology transfer embodies both the **transfer of documentation** and the **demonstrated ability** of the **receiving unit (RU)** to effectively perform the critical elements of the transferred technology, to the satisfaction of all parties and any applicable regulatory bodies.
- Transfer of technology requires a documented, planned approach using **trained and knowledgeable** personnel working within a quality system, with documentation of data covering all aspects of development, production and quality control. Usually there is a **sending unit (SU),** a receiving unit and the unit managing the process, which may or may not be a separate entity.

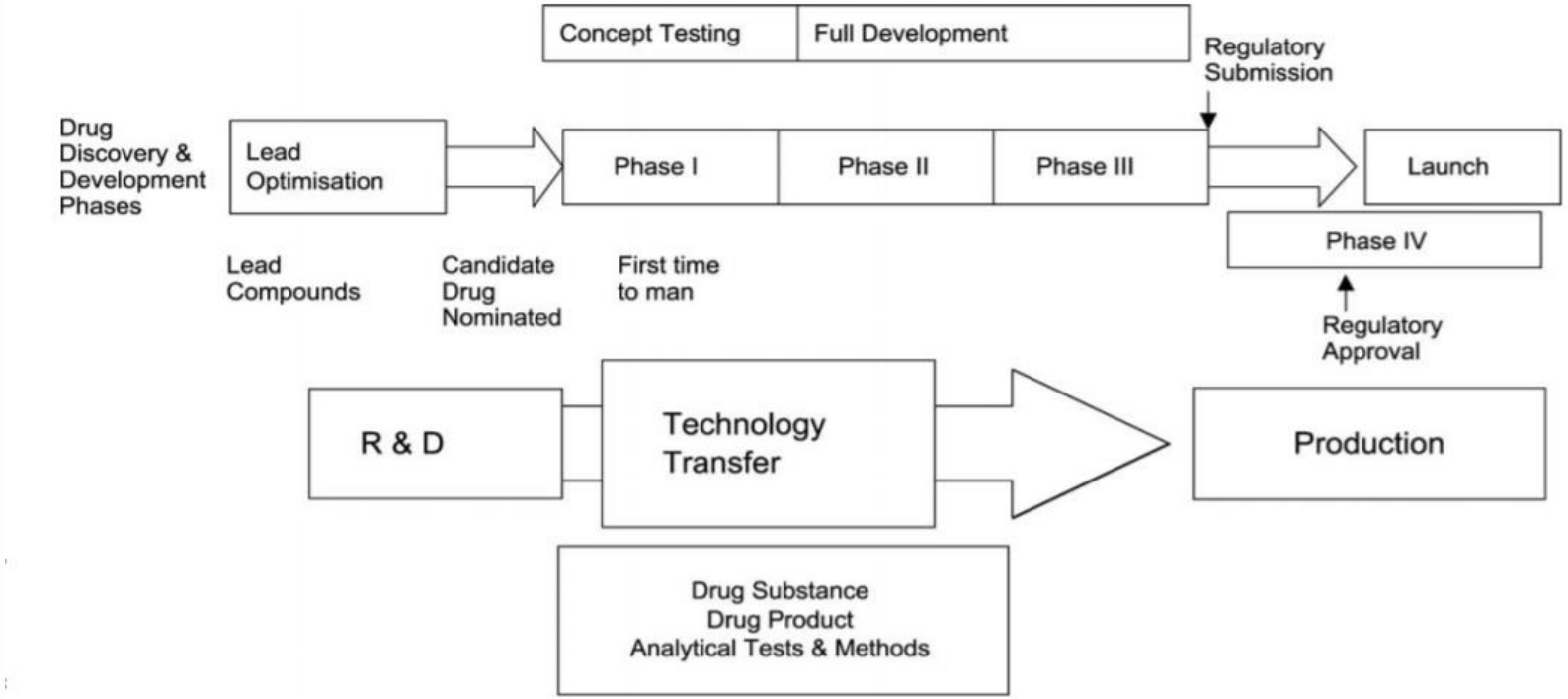
Ref. : https://www.who.int/medicines/areas/quality_safety/quality_assurance/TransferTechnologyPharmaceuticalManufacturingTRS961Annex7.pdf?ua=1

A typical product lifecycle involves the following

- Pharmaceutical Development:
  - Drug substance development;
  - Formulation development (including container/closure system);
  - Analytical method development.
  - Manufacture of investigational products;
  - Delivery system development (where relevant);
  - **Manufacturing process development and scale-up**;
- Technology Transfer:
  - **New product transfers** during Development through Manufacturing;
  - **Transfers within or between manufacturing** and testing sites for marketed products.

