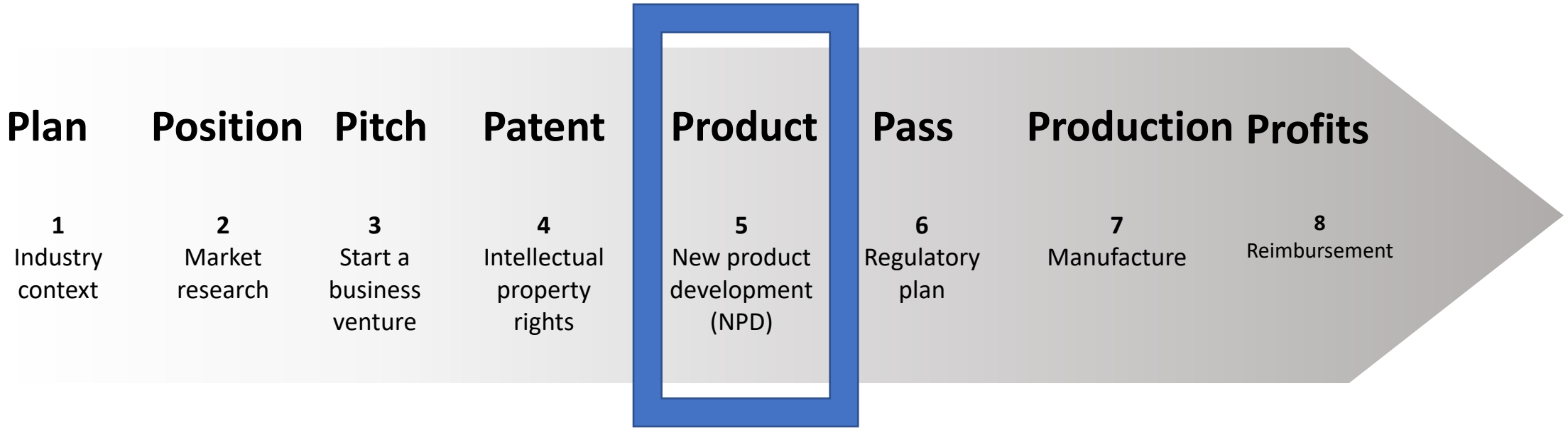
Commercializing Successful Biomedical Technologies 2nd Ed.

Shreefal Mehta



© 2022 Shreefal Mehta

Commercializing Successful Biomedical Technologies

Shreefal Mehta

Chapter 5

Why have a new product development (NPD) process

- Developing new products requires input from, and interaction with, almost all functions in a company.
- Most large companies will have an integrated multidisciplinary product development team or a review board.
- If you are in a small company, you still need to consider the product from the viewpoint of all these disciplines.

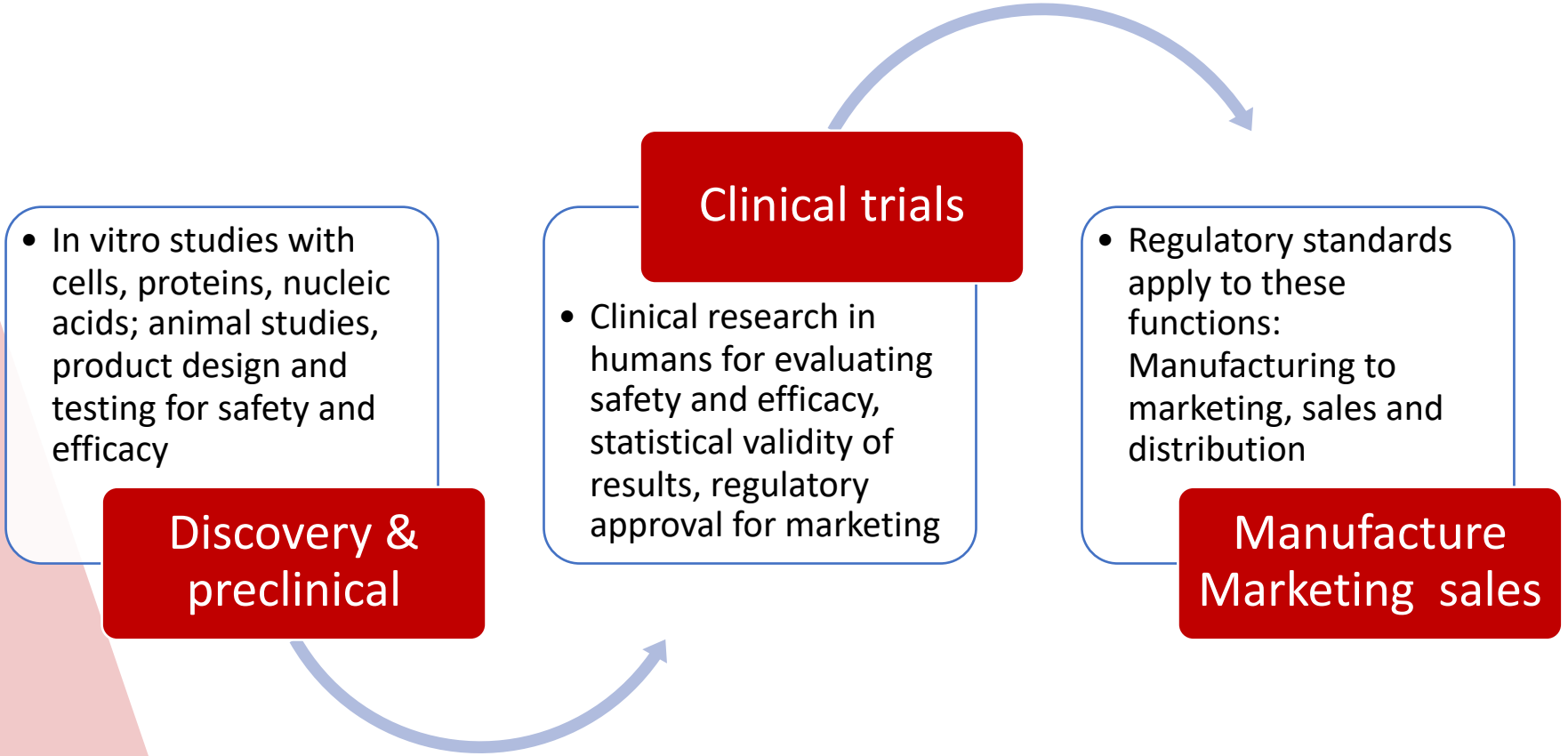
The goals of investing in creating and maintaining a process for new product development (NPD) are:

- ✓ Defined process is required and reviewed by the FDA
- ✓ To get quality certifications
- ✓ To define the product characteristics by writing out a target product profile (TPP)
- ✓ To bring products from concept to market
- ✓ To minimize time, effort, cost.
- ✓ To ensure quality and safety

Unique features of NPD process for biomedical technologies (drugs, devices, and diagnostics)

- A development scientist or engineer can better design a successful product if they have an understanding of the target market and its needs.
- The management team engages in strategic planning and thinking about new product development

There are three functionally different stages, each with regulatory controls:



