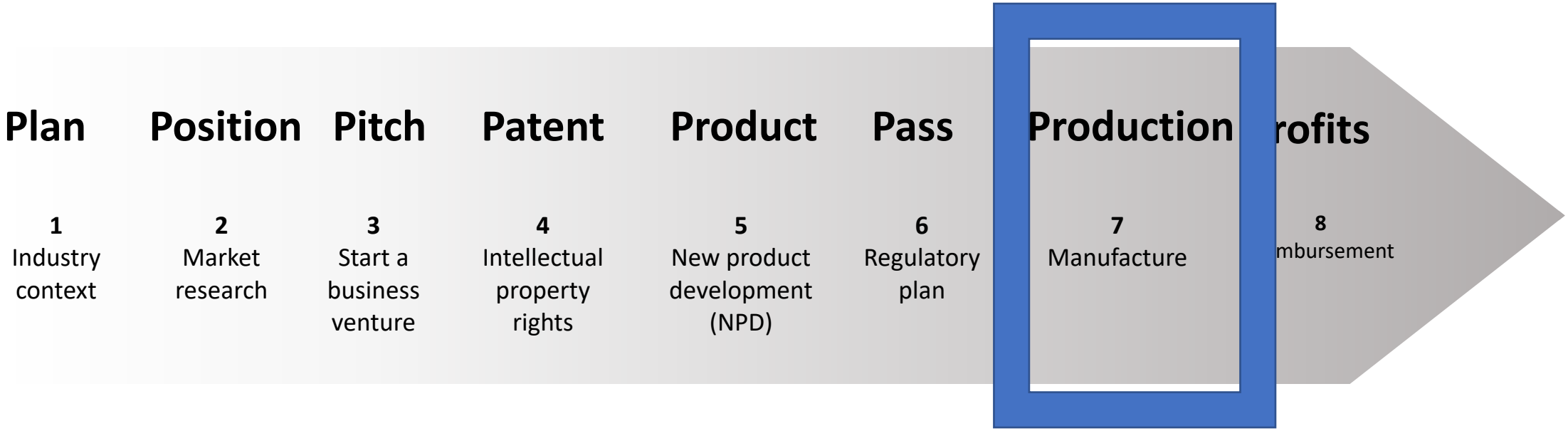
Commercializing Successful Biomedical Technologies 2nd Ed.

Shreefal Mehta



Manufacturing

Shreefal Mehta

Chapter 7

Technology transfer to manufacturing operations (drugs, devices, and diagnostics)

"Technology transfer" : the process of converting R&D small scale processes or early design and laboratory prototypes to larger scale bulk manufacturing processes and specifically involves the transfer of the product and production know-how from the R&D group to the commercial operations group ("Operations")

Information that was developed in R&D may not have the same relevance in this new, larger-scale environment

Manufacturing culture and values:

- Reproducibility
- Reduction of defects per thousand/million products made
- Adhering to the highest degree of regulatory compliance
- Accountability in highly documented processes

R&D unit culture and values:

- Scientific innovation
- Novelty
- Creativity
- Flexibility
- Development speed

Technology transfer to manufacturing operations (contd.)

Why do "technology transfers" frequently fail?

- "Over the fence" transfer (sharp transfers)
- Lack of respect
- Lack of engagement of either party
- Lack of ownership following transfer
- "Not invented here" syndrome
- Lack of common goal
- Too many transfers
- Incomplete, inadequate documentation

Three models of technology transfer

I. **Push** (let R&D drive the transfer);
II. **Pull** (production shares "ownership" in the development process)
III. **Participatory** - Personnel transfer

Personnel transfers from R&D to Operations are usually the most successful

Regulatory compliance in manufacturing

Most manufacturing sites are visited by the FDA before final approval of a new product (pre-approval inspection) and these visits continue post-approval

Current good manufacturing practices (cGMP)

- Defined as "a set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products."

A quality system involves quality control (QC) and quality assurance (QA).