Ref: ICH Q 10

Technology transfers occur at multiple stages during development



Ref: https://store.pda.org/TableOfContents/Tech_Transfer_Ch01.pdf

What is success defined as?

- Technology transfer can be considered successful if there is **documented evidence** that the RU can routinely reproduce the transferred product, process or method against a predefined set of specifications as agreed with the SU.
- There are **no deviations** during routine manufacturing.
- Slight variations which are within the acceptance criteria for equipments **do not lead to any OOT** (Out of trend) **or OOS** (out of specification)**.**
- The product does not come back to the lab!

Robust formula/ process leads to successful transfer!

Key Elements of Success

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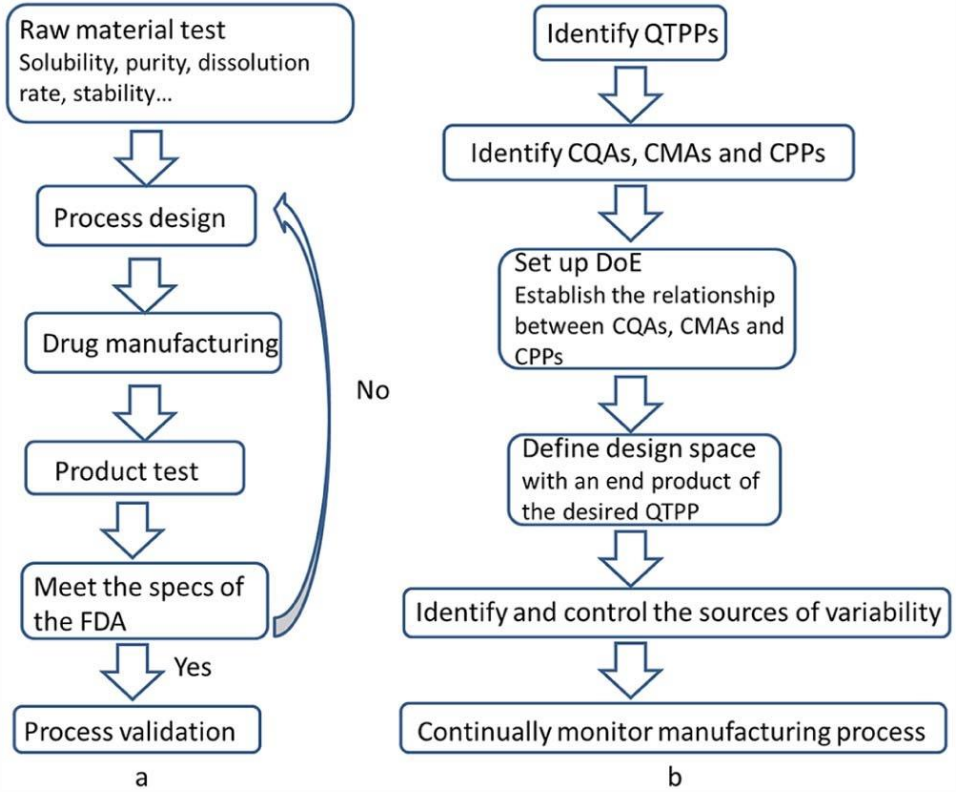
Prerequisite for a successful scale up and technology transfer is – successful product development.

Pharmaceutical Development Q8 (R2)

- Describes **science and risk-based** approaches for pharmaceutical product and manufacturing process development
- Introduced concepts of design space and **flexible regulatory approaches**
- Introduced concepts of Quality by Design (QbD) and provided examples of QbD development approaches and design space.
- The Pharmaceutical Development section should describe the **knowledge** that establishes that the type of dosage form selected and the formulation proposed are **suitable for the intended use.** This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged where they add clarity and facilitate review.
- At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing **processes that are critical to product quality** should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the **extent to which their variation** can have impact on the quality of the drug product.