© 2022 Shreefal Mehta

Product development process - getting started

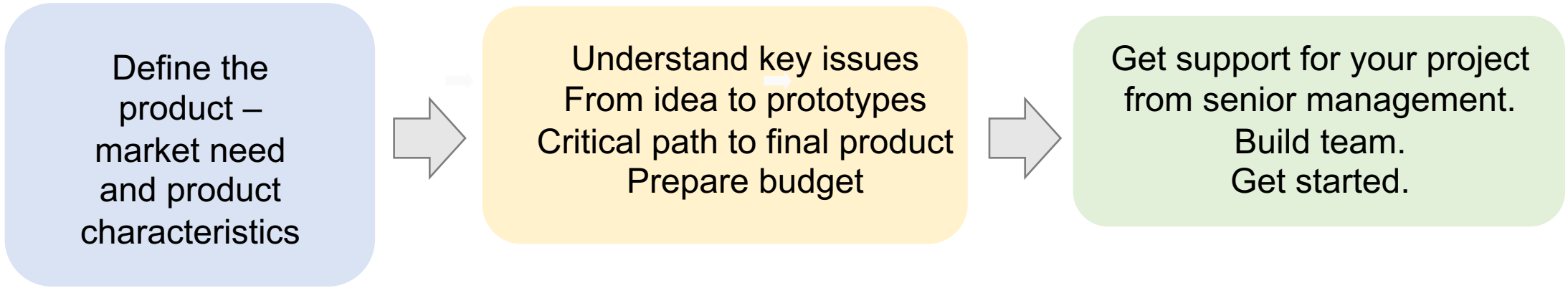


Figure 5.3

© 2022 Shreefal Mehta

The project proposal document

INPUT

- Company strategy, business model
- Product life cycle
- Market research
- Indication and market expansion
- Unknowns and uncertainties in process
- Process steps and milestones
- Time and cost
- Regulatory strategy
- Reimbursement issues

Product development planning

PROJECT PROPOSAL

- Product definition
- Markets addressed
- Significance to company (fit with technology platform, strategy)
- Business case (revenues, profitability projections, market positioning)
- Key milestones and risks
- Timeline
- Budget
- Team requested

Planning for product development and proposal inputs

© 2022 Shreefal Mehta

Product life cycle planning

- Each product has a reasonably well-defined life cycle from concept to market, to peak sales, and finally to declining sales and obsolescence.
- The new product must fit into the current product line and market-based development cycles
- ***Life cycle planning strategy for a device might be to develop a broader, technically complex, fully configured platform at the first run and then introduce various parts/features***

Market research inputs

- The market research should :
- Identify the product characteristics and define the product and target market
- Define primary indication and indication expansion strategies.
- Design tools such as a **"house of quality"** can be used to synthesize product characteristics obtained from **market research** inputs

© 2022 Shreefal Mehta

Identify key unknowns and risks

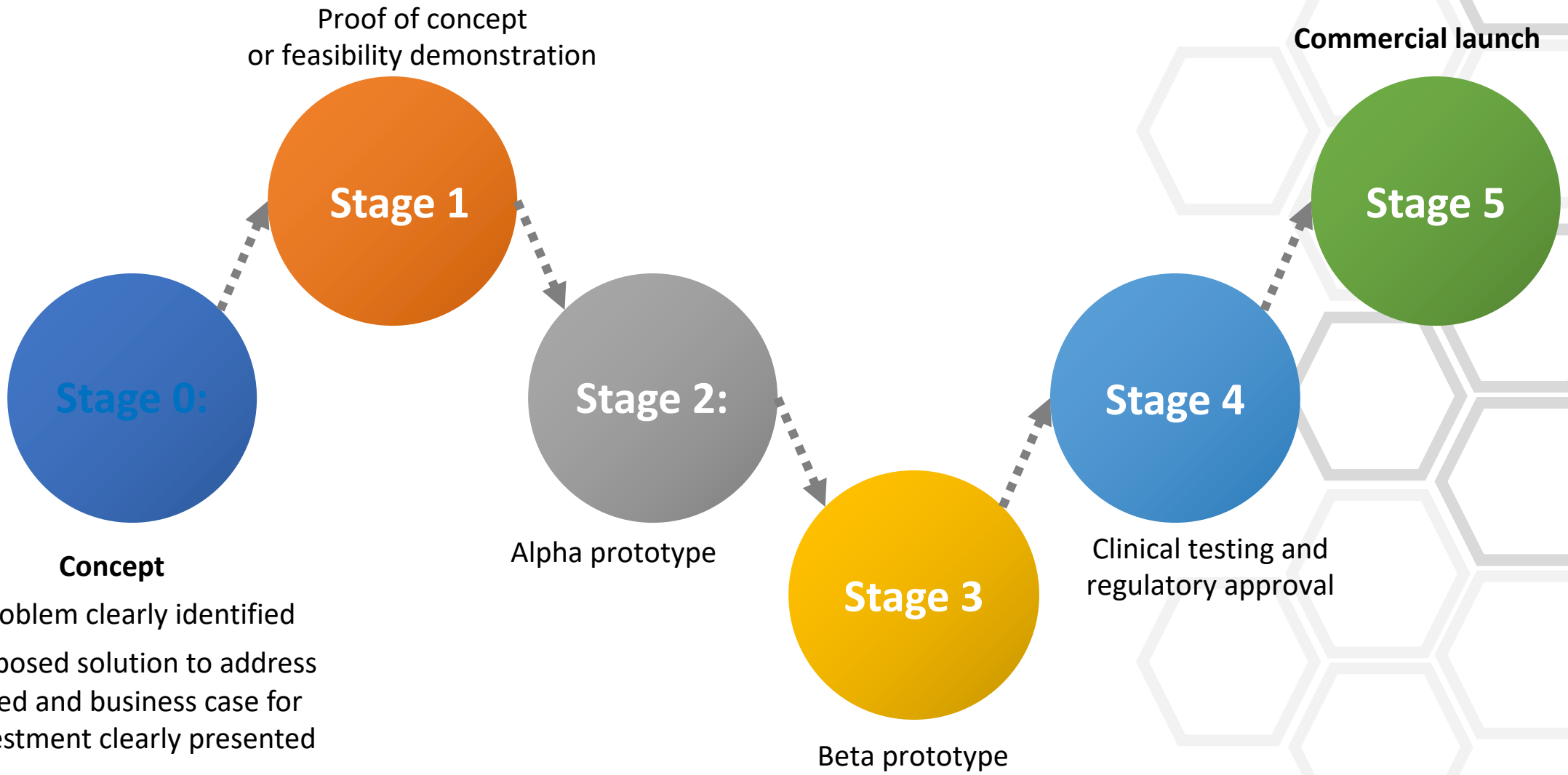
- Knowing where the hurdles are makes it more likely that the choices will enable a successful product launch.
- Major risks such as toxic side effects must be addressed as early as feasible.
- Identifying key unknowns can help to clarify the priorities of the development testing and studies.

Build a milestone-based plan for product development

- Milestones are results of tests that show key reductions of risk in NPD.
- Milestone for a device could be the successful mechanical testing of the device functions in repeated cycles
- A milestone for a drug could be the demonstration of efficacy in an animal model showing improvement
- The more specific the milestones, the easier it will be to build a convincing NPD plan.