The cGMPs are constantly being revised to accommodate advances in technology

Validation

- ✓ Validation is defined as "the act of proving that any process, procedure, equipment, material, activity or system leads to expected results."
- ✓ Process validation is a part of current good manufacturing practice and is required in the United States and EU for a manufacturing license.
- ✓ A validated manufacturing process has a high level of scientific assurance that it will reliably and consistently produce acceptable product
- ✓ Validation in devices includes checking the product characteristics against initial customer and design inputs

Drug manufacture regulations – control systems

- ***Pharmaceutical cGMP regulations*** : integrate quality systems and risk management approaches.
- Emerged due to a high number of prescription drug recalls, largely related to manufacturing quality issues
- Compliance with manufacturing regulations and standards requires that six distinct control processes and systems must be in place at any organization:
  1. Materials system
  2. Production system
  3. Packaging and labeling system
  4. Laboratory systems
  5. Facilities and equipment system
  6. Quality system

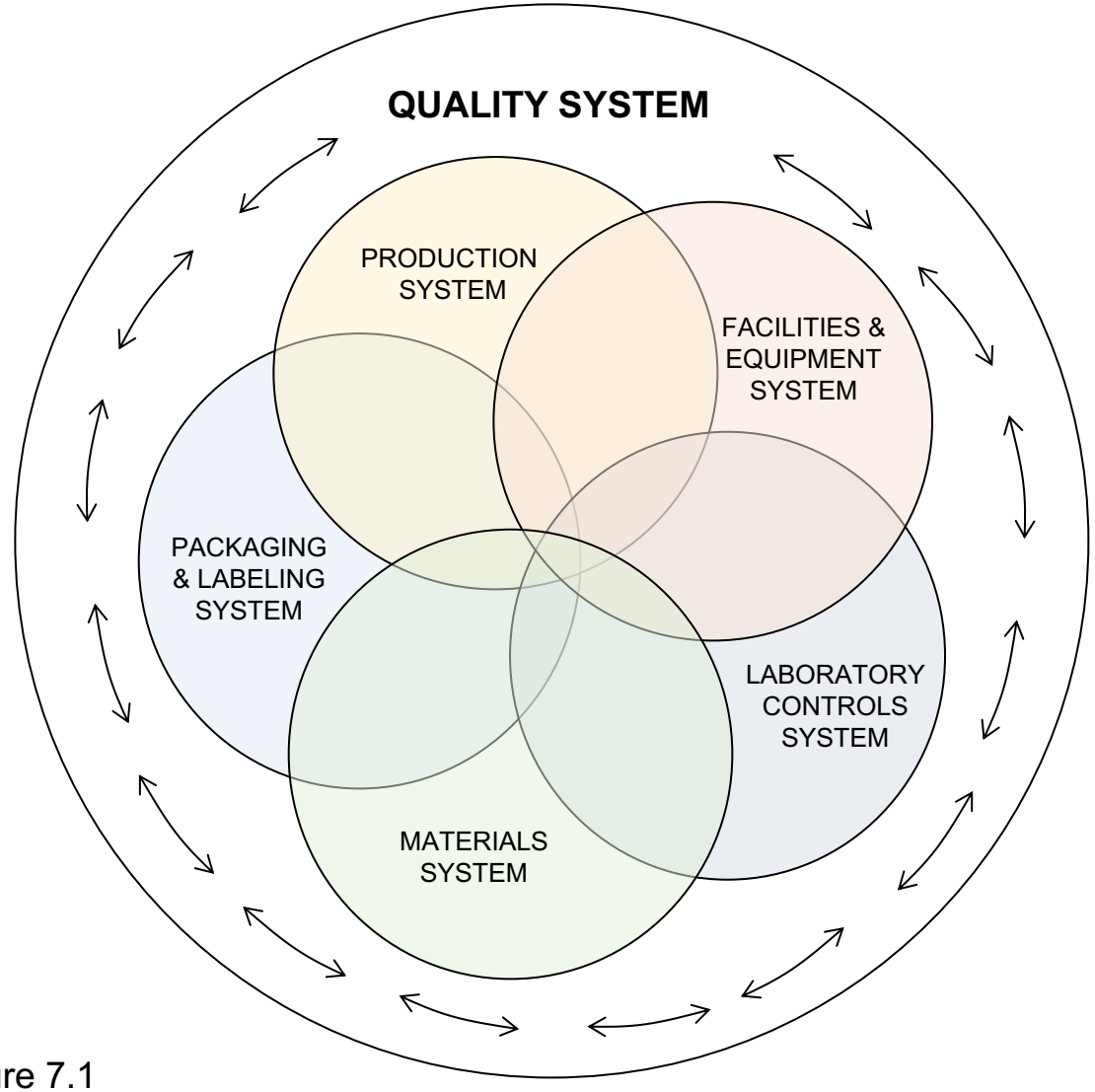


Figure 7.1

Device and diagnostic manufacture regulations

- The QSR rules for device development and the cGMP rules for pharmaceuticals both have a common goal – to ensure that the manufacturer has put a set of reproducible processes in place to safely and reliably make commercial devices on which people's lives depend

Quality System

Major subsystems that form the basic foundation of a medical device firm's quality management system:

I. Management Controls
II. Design Controls
III. Corrective and Preventive Actions (CAPA), and
IV. Production and Process Controls (P&PC).

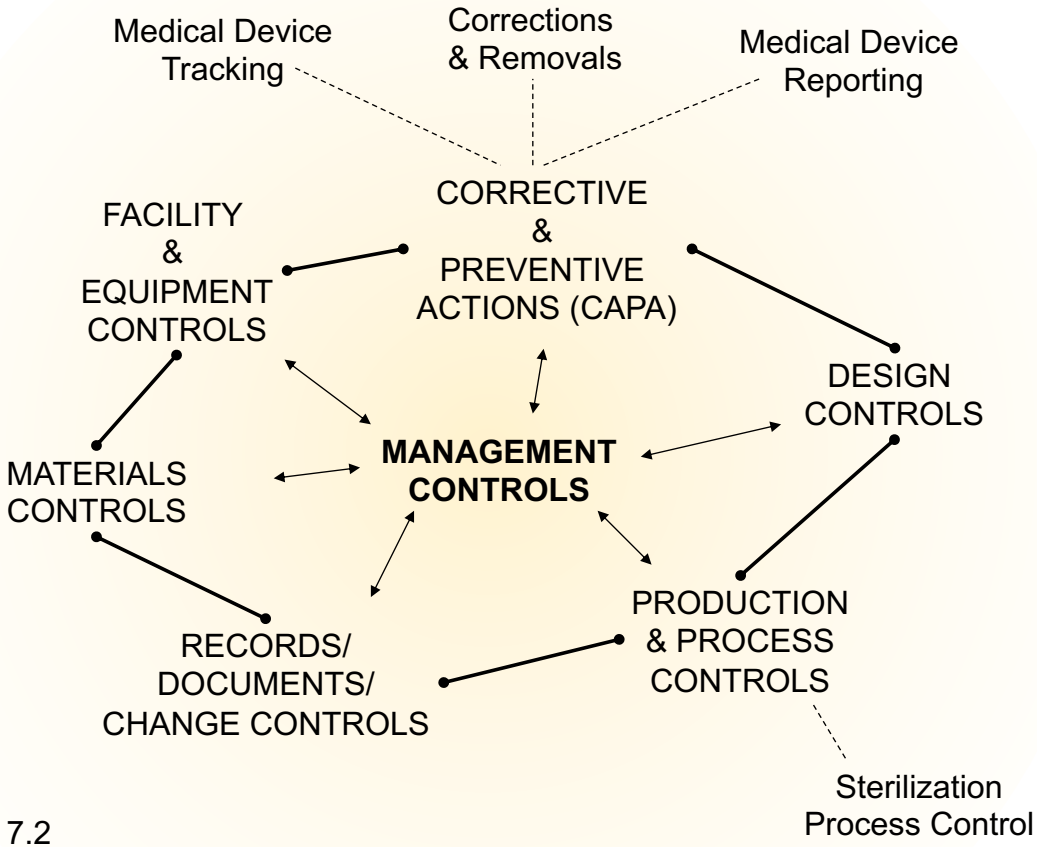


Figure 7.2

Manufacturing standards

- Standards are useful tools to communicate between groups
- Can be used to set thresholds of acceptance.
- Demonstrate compliance to regulations
- Give assurance to the users who see a certification of having met a recognized standard, on the product.