First steps to Scale up and tech transfer

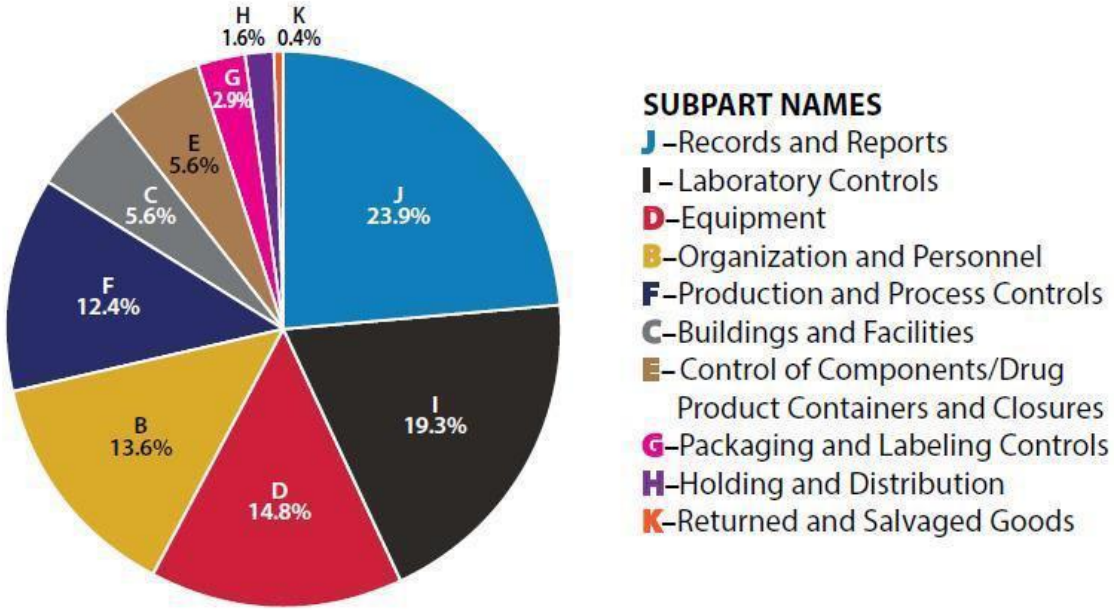


- QbT versus QbD
- Writing an **effective technology transfer protocol** is very important
- Documented data – **intangible experience based inputs**- need to be translated effectively
- Visual observation – e.g. end points – translated to values
- **Additional Sampling and testing** to ensure robustness– IPQC testing
- Challenges of scale –API sifting
- Identify potential causes for variability

Ref.: https://www.sciencedirect.com/science/article/pii/S1818087616300575

FDA Inspectional Observations

Figure 5. 21 CFR 211 Subpart Citations in FY19



Do not directly refer to technology transfer.

However product failure investigations are referred back to the PDR and the development process itself.

What is technology transfer strategy?

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Technology transfer is managed at multiple levels

Management Level

Project Governance Level

Technology transfer strategy encompasses many aspects

- Define the **scope of transfer-** new product / new dosage form / additional strengths / new site
- Document the activity **step wise** and with timelines - granularity
- Identify critical and supportive stakeholders and their priorities – **decision makers**
- Get stakeholder buy in – **align cross functional** priorities
- Provide sufficient time for digestion of information prior to expecting a response
- **Follow up**

Start with a **kick off** meeting

Ref: http://www.pharmtech.com/keys-executing-successful-technology-transfer?pageID=2

What does a successful scale up and technology transfer have?

- The project plan should encompass the quality aspects of the project and be based upon the principles of **quality risk management**;
- The **capabilities** of the SU and at the RU should be similar, but not necessarily identical, and facilities and equipment should operate according to similar operating principles;
- A comprehensive technical gap analysis between the SU and RU including technical risk assessment and potential **regulatory gaps**, should be performed as needed;
- Adequately **trained staff** should be available or should be trained at the RU:
  - regulatory requirements in the countries of the SU and the RU, and in any countries where the product is intended to be supplied, should be taken into account and interpreted consistently throughout any transfer programme project; and
  - there should be effective process and product knowledge transfer

Ref. : https://www.who.int/medicines/areas/quality_safety/quality_assurance/TransferTechnologyPharmaceuticalManufacturingTRS961Annex7.pdf?ua=1

Key elements for successful technology transfer generally include the following

- Direct involvement and engagement among technical staff on both sides throughout the course of transfer activities
- Well-defined leadership and governance and competent project management
- Multifunctional involvement (cross functional or matrixed teams) with appropriate competencies on both the transferring and receiving ends
- Meaningful demonstration of success –repeatable independently (e.g., a successful good manufacturing practice [GMP] manufacturing campaign resulting in comparable material)
- Good documentation of what is transferred, how it is to be transferred, and the results of that transfer.
- **Agreement on the outcome with formal sign off**

Kick off meeting is key!