© 2022 Shreefal Mehta

PRODUCT DEVELOPMENT STAGES



© 2022 S r efal Mehta

Specific risks

Factors that prevent <u>drug candidate molecules</u> in development from reaching the market:

- Poor ADME characteristics
- Lack of efficacy
- Toxicity
- Market or business reasons

Factors that cause <u>medical devices</u> to fail in development

- Failed to meet efficacy
- Safety, toxicity or instability in device behavior/mechanics
- Biocompatibility
- Business or market reasons

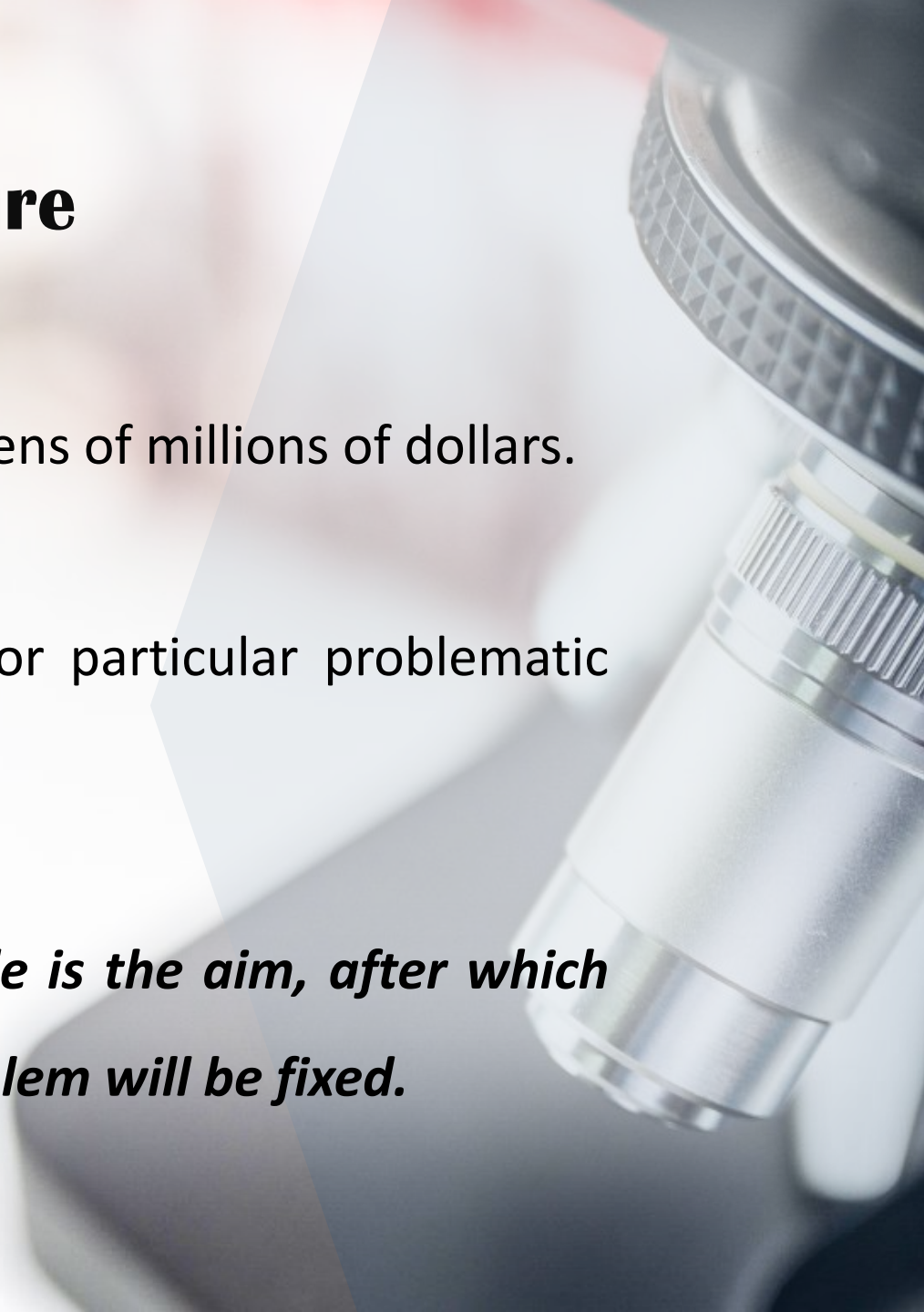
Factors that cause <u>diagnostic products</u> to fail in development

- Lack of clinical utility
- Needed sensitivity/specificity of the assay not verified in subsequent clinical studies.
- repeatability and precision not achieved
- Wrong test principle
- Wrong test format
- Test is too complicated versus existing format
- Nonlinear response of assay in clinical use
- Patents are not comprehensive or valid

© 2022 Shreefal Mehta

Early failure is better than late failure

- Clinical testing for medical products can go into tens of millions of dollars.
- Testing early for well-known safety issues or for particular problematic elements is of great importance.
- ***Correctly identifying the risk as soon as feasible is the aim, after which the project will either be abandoned or the problem will be fixed.***



Uncertainty-based view of product development processes

There are four main uncertainties in all product development

- Resource uncertainty
- Organizational uncertainty
  - Occur because the project may not have the right amount of funding
  - The team in charge of the project may disband
  - market channels may be new or unknown

- Technical uncertainty
  - addressed by engineers and scientists
- Market uncertainty
  - can be factored into the product development processes and product definition

} Management can control

} Management has to adapt and adjust

© 2022 Shreefal Mehta

Uncertainty-based view of product development processes

Types of risk/uncertainty

- Technical uncertainty
- Market uncertainty
- Resource uncertainty
- Organizational uncertainty

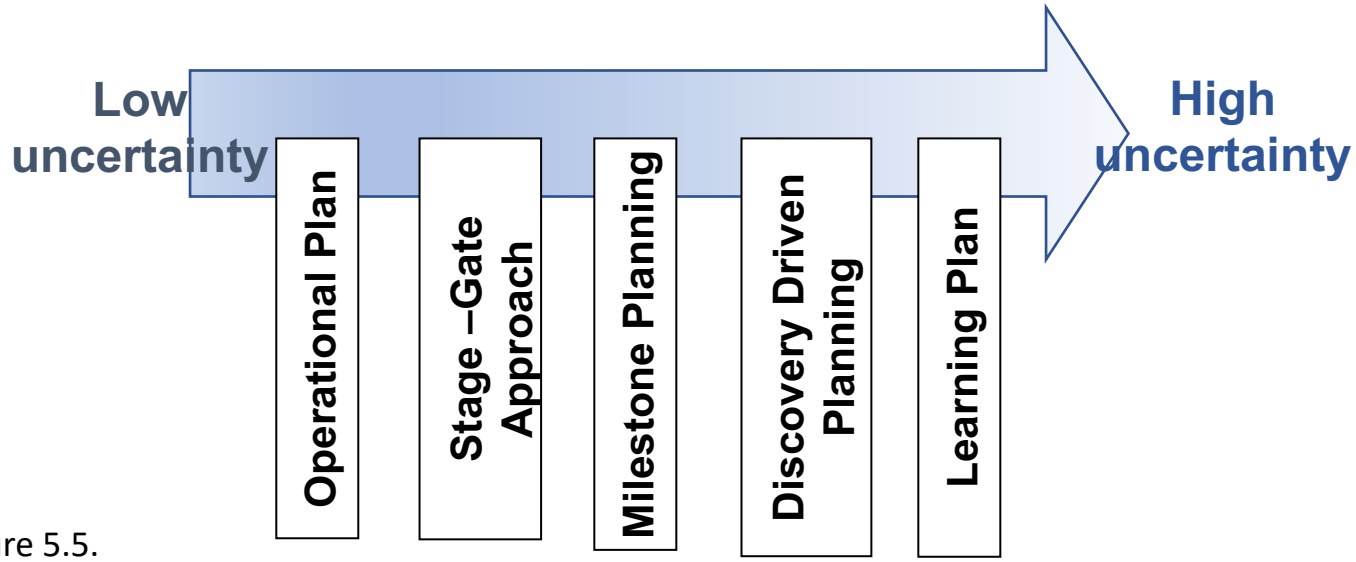


Figure 5.5.