Standards can be classified into:

Process standards

Testing standards

Product or service standards

Who sets standards?

- Various professional bodies in different fields set the standards.
- International Organization for Standardization (ISO) produces the largest number of internationally recognized Standards.
- ISO is a non-governmental organization

Professional societies have committees that meet regularly to set and update standards. For example, the American Society for Testing of Materials (ASTM)

- The best practical ways to find the standards that should apply to the product being developed:
  - ✓ Check FDA special controls and other guidance documents.
  - ✓ Check industry association
  - ✓ Examine existing marketed products and associated literature
  - ✓ Speak to insurance companies as to their requirements to insure your facility or your products

What are “clean room” standards?

- An important segment of standards applies to the manufacturing environment
- Clean rooms are frequently used in final manufacture of biomedical products. A clean room is an environmentally controlled area that has a low level of environmental pollutants such as dust, microbes, aerosol particles and vapors. Clean rooms have special air handling systems
- The clean room environment can be a small room or can be an entire manufacturing plant.
- The class of a clean room is determined by measuring the number of particles greater than 0.5 microns in 1 cubic foot of air. The clean room classifications (under the U.S. standards) range from Class 1 (1 particle/cu-ft of air) to Class 100,000 (100,000 particles/cu-ft of air).
- ISO Class 1 (0 particles >0.5 microns/cu-m of air) to ISO Class 9 (35,200,000 particles).

ISO 13585 standard for medical device manufacturers

- ISO 13485 is the ISO standard for Quality Systems that medical device manufacturers have to have in place, in order to comply with regulations internationally
- The ISO 13485 based quality system required for medical device manufacturers internationally, includes most of the requirements of ISO 9001 but adds a specific focus on documentation and safety requirements in the quality system and related management controls.

Manufacturing in drug development

Small molecule drugs are made in large-scale chemical reactors, filters, and dryers in chemical factories.

Elements to monitor in the final output are: by-products of the chemical reactions, removal of all solvents, and other properties of the API molecule, such as appropriate chirality or mix of enantiomer (impacts biological activity of the drug), crystalline forms of compound, purity of final product, and other parameters.

Biological drugs are typically made using bacterial or mammalian cells, with a selected cell line grown in a tailored and controlled environment. A whole bioreactor is filled with these cellular mini-factories, each cell secreting multiple quantities of the desired

Elements to monitor in the final output are: more complex like protein mass spec analysis; real time process monitoring is of importance to ensure reproducibility.

Commercial manufacturing planning

A typical commercial manufacturing plan includes:

- Product development/approval timeline
- Commercial Forecast (number patients, dosage/s, regional requirements)
- Commercial product definition (marketed package)
- Target commercial manufacturing concept (processes, scale, batch size)
- Supply chain (including make vs. buy, single/multi-source, strategic relations)
- Facility requirements (scope and capital estimate)
- Organizational requirements
- Cost of goods
- Commercialization estimate
- Risk management plan (including mitigation plans for highest risks)

The key issue here is the large investment needed ($15–$50 million) and the still-lingering uncertainty (the product still has an industry average of 50% chance of success at this point).