- Clearly state the agenda & state the expected goals
- Alignment -Management ⇒ Business Unit ⇒ Department(s) ⇒ Group Leads ⇒ ME
- Share a **detailed presentation** upfront (at least 48 hours prior to kick off)- covering product data and desired timelines along with expected roles and responsibilities
- Ask for all inputs on possible road blocks –**LISTEN** with an open mind!
- Obtain stakeholder commitment on **dates**
- Learn from others experience- shop floor personnel (**Experience speaks**)
- Seek help to address the potential road blocks proactively
- Red flagged issues to be followed up during the entire project
- **Identify gaps** and provide mitigation plan based on the gap analysis

Minute the meeting and share and follow up on the agreements reached

Gap Analysis – identify gaps across the whole process

- API lot differences- stage of API development (process / solvents / purity)
- Raw material **vendors**- critical versus standard – cost / vendor qualification
- Procurement **lead times** – API/ RM /PM/ change parts
- Equipment availability -types / size/ scale
- **Instrumentation** for sampling & testing
- **Storage** requirements –cold storage?
- **Hold time** impact
- Risk assessment
- Risk mitigation plan

Effective **stake holder management** is needed to Facilitate Technology Transfer

- Project Plan – management buy in across levels
- **Project Management team** – knowledgeable and proactive
- Timelines / Gantt chart management – with a constant eye to improve the same
- **Task force-** core team – scientific issues
- **Stage Gate** reviews – frequency based on priority
- **Budget** & Cost control – additional batches / contingency
- **Communicate – effectively**. Extent of data sharing depends on need for the same. More rather than less.

Work as a team – common goals!

Cross functional team may consist of the following departments

PD (FD and AD)	Production	QC	Engineering & maintenance	QA/ Regulatory	Project management	Core Task force
i. Selection of raw materials, API, PM- formula process, methods. ii. Design and development of manufacturing process iii. Identification of critical process parameters iv. Establishing specifications and validation of analytical test methods.	i. Provide facility and equipments for performing operation. Ensure suitably trained personnel are available. ii. Perform operation with full understanding of criticalities. Provide feedback on possible improvements from efficiency perspective. iii. Record results of operation and controls	i. Quality testing of API/ RM/ PM, in-process material ii. Quality testing of finished product iii. Preparation of certificate of analysis (CoA) iv. Stability testing	Calibration and maintenance of equipments. Support for trouble shooting during process.	Preparation and review of documentation (protocol and reports) for all processes of technology transfer. For any deviation or OOS provide necessary support.	Timeline and cost management. Stakeholder management. Effective communication	Execution of tech transfer, conflict resolution and responsibility for success

Analytical Method Transfer is **critical** to Success

- Testing to meet the specification of raw material, intermediate, and/or ingredient and product is critical in **establishing the quality** of a finished dosage form.
- The transfer of analytical procedures (TAP), also referred to as method transfer, is the **documented process** that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended.
- When appropriate and as a part of pretransfer activities, the **transferring unit should provide training to the receiving unit**, or the receiving unit should run the procedures and **identify any issues** that may need to be resolved before the transfer protocol is signed. Training should be documented.

Ref. : USP Chapter <1224>

Technology transfer from one organization to another may have more hurdles

- **Contract** – legal document
- Licensing agreement / Master Services agreement
- Supply clauses – meeting specification / yields
- Data sharing and **Gap analysis** – multiple differences possible
- Align the **QMS** – collaborate to avoid conflict
- Minimum batch – MOQ or sudden increase in demand – prepare contingency
- Define **Roles and responsibilities**
- Define **resolution process**
- Document everything – MOM / data e-rooms / decisions

Oral Solid Scale up & Technology Transfer Principles

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Critical Planning Aspects that impact Scale up & TT for OSD

- Typically 1/10th of commercial batch size
- Orphan drugs – smaller batches
- **Expensive API** – smaller batches – justification needed. Cap on maximum commercial batches
- Raw Materials – free samples or **vendor qualified** by QA?
- Manufacturing Procedures and Equipment details – screens / **tooling availability** & lead times
- Blend / Granulation / Mix Analysis – justification of specifications
- **In-Process Controls and specifications** – with suitable justification
- Test Results with **Validated Methods** – for development batches including stability data
- Investigations/**Product Failures** – sharing the data from development
- Paper Based Site Review of equipments & Instruments– for identifying mis-match / gap

Well written Technology Transfer Protocol

Bio batch at development scale is manufactured with excessive care

- Executed by : the development scientist
- Batch size is usually **small** – sufficient for pilot BE and some stability
- Tested at multiple intervals
- All parameters are **strictly adhered** to
- Batch is closely **monitored**
- RM/API/ CC: are all as used in development trials
- Batch size being small – enables **quick completion**
- Documentation is per GMP & DQA controlled

Common issues that are many a times faced in scaling up

- API **vendor** change – do we know what parameters are important?
- Raw material **source differences**
- **Equipment differences** – type, speed and efficiency
- Equipment principle- SUPAC
- **Modification in process** due to operating principle differences
- **Batch run time** – maybe over multiple shifts
- Validation by sampling at multiple intervals
- Temperature / RH impact
- **Trained personnel** – especially for new technologies
- Hold time impact