Stage-gate Process

- Well-suited for biomedical product development.
- The regulatory gatekeeper (FDA) forces specificity and focus of application very early on in the development process

© 20

Stages and gates

- Stages are key areas of activity that define a functional area or focus.
- Gates are the decision-making evaluation points for each stage.

e.g. If a diagnostic test cannot demonstrate reproducibility to a certain level, then it cannot move on to clinical testing.

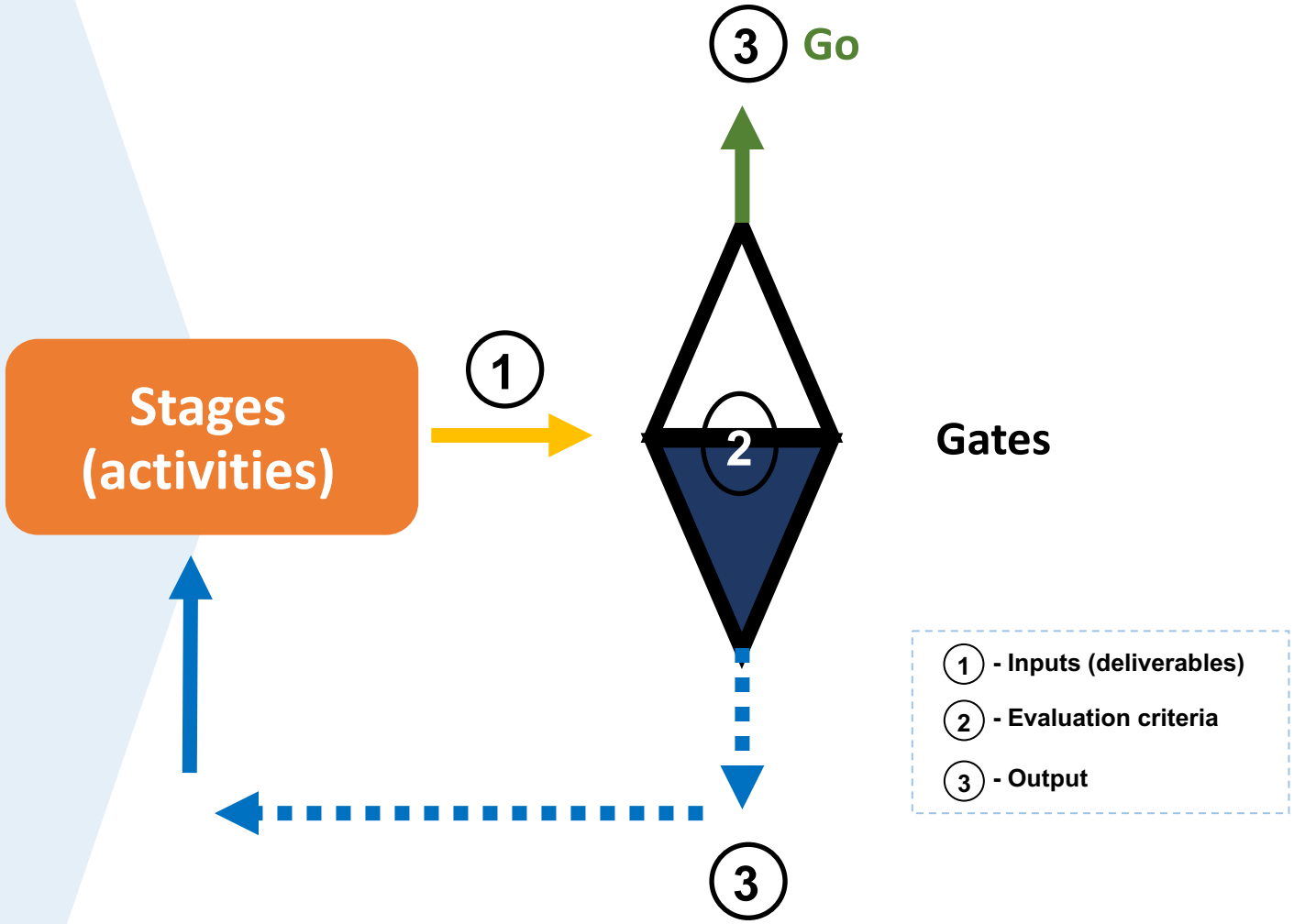


Figure 5.6

Stage-Gate process

© 2022 Shreefal Mehta

PRODUCT DEVELOPMENT STAGE GATE GENERAL MODEL

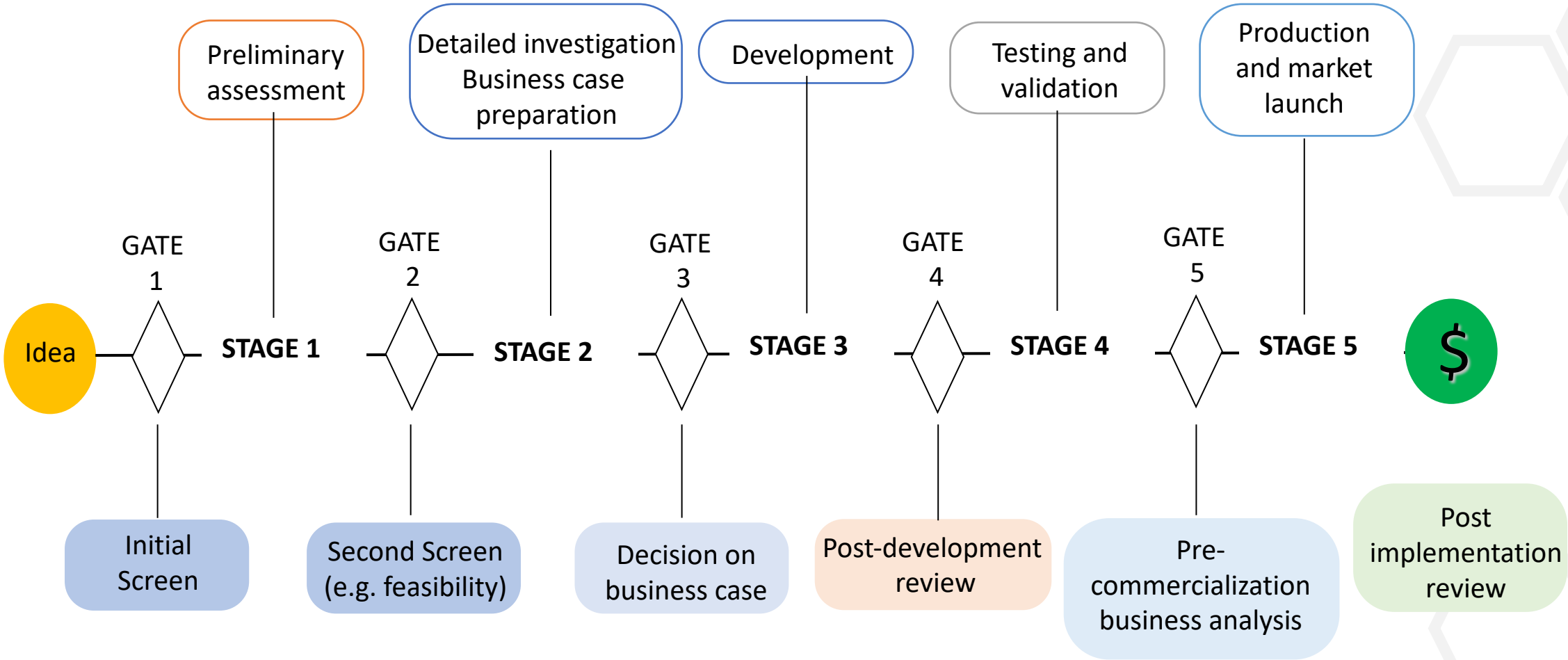


FIGURE 5.7

© 2022 Shreefal

Stage-gate process plan

- The stage-gate plan is the first plan for product development, identifying activities, success criteria and key milestones.
- It is useful for generating milestone-based budgets, resource-allocation plans, and critical path timelines for project management.
- Each company will have different processes and variations of the stages in place.

Unique features of biomedical development

- The regulatory review of data to obtain market approval is a unique feature of all regulated biomedical products
- The FDA reviews data that spans most of the development process and it is important to keep detailed records of a drug or device's development.
- Once the product is in final preparations to enter human clinical testing, the design is in effect "locked in"
- There are benefits to the public and eventually to the manufacturer, from this onerous regulatory process.

Ethical requirements in biomedical product development

- Ethics considerations formally enter the NPD process at the time of preclinical testing of a drug or device and continue through the clinical development and post-approval stages.

- If product development proceeds without regard to general ethical principles, the company can face negative consequences including a complete halt of all product development activities.

IACUC

IRB

©

IACUC

- Institutional Animal Care and Use Committee (IACUC) will review the specific study protocol.
- An animal care program must be managed in accordance with applicable federal, state, and local laws and regulations.
- The IACUC approves any experimental procedure that involves vertebrate animals.
- The IACUC reviews facilities and study protocols for the following:
  - ✓ Minimum standards of care and treatment.
  - ✓ Research facilities meet required standards of veterinary care and animal husbandry, etc.
  - ✓ Minimize the pain or distress caused by research or valid