Drug Product Scale Up Quantities - Production Planning

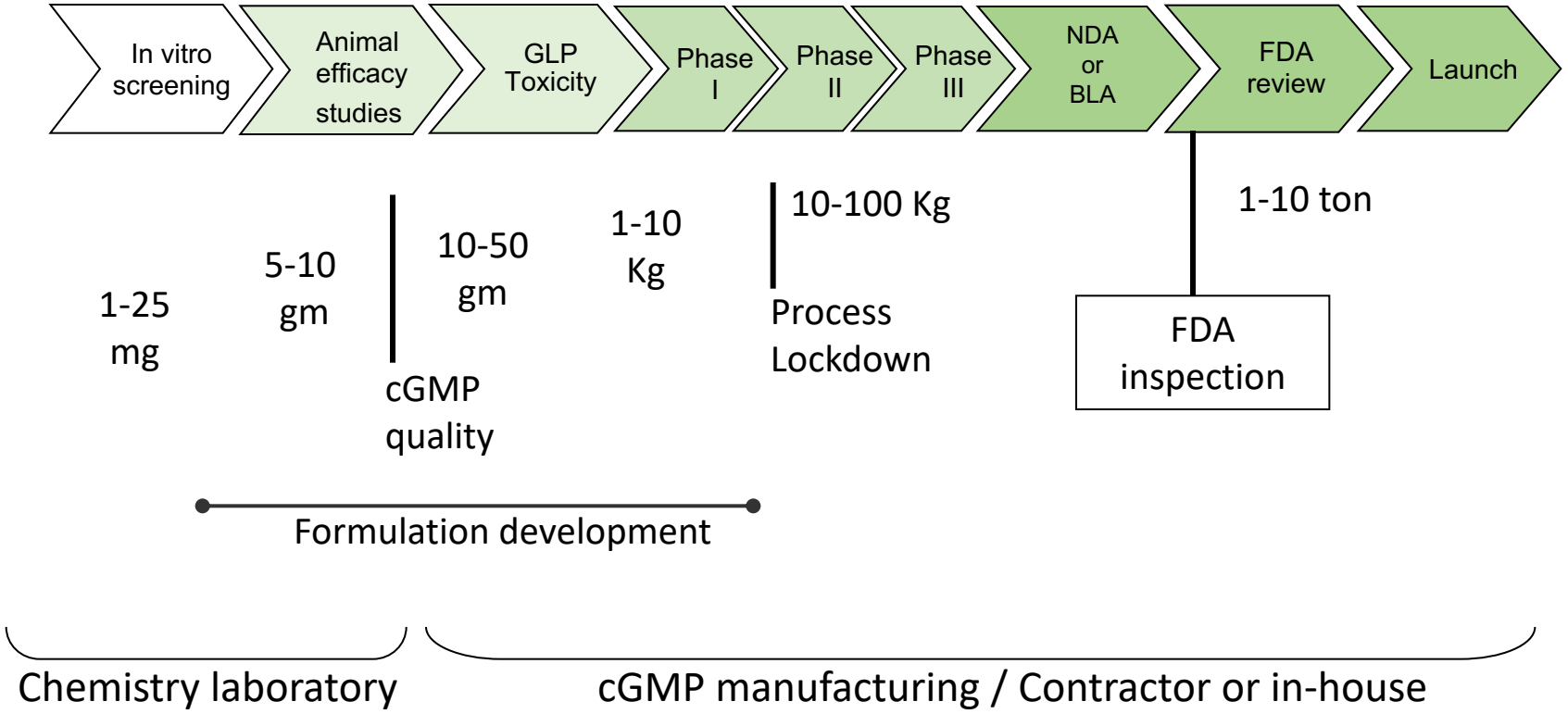


FIGURE 7.3

The buy vs build decision

- An important part of planning manufacturing activity is to understand the context of the manufacture for drugs
- Eg: barbiturates must be manufactured in a highly controlled and regulated environment, with only a few plants in the world currently configured to make those kinds of drugs
- The steps of packaging and filling usually require specialized plants and apparatus for these steps, and it is common to outsource these last steps of making the final oral (capsule, gel, tablet) or parenteral preparation to specialized filling facilities.
- Finally, the FDA will inspect the manufacturing site before approval of the drug for marketing.