Critical steps in OSD scale up include the below

- **Particle size distribution** of the active(s)
- **Sequence** of addition
- Blending **time** for the powder mix prior to granulation
- Granulating time and speed; amount of granulating fluid and binder concentration. Rate of addition. **End point identification**.
- Wet milling – need, impact on drying
- Drying time – final **moisture content**, granule particle size distribution
- Granule active content and **homogeneity**, blending time of external phase
- Coating issues – percentage coat, **efficiency** of coater
- Environmental controls / light sensitivity
- In roller compaction – impact of **change in roller size**

Case Study: Blend uniformity (BU) failure at scale up

- Blending and Mixing: The **reorientation of particles relative to one another** in order to achieve uniformity.

Operating Principles:

- Diffusion blending (Tumble)
  - V-blenders
  - Double Cone Blenders
  - Slant Cone Blenders
  - Cube Blenders
  - Bin Blenders
- Convection Mixing
  - Ribbon Blenders
  - Orbiting Screw Blenders
  - Planetary Blenders
- Pneumatic Mixing
  - no pneumatic mixer subclasses have been identified

Ref: https://www.fda.gov/media/85681/download

FDAs stand on Blend Uniformity

The CGMPs require that all sampling plans be scientifically sound and representative of the batch under test (see 21 CFR 211.160(b)). Further**, in-process testing of powder blends to demonstrate adequacy of mixing** is a CGMP requirement (21 CFR 211.110). Between- and within-location variability in the powder blend is a critical component of finished product quality and therefore should be evaluated. Drug product manufacturers need to use **a science- and risk-based sampling approach** to ensure

(a) adequacy of blend mixing and

(b) that sampling of the blend is done at a suitable juncture in the manufacturing process.

The sampling and analysis needs to ensure that **no differences exist between locations in a blend that could adversely affect finished product quality**. Traditional sampling using a powder-thief may have drawbacks and limitations, such as causing disturbance to the powder bed, powder segregation, or other sampling errors. However, powder-thief sampling remains widely used and provides reliable results in many cases. The Agency encourages firms to adopt more innovative approaches to ensuring adequacy of mixing (see, e.g., the guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*). If a manufacturer proposes to use a thief sampling method, the reliability of the method should be evaluated as part of analytical methods development

Case Study: BU acceptance criteria

- **BU Criteria: Individual values Not less than 90.0 % and not more than 110.0% of label claim**; **Mean Value** of the test results should not be less than 95.0% and not more than 105.0 % of label claim.
- **Blend Sample Criteria:** RSD is **≤** 5.0% and all individuals are within +/- 10% of **absolute** mean. The RSD value should be used to classify the testing results as either readily pass (RSD ≤ 4.0%), marginally pass (RSD ≤ 6.0%) or inappropriate for demonstration of batch homogeneity (RSD > 6.0%)
- **Absolute** as used to define the acceptable range (+/- 10%) in which individual blend sample values must fall and which is independent of the value of the mean. For example, if the mean of all blend samples is 95.0%, the absolute range is 85.0% to105.0%, (not 95.0% +/- 9.5%).
- In case of very low dose products – with adequate justification:
  - Individual assays: 85.0-105.0% of the label claim/mean value, RSD: NMT 5.0%
  - May be acceptable provided that uniformity of dosage units is satisfactorily demonstrated on tablets/capsules manufactured from blend lot with close to limit blend uniformity results

Ref: http://academy.gmp-compliance.org/guidemgr/files/5831DFT.PDF

Case Study : BU failure on scale up

Importance of sampling and specification setting:

- Sampling **location** -usually predetermined as part of qualification of the mixer (i.e. mostly GMP issue)
  - But, in the dossier, we at least check if periphery, center positions and various other positions are considered
  - Dead spots included?
  - Samples from each location are usually taken in triplicate
- Samples should also be taken from the **blend container *(Drum)*-** to evaluate impact of transfer
  - important for low dose products and particularly for DC processed blend
  - at least 3 replicate samples be taken from at least 10 locations in the powder blender -*all* replicate samples taken from various locations in the blender be evaluated to perform a statistically valid analysis
- Sampling should be done consistently and in away that does not disturb the bulk blend state – such aspects (e.g. type of sampling thief used) are better addressed at the time of inspection
- **Sample size** should be justified: 1x to 3 x, 5x to 10x?