IRB

- An institutional review board (IRB) review and approval of any study protocol that involves interactions with human subjects is required by the FDA.
- IRBs that approve studies of FDA-regulated products must be established and operated in compliance with 21 CFR (Code of Federal Regulations) part 56.
- IRB ensures that the rights and welfare (safety) of the subjects participating in a clinical trial and it also verifies that the sponsor has obtained all necessary permissions from the FDA.

Define the product and process

Indications and Endpoints

Indication: ***T*****he disease condition for which the product is approved to be marketed.**

- Each new indication for the same product needs a separate application to the FDA by the developer.

Endpoints - **The final statistical analysis of the study outcome, on which the approval is based.**

- Market research helps to identify the endpoints and specific indication.
- The product development plan and in particular the clinical studies are designed to reach a statistically significant endpoint.
- The final claim (marketing, efficacy, etc.) will depend completely on the evaluation of set of endpoints.
- Surrogate endpoints, typically used in drug development. statistically significant endpoints are useful for gaining market approval from the FDA.

© 2022 Shreefal Mehta

Define the product and process (Contd.)

Target product profile (TPP)

"The Product Profile (TPP)"- **is a detailed analysis of a potential new product in comparison to competitors and the existing standard of care.**

- The TPP identifies the primary indication, key claims or benefits over competitors and mechanism of action. It also lists the desired clinical outcomes or endpoints for human trials for registration.
- The TPP provides a framework that ensures that a company's product development program is efficient.

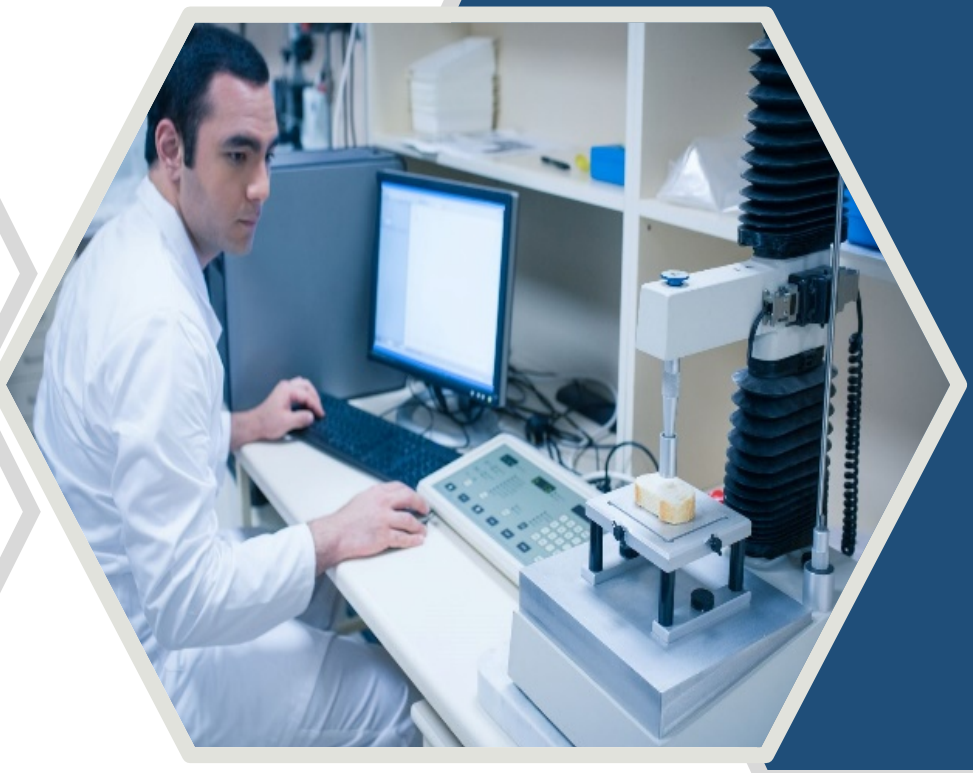
Minimum viable product (MVP)

"Minimum Viable Product" (MVP)- **partially completed product that has essential features for the application -** Depending on the product, a "minimum viable product" launch may be a part of the product development plan in the TPP.

- MVP launch for market and product learning is more commonly use in the software industry whereas Digital Health Software is a relatively new phenomenon in the biomedical industry.
- Example: LDTs are like an MVP launch for diagnostics. The laboratory-developed test (LDT)s are like an MVP launch of the in-vitro diagnostic test under development, allowing the market to learn more about the desired final product performance.

