Formulation, scale-up and post-approval changes

Learning objectives:
Students will be able to:

1. Define and explain the different stages of pharmaceutical formulation, scale-up, and post-approval changes.
2. Describe the purpose and benefits of SUPAC and the different types of post-approval changes that can be made to a drug product.

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1. Introduction

Formulation and scale up are complex processes, but they are essential for developing safe, effective, and acceptable drug products. By carefully considering all of the relevant factors, pharmaceutical scientists can create drug products that meet the needs of patients and help them to live healthier lives.

2. Formulation

Pharmaceutical formulation is the process of designing and developing a drug product that is safe, effective, and acceptable to patients. This process involves selecting the appropriate active pharmaceutical ingredient (API), excipients, and manufacturing process to create a drug product that meets all of the required specifications.
There are many factors to consider when formulating a drug product, including:

- The properties of the API, such as its solubility, stability, and particle size
- The desired route of administration, such as oral, topical, or parenteral
- The target patient population, such as children or adults with certain medical conditions
- The desired dosage form, such as a tablet, capsule, or liquid
- The desired shelf life of the drug product

The most common pharmaceutical manufacturing steps and equipment are listed here in a chronological order:

Step	Industrial equipment
Weighing the API and excipients	Weighing balance, volumetric dispenser
Sieving the API and excipients to remove any large particles	Sieve, sifter
Blending the API and excipients together to form a uniform mixture	Blender, mixer
Granulation (optional step) to convert the powder mixture into a granular form	Fluid bed granulator, high-shear mixer

Drying the granules to remove moisture	Fluid bed dryer, vacuum dryer, spray dryer
Milling (optional step) to reduce the particle size of the granules	Hammer mill, roller mill
Compression to compress the granules into a solid form (tablets)	Tablet press
Coating (optional step) to apply a thin layer of material to the surface of the tablets	Fluid bed coater
Filling the capsules with the powder or liquid	Rotary Capsule filling machine
Sealing the capsules to prevent the contents from leaking out	Banding Capsule sealing machine
Printing (optional step) to print identification markings on the capsules	Inkjet Capsule printing machine
Mixing the liquid dosage forms (syrups, suspensions, etc.)	Liquid mixer
Filtration (optional step) to remove any impurities from the liquid dosage forms	Filter press, cartridge filter
Sterilization (optional step) to destroy all microorganisms in the liquid dosage forms	Autoclave, gamma irradiator
Emulsification (optional step) to disperse one liquid in another liquid in the form of small droplets	Homogenizer, colloid mill
Packaging the drug products in bottles, vials, or other containers	Filling machine, capping machine, labeling machine
Labeling the drug products with the necessary information	Labeler
Shipping the drug products to pharmacies or other healthcare providers	Conveyor belt, palletizer, forklift

Additional notes:

- The exact order of the steps may vary depending on the dosage form being manufactured.
- Some steps, such as granulation, milling, and coating, are optional and may not be used for all dosage forms.
- Sterilization is only required for injectable dosage forms.
- Emulsification is only used for cream and ointment dosage forms.
- Gelling is only used for gel dosage forms.

3. Scale-up

Scale-up is the process of increasing the production of a drug product from a small-scale (e.g., research lab) to a large-scale manufacturing process (e.g., commercial). This is a complex process that requires careful planning and execution.

Scale-up aims to ensure the safe, efficient, and cost-effective transition of a drug formulation from small-scale development to large-scale production.

There are a number of challenges associated with scale-up, including:

- Maintaining the quality of the drug product
- Ensuring the safety of the manufacturing process
- Controlling the cost of the manufacturing process

In addition to that, the major challenges of scale up reside in similarity:

- **Geometric similarity**: It is difficult to maintain geometric similarity perfectly when scaling up a system. This is because the surface area to volume ratio changes as the size of the system changes. This can lead to problems such as heat transfer and fluid flow.
- **Dynamic similarity**: Dynamic similarity requires that the ratios of forces, velocities, and accelerations remain the same when scaling up a system. This can be difficult to achieve, especially for complex systems.
- **Kinetic similarity**: Kinetic similarity requires that the ratios of chemical reaction rates remain the same when scaling up a system. This can also be difficult to achieve, as chemical reaction rates are influenced by a number of factors, such as temperature and concentration.