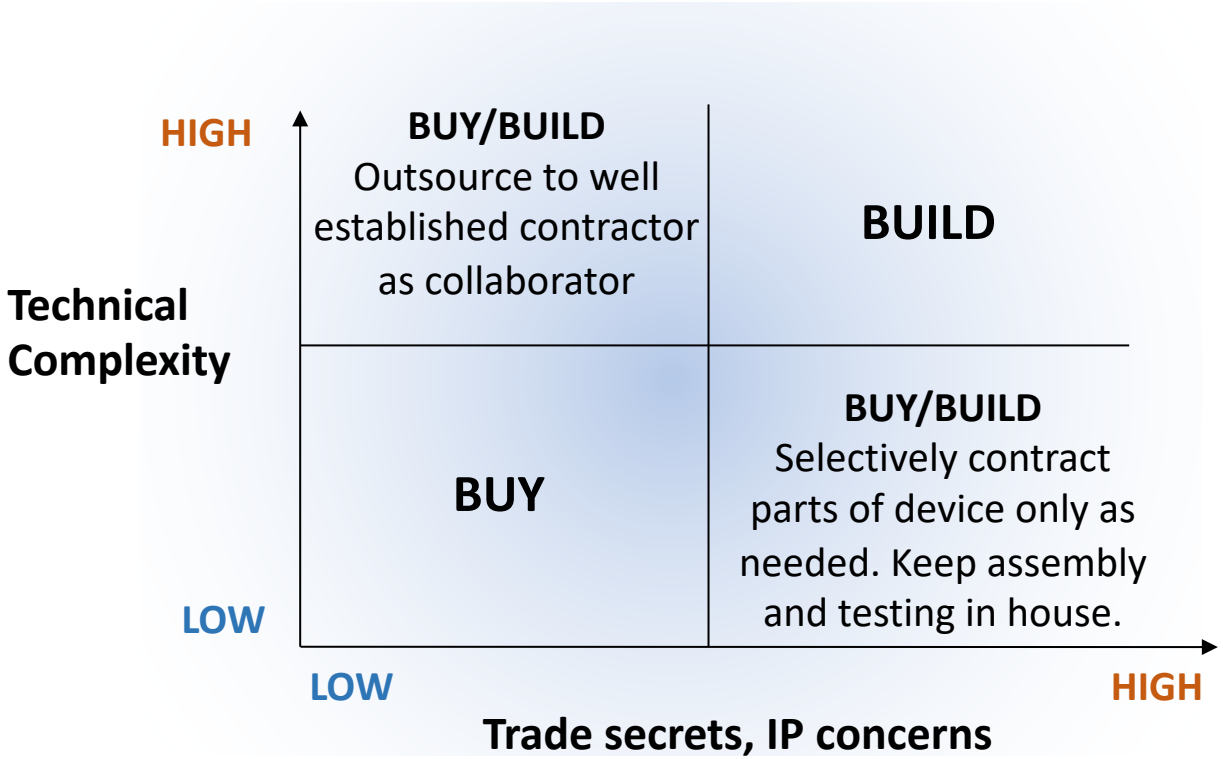


Figure 7.5

Manufacturing in devices and diagnostics

- Early prototypes are made in machine shops and used for proof of concept testing and design optimization,
- Pilot production needs could be met without full GMP processes,
- GMP-compliant production facility will be needed to make validation batches of products

- At the pre-manufacture stage,

  ✓ Verify and validate (V&V) customer needs

  ✓ Verify and Validate (V&V) needs translated to design requirements and performance

  ✓ Material selection

  ✓ Preclinical testing

- Make tens-hundreds of devices during early stage preclinical testing.
- Several hundred more under GMP to complete human clinical studies.
- This count includes product used internally for reliability testing, production lot sampling and units kept aside for stability testing
- Gain confidence in design and understand manufacturing process parameters
- Improve process consistency early to minimize changes after clinical trials

Packaging and sterilization

- Depends on the product design
- Packaging depends on sterilization method
- The design should be reviewed with a “manufacturability” lens early in the iterative design process