© 2022 Shreefal Mehta

Drug Product Development Process



Drug development process costs

- It takes 8-10 years for drug development, from the definition of the problem and identification of drug target to market approval from the regulatory body. The process has been estimated to cost over $800 million

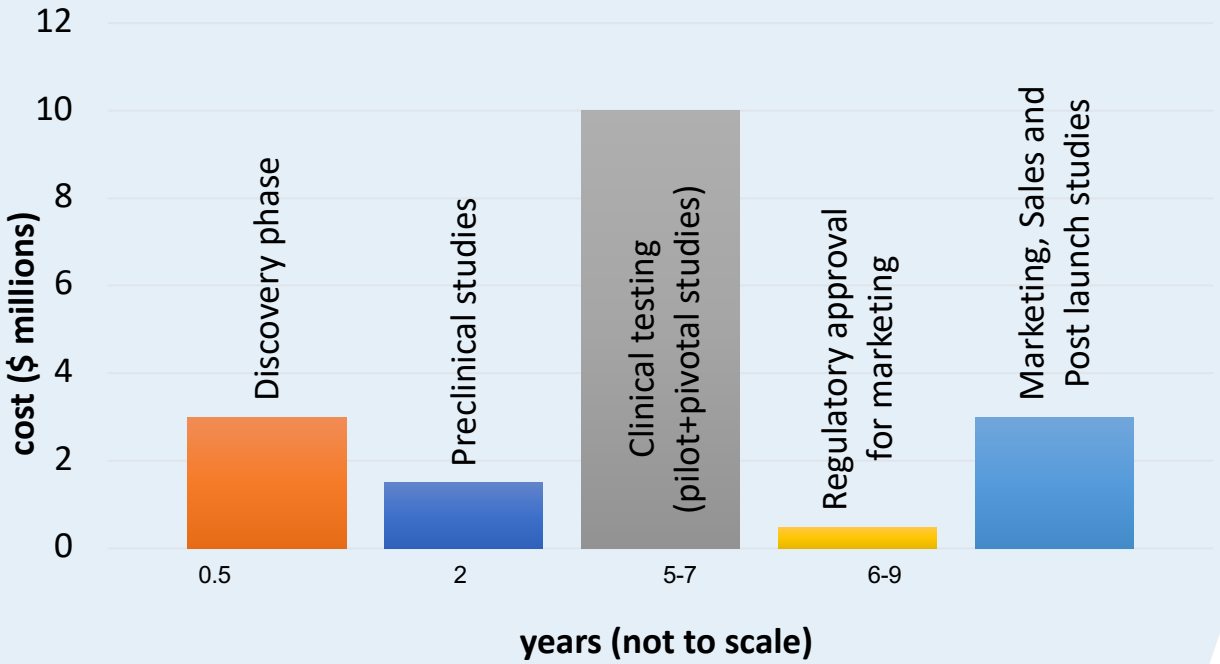
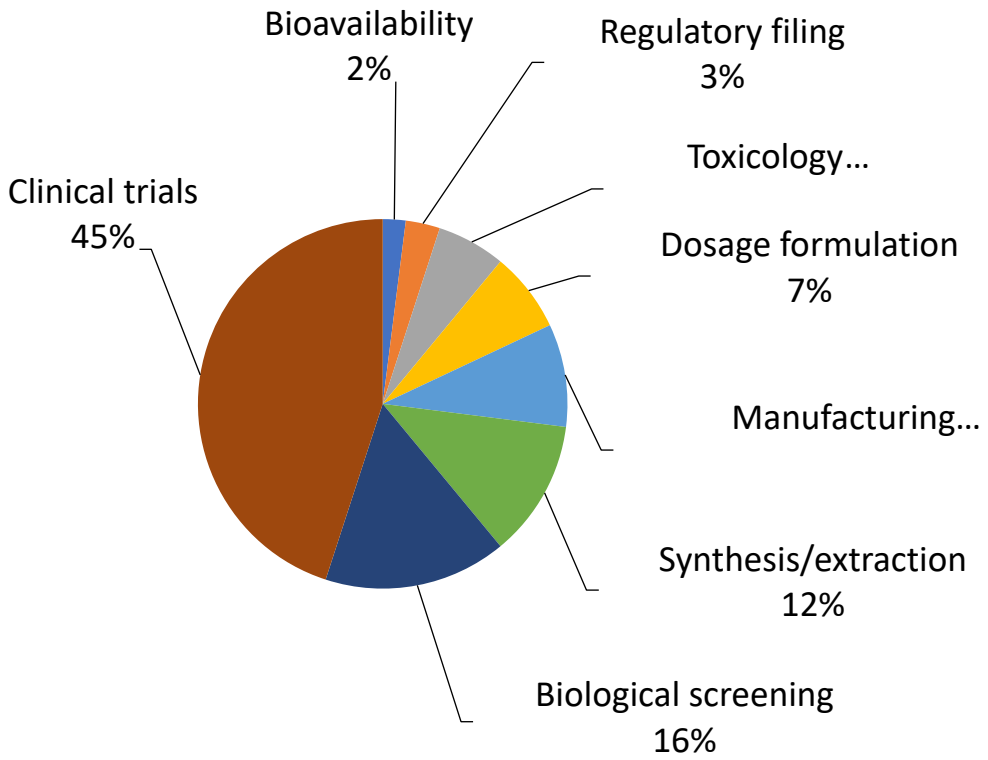


Figure 5.8A



Pie chart illustrates, in percentages, the allocation of development costs. Data from Parexel's Bio/Pharmaceutical Statistical Sourcebook (2005).

