Producing a Pharmaceutical or Biopharmaceutical

The Manufacturing Process
Process development

- Scientists and engineers begin to figure out how to “scale up” production of a drug even before it receives FDA approval.
- Manufacturing processes might be quite different than the small-scale lab procedures.
Production of a pharmaceutical or biopharmaceutical involves many different, complex, and lengthy steps:

- Synthesis (chemical or cell culture)
- Purification
- Formulation
- Final dosage form preparation
Step 1: Synthesis

- Order the raw materials needed to make the product.
- Test all raw materials to be sure they meet quality standards.
- For biomanufacturing, equipment and materials need to be sterilized to avoid bacterial and other contamination to the cell cultures.
Step 1: Synthesis

- The product then is created.
  - For pharmaceuticals, there are chemical processes involved (chemical synthesis).
  - For biopharmaceuticals, cell culture or fermentation is involved.
  - The product is referred to as the "active ingredient."
Step 1: Synthesis

- For the biopharmaceutical, the original cell culture is started in small bottles (around the size of large soda bottles)
- As the cells grow and multiply, they are introduced into a small bioreactor.
- Eventually they are grown in large bioreactors, which can be several stories tall!
Step 1: Biosynthesis

A small bioreactor in the foreground, with a larger one behind it.
Step 2: Purification

- After the active ingredient is synthesized, it must be purified.
- Purification involves removing the chemicals used in the process.
- For biopharmaceuticals, purification involves separating the cells from the cellular nutrients and byproducts (the “soup”) they grew in.
Step 2: Purification

- The end result of production is called the bulk product.
- The bulk product may be sold as is, processed further at the same plant or shipped to another plant for further processing.
Step 3: Formulation

- Several other operations are required to get bulk product into its final form.
- Formulation involves chemical mixing operations to blend the active ingredient with other substances, such as fillers, needed in the final form.
Step 3: Formulation

- The final form may be a solid (tablet or capsule), liquid, gels/creams or aerosols.
- Biopharmaceuticals usually are sold as sterile liquids or sterile powders.
Step 4: Final dosage form preparation

- The formulated preparation is made into its final form.
- The final form is dispensed into containers.
- The containers are labeled and packaged.
Quality matters

- The standards of quality are high because the stakes are high.
- Poor quality products can harm or even kill consumers.
- Companies must conform to the stringent Good Manufacturing Practice (GMP) regulations established by the FDA.
Ensuring quality

- Manufacturers have three departments that ensure quality:
  - Quality control (QC)
  - Quality assurance (QA)
  - Validation
Quality control

QC employees sample and test the raw materials and the product during many stages of the manufacturing process.
Quality assurance

- QA ensures product quality by setting up and checking the systems of standard operating procedures (SOPs) and of documentation.
- SOPs guide every task by defining each procedure in detail so it can be performed exactly the same way every time.
Quality assurance

- Companies are required to prepare and follow SOPs by the FDA.
- Any deviation from the SOP must be documented and approved by the QA department.
- Critical deviations that could affect product quality are investigated further.
Quality assurance

- Documentation proves that a company has done what it said.
- A company is required to have a traceable, written record of all processes and checks.
- “If it isn’t written down, it doesn’t exist. If it isn’t written down, it never happened.”
Validation

- Validation proves that a manufacturing process will consistently produce the product to predefined specifications.
- The operation of every part of the plant that affects quality must be validated.
Validation

- If a manufacturing process is changed or if a new product is introduced, all processes and equipment that affect quality must be validated.
- Validation scientists and engineers have extensive experience because they must be very familiar with the regulations.
Five rules for quality

1. Understand customer needs
   - Companies have internal customers (fellow employees) as well as external customers.
   - For a process technician, your internal customer is your coworker at the next stage of the process.
Five rules for quality

2. Say what you do — write down procedures

- Standard procedures and forms are required for every step.
- Batch records define the steps required to manufacture the product, the materials used, etc.
Five rules for quality

3. Do what you say — follow procedures
   - Manufacturers are required to consistently and exactly follow procedures.
   - SOPs are vital, and there are SOPs for every step.
Five rules for quality

4. Prove it — keep records
- Companies must have traceable, written records of all processes.
- Again, “If it isn’t written down, it doesn’t exist. If it isn’t written down, it never happened.”
Five rules for quality

5. Improve it

- Companies must continually evaluate its processes and procedures.
- They should take steps to make them better.
- Of course, new procedures must be validated!
Standard Operating Procedures

- SOPs define a particular process in detail so it can be performed the same way, every time.
- Lengthy regulations related to manufacturing are found in the *Code of Federal Regulations*.
- Good Manufacturing Practice (GMP) regulates methods, equipment, facilities and controls.
What is included in SOPs?

- Effective date
- Purpose
- Scope
- Responsibility
- References (other SOPs)
- Materials and equipment
- Procedures
- Approval signatures