Medical Device Scale Up Quantities - Production Planning

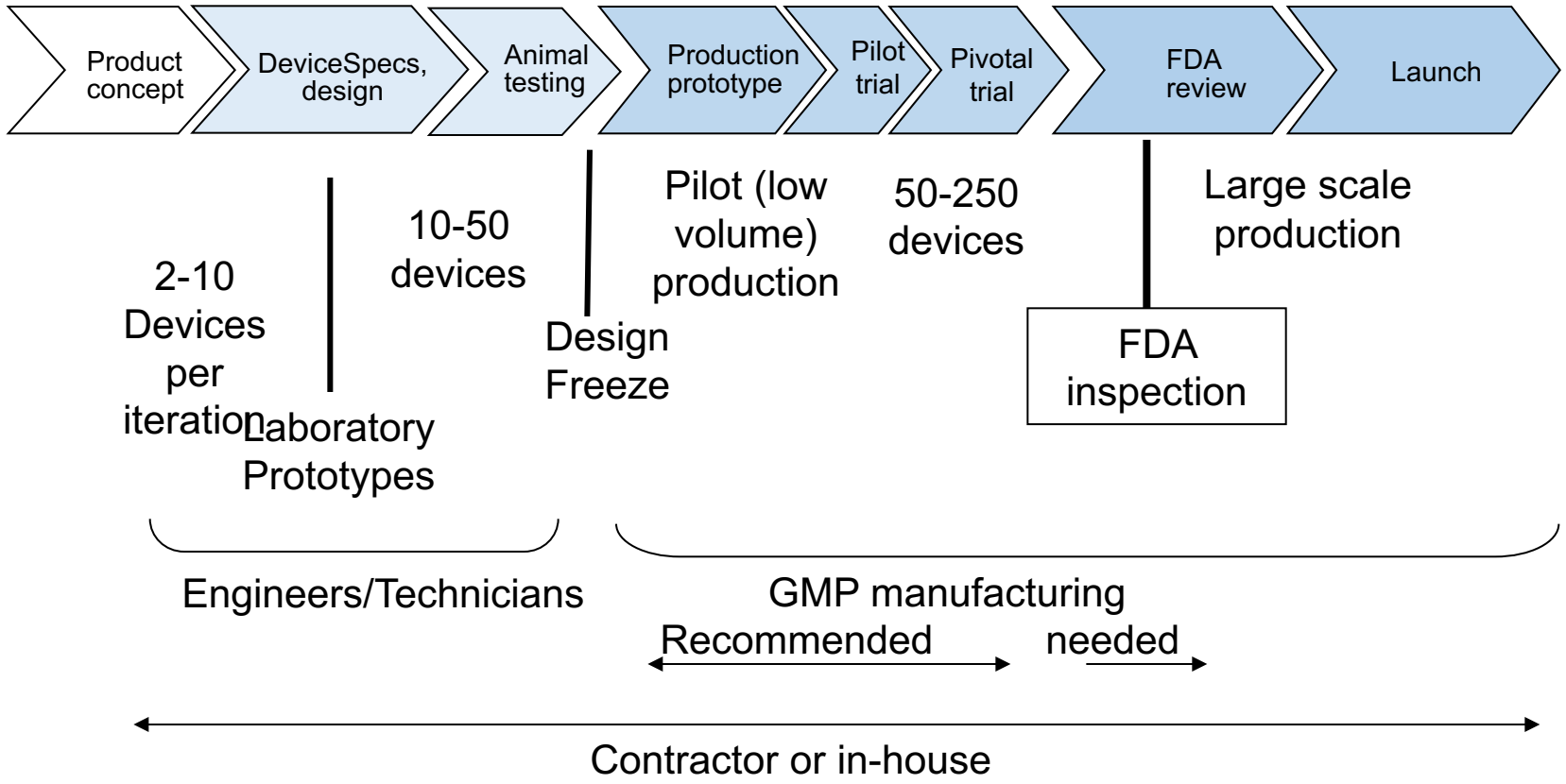
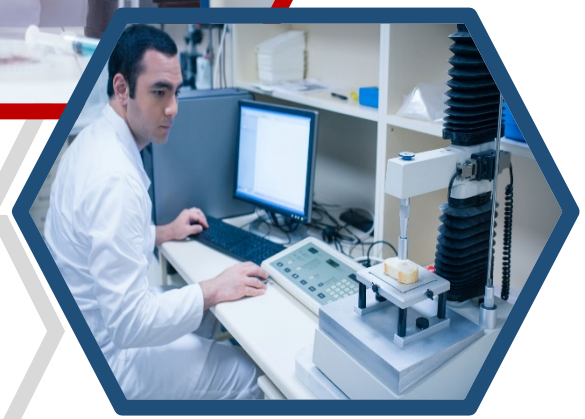


FIGURE 7.4



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Thank you…