Figure 5.8B

Activities in drug development

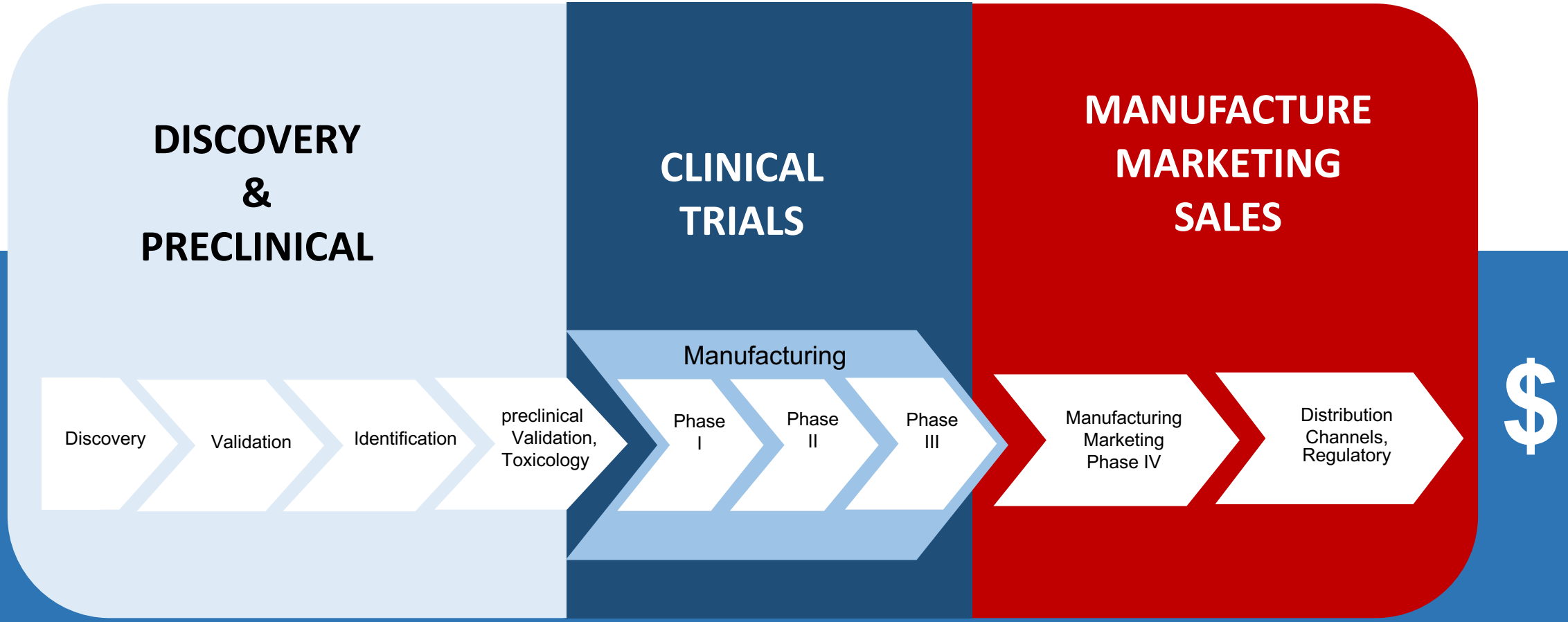


Figure 5.9

Discovery and preclinical testing

Target discovery and validation

- A drug development project often starts with the identification of a disease problem lacking adequate treatment.
- Discovery of new targets is likely to happen in corporate research settings as well.
- Once discovered, the target has to be validated – experiments must be carried out to show that changing activity of the target protein will affect the disease outcome positively.

Preclinical toxicity

- If the drug candidate has passed the screening gates on specific characteristics, then it enters a formal toxicity testing program and scale of production under regulatory guidelines.
- The drug molecule (active pharmaceutical ingredient or API) is tested as a product formulation (solid, liquid, suspension) with excipients.
- Toxicity testing usually requires studies on at least two animal species.
- Only FDA approved and inspected facilities can manufacture the drug compound for human testing.

Preclinical Drug Development Process

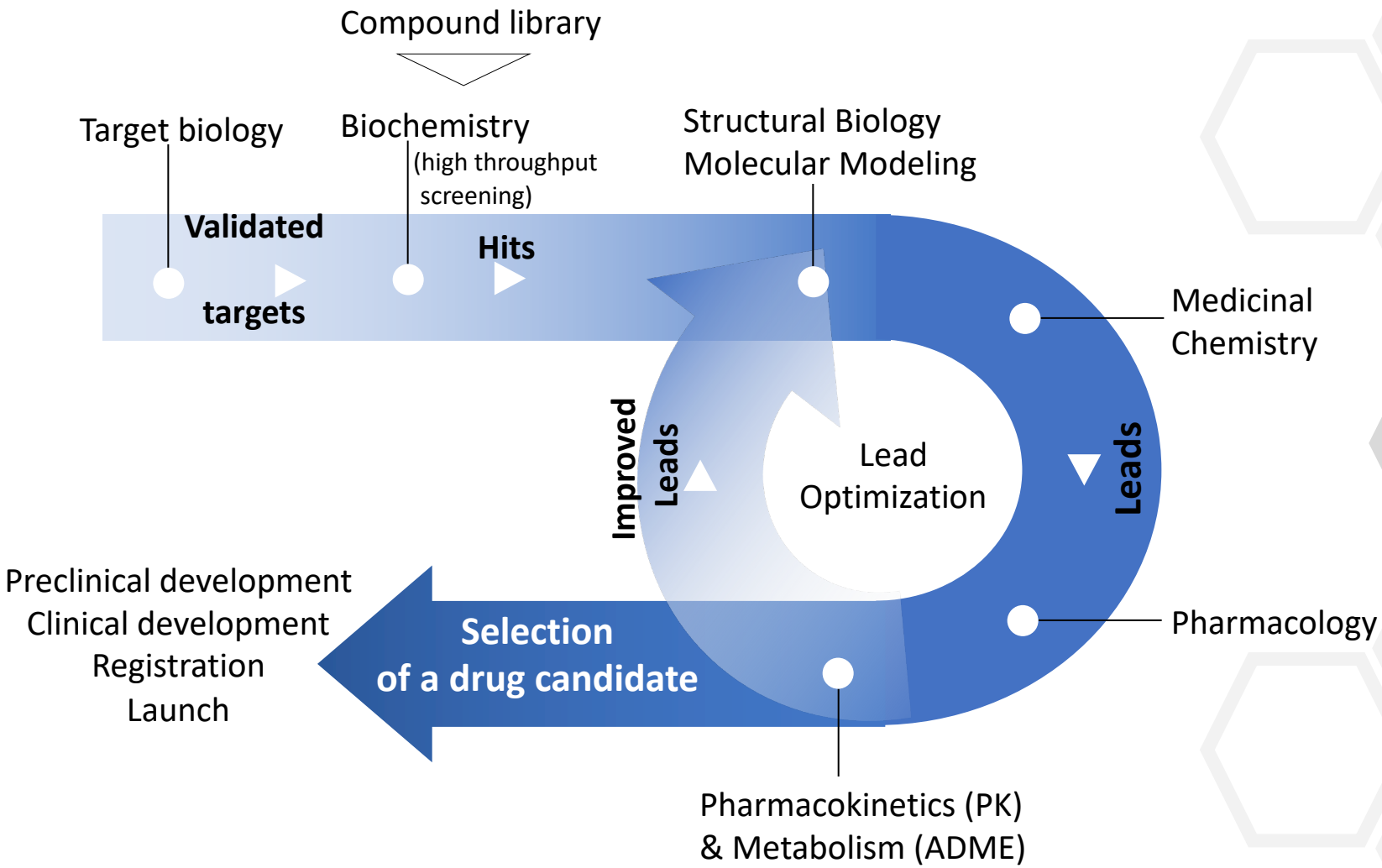


Figure 5.10

© 2022 Sarfaraz Mehta

Distinctions in preclinical development of biotechnology drugs

- A drug development project often starts with the identification of a disease problem lacking adequate treatment.
- Discovery of new targets typically in academia, but is likely to happen in corporate research settings as well.
- Once discovered, the target has to be validated – experiments must be carried out to show that changing activity of the target protein will affect the disease outcome positively.