Ref.: https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practices-production-and-process-controls#:~:text=Section%20V%20(Exhibit%2FValidation%20Batch,to%20assess%20powder%20blend%20uniformity.

Case Study : BU failure

- Capsule dosage form with BCS class I drug
- Development equipment and scale up equipment follow same operating principle – 5 kg to 50 kg scale up (1x to 10x)
- API is crystalline and forms 25% w/w of the fill weight. Fill weight 100 mg / size 2 capsule.
- Formula and process are replica of RLD- process is simple sifting / blending / lubrication followed by capsule filling.
- **Issue**: Basis the equipment qualification protocol – the blending time and speed were set for the first scale up batch- **BU failed**, CU was passing.
- **Root cause**: Segregation of blend during sampling, inadequate replicates, less that ideal sample size (1x to 3X), difference in API particle size distribution between development and scale up
- **Resolution:** Increase sample size to 3x to 5x, justify with CU data of failed BU batch, re-define API PSD , use personnel trained in sampling, revise blending time.
  - 2 more batches were repeated and both BU and CU were satisfactory. (BU samples at blending and lubrication). All locations tested.
  - FDA DRL (Discipline Review Letter) pinpointed this issue and discussed it further- validation batches commitment to sampling

Case Study: Environmental Impact

- Antimalarial product: High dose API; FC IR tablet; wet granulated product
- % Moisture Content (MC) in the granules prior to tableting: 1-2.5 % w/w in development
- No capping observed; no friability issues
- Batch size maximum- 2.5 kgs in development
- Scaled up to: 200 kgs
- **Issue**: Capping of tablets in scale up batch
- **Root cause**: Loss of moisture from granules on running the compression over long periods- bulk granules exposed to controlled temperature and humidity.
- **Resolution:** Revise the LOD limits of granules marginally- more stringent limits; Load the hopper minimally, keep the granules well covered in drums- avoid too many transfers.
  - Between shifts – remove granules from turret and discard.

Case Study: Equipment size /scale impact

- Equipment Size impacts process
- API-Anti emetic; low dose API, BCS Class I, Degrades on aqueous processing
- Lab scale compactor- small auger and rolls- water jacket circulation; good compacts; desirable flow, dissolution and stability. Output 750 gms to 3 kg/hour
- Plant scale: 400 kg/ hour output
- **Issue:** jamming of rollers; formation of flakes
- **Root Cause**: Heat generation; material fuses to form flakes; lumps formed due to intense heat in the process of compaction. Yield, dissolution and stability affected adversely – specification failure.
- **Resolution**: Replace partially water insoluble components with soluble ones – formula change (**!**); ensure cold water circulation jacket; slow down Auger speed.
  - Additional In process test – added granule dissolution.

Case Study : API properties impact in an Antiepileptic Capsule dosage form

API characterized for:

- Percentage w/w of API
- Particle size and distribution
- Bulk and tapped density
- Form- crystalline / amorphous
- Flow ability

- Drug – ~50 % w/w
- Capsule size 2
- Lab trials with API from small scale manufacture of API
- Pivotal trials with bulk manufactured API
- **Issue**- final blend low BD and TD – does not fill capsules
- **Root cause** - API form- amorphous versus crystalline
- Specs set during development inadequate

Resolution:

- API re-crystallized
- API spec revised – test added
- Manufacturing Process changed

Case Study: Granulation Process failure

- Granulation principle : Excess shear has potentially detrimental effect. Over granulation / under granulation impact differs from smaller to larger equipment.

Scale of operation:

Lab scale RMG	⇒	Pilot Scale RMG	⇒	Production scale RMG
3 kgs	⇒	25 kgs	⇒	110 kgs
12 litres	⇒	125 litres	⇒	600 litres

- Product: Antiepileptic Dosage form: FC tablet
- High dose API- about 66%w/w of product, BCS Class II moiety- *in vitro* dissolution indicates probable *in vivo* performance
- Dissolution profile **matched** from lab pilot bio batch to manufacturing level pilot plant batch.
- **Pivotal batch dissolution failed-** slower by more than 30% from initial data
- Granules PSD similar, Bulk density higher for pivotal batch granules
- **Opening pattern** in the dissolution bath different

Granulation process failure: Root cause analysis

- Investigation performed at each stage of operation
- Dry blend; granules (un-milled & milled), lubricated blend, core and coated tablets subjected to dissolution.
- **Issue:** Drop in dissolution observed post granulation

  Granules PSD comparable; bulk density higher- forms a heap at the bottom of dissolution vessel
- **Root cause**: MCC behaviour – Hypothesized that MCC tends to undergo plastic deformation and form a pseudo –plastic mass on over kneading.