Based on those challenges, there has been three major approaches to pharmaceutical scale-up, which are summarized in this table with simple examples

Approach	Description	Example
Linear scale-up	This is the simplest approach to scale-up, and it involves simply increasing the size of all of the equipment and processes by a proportional factor.	For example, if you are scaling up a batch process by 10x, you would increase the size of the reactor, mixer, and other equipment by 10x. You would also increase the amount of raw materials and ingredients by 10x.
Empirical scale-up	This approach involves developing a scale-up model based on data from small-scale batches. This model can then be used to predict the performance of the process at larger scales.	For example, you could develop a scale-up model for a mixing process by measuring the mixing time for different batch sizes. You could then use this model to predict the mixing time for a larger batch size.
Quality by Design (QbD) approach	QbD is a systematic approach to product development that focuses on identifying and understanding the critical quality attributes (CQAs) of a product and the process parameters that affect the CQAs. This information can then be used to develop a process that is robust and can consistently produce high-quality products.	For example, you could use QbD to develop a scale-up plan for a tablet manufacturing process. You would first identify the CQAs of the tablets, such as tablet weight and hardness. You would then identify the process parameters that affect the CQAs, such as mixing time and compression force. You would then use this information to develop a scale-up plan that ensures that the tablets meet all of the required specifications.

The stages of technology transfer in terms of scaling up are presented here:

Stage 0 of Pre-formulation Studies: API and Excipients

- Understand the Active Pharmaceutical Ingredient (API) and the selection of appropriate excipients.
- Preliminary studies assess the physical and chemical properties of the API and excipients to determine compatibility and feasibility.

Stage I Product Design and Development: 1X laboratory scale (1-10 kg)

- Product design and development studies, investigating upper and lower limits
- Measure process parameters that are further explored during the scale-up phases

Stage II Preparation of Batches for Clinical Trials: 10X pilot scale (10-100 kg)

- Product optimization and process characterisation studies using Design of Experiment (DoE)
- Its size is generally between 10 and 100 kg, 10 and 100 L or 10,000 to 100,000 units.
- Evaluate the safety, efficacy, and dosage regimen of the drug in clinical trials.

Stage III Industrial Scale-Up and Evaluation: 100X Industrial scale (100 kg-1000 kg)

- Process optimization using Process Analytical Technology (PAT)
- The manufacturing process is scaled up to produce commercial quantities.
- Quality control and assurance are emphasized to ensure consistency and safety.

Stage IV Formal Validation of the Process

- Thorough testing and documentation to ensure the process consistently produces a product that meets quality and regulatory standards.
- Regulatory agencies often require validation data for approval.

These stages and steps represent a systematic approach to pharmaceutical development, from initial pre-formulation studies to large-scale production and formal validation. Each stage plays a crucial role in ensuring the safety, efficacy, and quality of pharmaceutical products.

4. Post approval changes

SUPAC stands for Scale-Up and Post-Approval Changes, it is a set of guidance documents issued by the US Food and Drug Administration (FDA) to provide guidance to pharmaceutical companies on how to make changes to drug products after they have been approved. It covers the following product categories:

- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms
- SUPAC-MR: Modified Release Solid Oral Dosage Forms
- SUPAC-SS: Nonsterile Semisolid Dosage Forms

Scientific Rationale

- Accelerate change processes after approval of pharmaceutical products
- FDA can ensure their safety and effectiveness.
- Reduce regulatory burden on industry

These guidelines provide recommendations for approval of changes in:

- Components and composition
- Site changes
- Batch size (Scale-up/Scale-down)
- Manufacturing (Equipment and process)

There are three levels of change:

• **Level 1 change:** Those that are unlikely to have any detectable impact on formulation quality and performance.

Here are some examples of Level 1 changes:

Type of change	Examples
Components and composition	Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
Site	Within a single facility
Batch size	Up to and including a factor of 10 times the size of the pilot/biobatch,
Manufacturing	Change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients

• **Level 2 change:** Those that could have a significant impact on formulation quality and performance.

Here are some examples of Level 2 changes:

Type of change	Examples
Components and composition	Change in the technical grade of an excipient. (Example: Avicel PH102 vs. Avicel PH200.)
Site	Within a contiguous campus, or between facilities in adjacent city blocks
Batch size	Beyond a factor of ten times the size of the pilot/biobatch
Manufacturing	Change in equipment to a different design and different operating principles.

• **Level 3 change:** Those that are likely to have a significant impact on formulation quality and performance.

Here are some examples of Level 3 changes:

Type of change	Examples
Components and composition	Changes in the filler with over ±10% w/w out of total target dosage form weight

Site	Change in manufacturing site to a different campus
Batch size	N/A
Manufacturing	Change from wet granulation to direct compression of dry powder.

Conclusion

Formulation and SUPAC are important but complex steps in the pharmaceutical development process.

- Formulation involves designing and developing a drug product that is safe, effective, and acceptable to patients.
- Scale-up involves increasing the production of a drug product from a small-scale to a large-scale manufacturing process.
- Post Approval Changes provides guidance to pharmaceutical companies on how to make changes to drug products after they have been approved.

All three of these steps are essential for ensuring the quality, safety and efficacy of drug products.

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