  This leads to lower compressibility of granules, higher binding and harder granules and therefore decreased solubility of the API
- **Resolution**: Granulation optimized to obtain light granules , dissolution at granulation stage introduced as an additional test till validation and commercialization.

Scale up & Technology transfer of Topical Products

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Unit operations in Topical Products

- **Unit operations** involved in the manufacturing of Topical products varies depending on the nature of the product.
- Ointment / gel/ cream / lotion etc.
- Typical unit operations :
  - **Mixing**
  - **Heating and Melting**
  - **Homogenization**
  - **Cooling and deaeration**
  - **Filling**
- Critical quality attributes affected include **description, assay, uniformity, related substances, globule size, viscosity, specific gravity** etc.

Key considerations for Scale up

- Apply the principles of QbD and Risk assessment to identify potential CPPs , and the CQAs they are likely to impact. **Establish acceptable range** of CQAs, which will not affect product quality.
- Establish a range of **scale independent** parameters at lab scale via a DoE or OFAT experiments.
- **Challenge scale dependent** parameters thoroughly at lab scale to understand the nature and level of their impact on CQAs, even though the range at lab scale might not be valid at higher scale.
- **Opt for equipments of similar geometry and design**, and apply engineering principles like tip speed calculation to minimize scale up failures.
- Don’t forget the CMAs : API PSD, Melting point of excipients etc

Critical aspects of Topical product manufacturing

Mixing : The reorientation of particles relative to one another to achieve uniformity or randomness. This process can include wetting of solids by a liquid phase, dispersion of discrete particles, or deagglomeration into a continuous phase. Heating and cooling via indirect conduction may be used in this operation to facilitate phase mixing or stabilization

- Potential CPPs :
  - **Type and geometry** of mixing apparatus : Propeller, Anchor, etc
  - Mixing time and Speed : Tip Speed
  - Occupancy of mixing vessel
  - Order of Addition of ingredients
  - Application of heat / rate of application
- Affected CQAs :

  Assay, uniformity, related substances

Ref. : https://www.fda.gov/media/85681/download

Critical aspects of Topical product manufacturing

Heating and melting.

- Potential CPPs :
  - Type and geometry of mixing apparatus : Propeller, Anchor, etc
  - Heating temperature
  - **Order of Addition** of ingredients

- Affected CQAs :

  Description, Related substances, viscosity

Ref. : https://www.fda.gov/media/85681/download

Critical aspects of Topical product manufacturing

Homogenization / Emulsification: The application of physical energy to a liquid system consisting of at least two immiscible phases, causing one phase to be dispersed into the other

- Potential CPPs :
  - Type and geometry of homogenizer
  - Order of Addition of ingredients
  - Speed and time of homogenization : Tip speed
  - Temperature of homogenization
  - **Number of cycles**
- Affected CQAs :

  Assay, uniformity, related substances, Viscosity, globule size etc

Ref. : https://www.fda.gov/media/85681/download

Critical aspects of Topical product manufacturing

Deaeration and Cooling: The elimination of trapped gases to provide more accurate volumetric measurements and remove potentially reactive gases

- Potential CPPs :
  - **Cooling rate**
  - Shear during cooling : cooling under mixing vs cooling under homogenization
  - **Application of vacuum**
  - Temperature of cooling
- Affected CQAs :

  Viscosity, Specific Gravity etc

Application of QbD and Risk assessment for manufacturing of Topical products

Typical example of risk matrix of unit operations Vs Critical quality attributes

Process Step	Process parameters	Scale dependent/ Independent	Affected CQA	Risk Ranking	Justification and Mitigation strategy
Homogenization	Homogenizer type and Geometry	Independent	Assay, uniformity, viscosity, Globule size	Low	**Same make and geometry as lab scale**. No mitigation strategy required.
	Order of addition	Independent	Related substances, Viscosity	Low	**Studied and established in lab scale**. No mitigation strategy required.
	Speed and Time and number of cycles	Scale dependent	Viscosity, Globule size, Assay, Uniformity	High	**Speed and time** to be optimized based on tip speed

Tips for successful scale up of topicals

- **Expect increase in mixing times**, even though the composition is exactly the same as that of lab scale. For e.g., a dispersion of Carbopol or even solubilization of some APIs.
- Expect overall **increase in processing time**, consider API exposure to different phases and temperatures during scale up.
- Typically **higher scale equipments produce more shear** even if tip speed calculation is maintained. Consider impact on viscosity, globule size etc.
- At times, **process efficiency might increase** during scale up, like cooling rate can be faster or vacuum applied can be stronger. Consider impact on viscosity, specific gravity etc.
- Develop tools like **IVRT** (*in vitro* release testing) **during development** to understand impact of CPPs better

Parenteral Scale up Principles

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Parenteral Preparations

- **Definition**:Parenteral preparations are defined as solutions, suspensions, emulsions for injection or infusion, powders for injection or infusion, gels for injection and implants. They are **sterile preparations** intended to be administrated directly into the systemic circulation in human or animal body.
- Main challenge for clear solution sterile parenteral products is **mixing time and equipment.**
- For suspensions: **particle size** post homogenization
- For emulsions: **distribution of phases**

Ref: https://gmpua.com/Process/ProcessScale-Up.pdf

Properties of Parenteral preparations

They must meet the following **minimum** compendia criteria:

- Must be **sterile** and **pyrogen-free**
- Must be **clear** or practically exempt of visible particle and to be free from sub-visible particles as required by pharmacopeias EP, USP and JP;
- There should be **no evidence of phase separation** for the emulsions, or aggregates formation for aqueous dispersion such as injectable Mab (monoclonal antibody) preparations; and
- In the case of suspensions, the use of appropriate particle size and any sediment should be **readily dispersed upon shaking** to give stable formulations and ensure the correct dose to be withdrawn and injected.

Importance of Container Closure Systems

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

CDER and CBER approve a container closure system to be used in the packaging of a human drug or biologic as part of the application (NDA, ANDA or BLA) for the drug or biologic.

Table 1 illustrates the correlation between the **degree of concern regarding the route of administration with the likelihood of packaging component-dosage form interactions** for different classes of drug products.

For the purposes of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid).
As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.

Ref.: https://www.fda.gov/media/70788/download

Important aspects related to manufacture of parenteral products include

Process

- Mixing
- Homogenization
- Filtration
- Filling & sealing
- Sterilization - terminal sterilization or aseptic fill

Tests

- Description
- Potency & Purity
- Preservative content
- Volume/Dose Uniformity
- Bacterial endotoxin
- Sterility
- pH
- Redispersion - suspensions
- Reconstitution - Lyo

Critical parameter

- **Order of addition** of components, including adjustments of their amounts.
- **Mixing speed** and mixing time.
- **Rate** of addition of drugs and buffers
- Heating and cooling rates.
- Filter sizes for sterile manufacturing
- **Lyo cycles** and temperatures

Additional specifications

- **Absence** of Particulate matter (all solutions)
- **Dissolution rate** (implant, suspensions)
- Particle size distribution (suspension /emulsion)
- Osmolarity
- Preservative content
- **Antioxidant** content
- Resuspendability
- **Extractables and Leachables**

Critical steps & In-process controls to be monitored during scale up and technology transfer

- **Sterilization**/depyrogenation **processes** – with justification
- Sterilization parameters for the product and **all items in contact** with the sterile product
- Validation reports (**heat penetration and performance validation**):
  - Results for three consecutive runs
  - Loading chart(s)
- **Filter validation report** – Bacterial retention, chemical compatibility, extractables, absorption – Flush volume – Filter integrity testing
- Environmental controls – **no sterility failures**
- **Media fill studies** and process validation runs

Example of failed technology transfer

- Product needs lyophilization so as to **maintain stability**
- Successfully developed in lab- two process cycles established
  - API is poorly soluble and needs solubility enhancers- is high dose
  - Formula without ethanol meets Q1/Q2
  - Formula with ethanol is also stable – needs regulatory justification
  - CC (Controlled correspondence) with FDA signals use of formula without ethanol
- **Issue:** Batch transfer to manufacturing site – first batch is successful- meets AQL though not ideal (acceptable quality limits)
  - Second, third and fourth batch – collapse

Root cause analysis: risk assessment due to manufacturing equipment and **lyophilization conditions not established appropriately**

Resolution: Not achieved yet. Equipment parameters for lyo cycles are suspected.

Industry Academia Collaborations – my personal view

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Asking the right questions

- Trust – respecting the CDA
- Scoping of the project – with details
- Full understanding of timelines and future course for the company
- Academia should have access to industry trained personnel to assist / advice
- Access to right quality of API / RM/ PM
- Autonomy – ability to take decisions independently

Equipment sizes and types and likely gaps between academia and industry

- Transparent Information exchange prior to project start
- Understanding the gaps – and partnering effectively to close the same
- **Documentation standards** / Calibration of equipment / adherence to timelines
- Identifying possible **additional** actions at the time of scale up & technology transfer- additional timeline and budget

My view: success is possible with collaboration:

- Abbess Healthcare in Bharati Vidyapeeth

Thank You!

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