Drug candidate clinical testing to market approval

- All clinical studies must be carried out using current good clinical practice (cGCP) guidelines.
- Planning for clinical studies usually must incorporate the following considerations.
- Clinical endpoints must be carefully selected
- Patient inclusion and exclusion criteria must be defined

- Clinical study design and protocol
- Size and length of the clinical study must be determined by a robust statistical analysis
- Data analysis techniques

© 2022 Sir efal Mehta

Stages/Gates for Drug Development

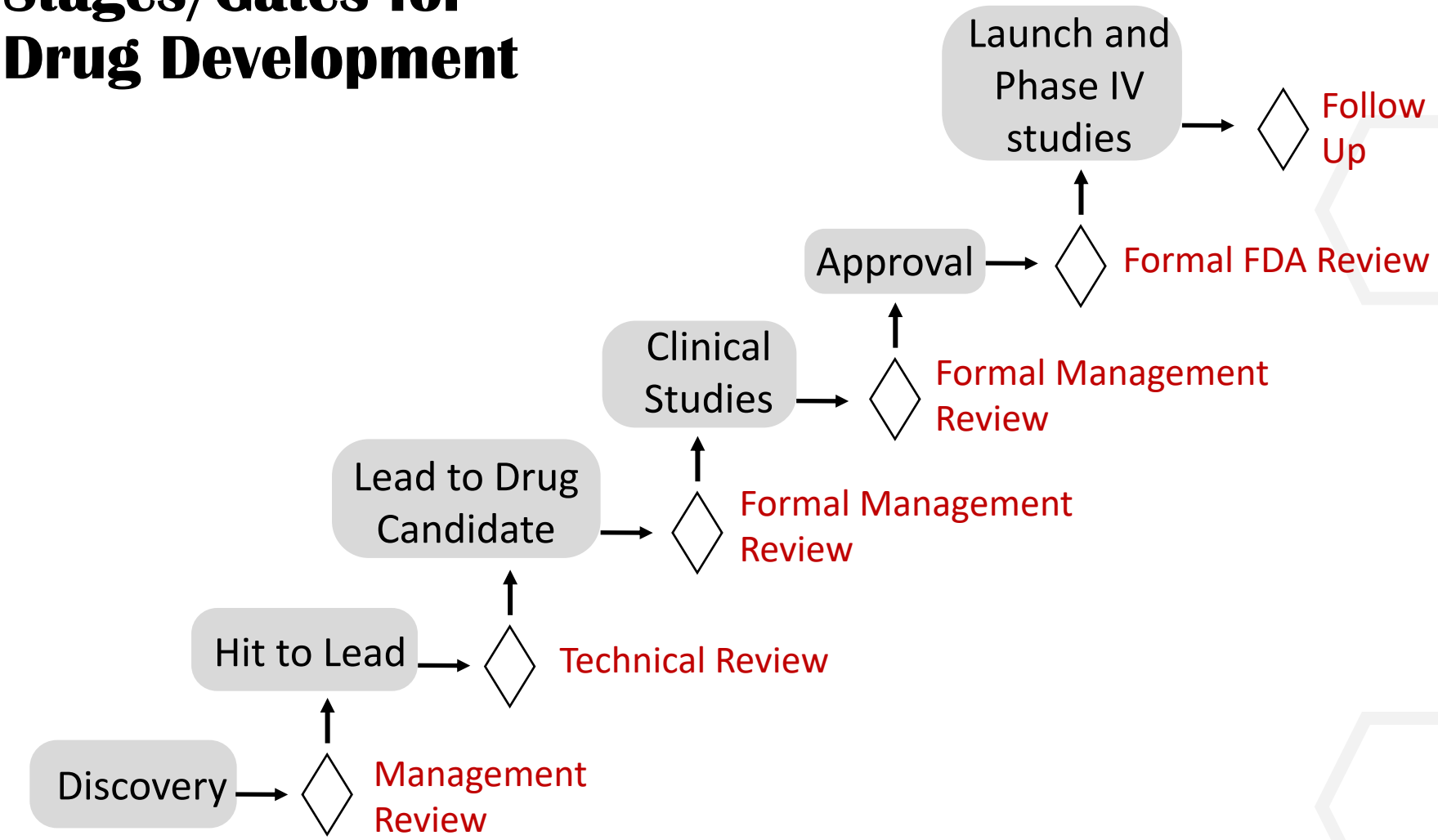
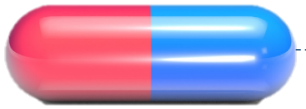


Figure 5.11

© 2022 Sunrefal Mehta



Stage 1

Gate 1

Target discovery and validation

Stage 2

Gate 2

Hit to lead

Stage 3

Gate 3

Lead to drug candidate

Stage 4

Phase I clinical studies

Gate 4

Stage 5

Phase II clinical studies

Gate 5

Stage 6

Phase III clinical studies

Gate 6

Stage 7

Phase IV – post-market approval clinical studies

Gate 7

No significant adverse event and no added toxicity finding. New indication added with selected patient group.

-Stage-gate criteria for drug development-

© 2022 Shreefal Mehta

Human clinical testing stages for drugs

Phase I Clinical studies

- The drug is first tested in a set of normal healthy patients to determine the toxic thresholds and thus define the therapeutic window for dosage.
- Lower bounds of the therapeutic window are set by the early cellular or in vivo animal experiments
- Upper bounds are set by these Phase I studies.
- Each participant is given a single dose and is closely monitored, If none adverse reaction occurs, the dose is progressively increased until a predetermined dose or serum level is achieved.

Phase 2 Clinical studies

- Phase II studies is to determine the correct dose–response range for the new drug and to verify its efficacy
- These studies are carried out in 20 to 100 patients randomly placed in placebo
- The data from this phase are crucial in determining whether to proceed with more extensive studies in large populations

© 2022 S r efal Mehta

Human clinical testing + Market launch

Phase III Clinical studies

- The Phase III studies are intended to verify the efficacy of the drug in much larger populations.
- When sufficient data are collected, a rigorous statistical analysis is carried out.
- Data and completed analysis are submitted to the FDA with a request for approval to market the drug.

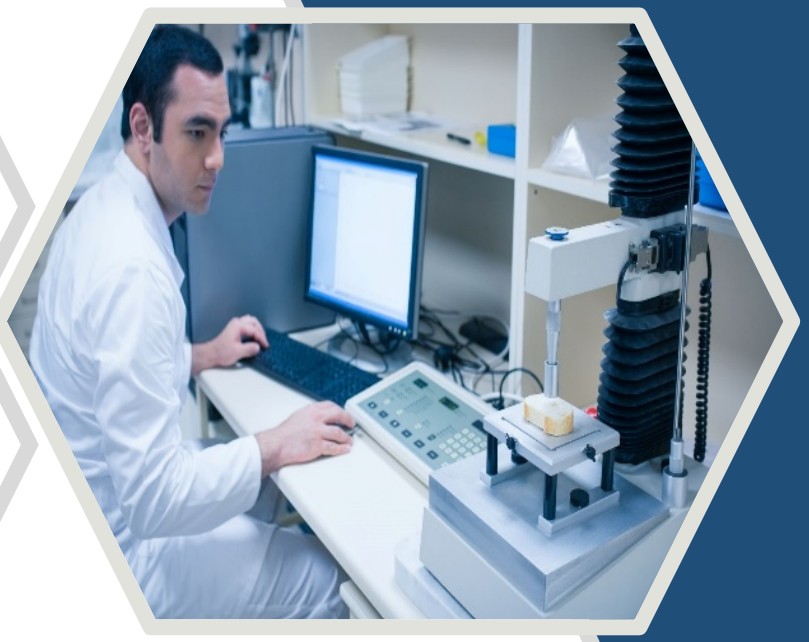
Phase IV (post-market) Clinical studies

- Studies that are conducted after the drug is marketed.
- The FDA's concern in sometimes requiring Phase IV studies is to monitor specific safety concerns.
- Reports must be sent to the FDA every 3 months during the first year.
- The sponsor must notify the FDA of any unexpected adverse effects, injury, and toxic or allergic reactions.

Manufacturing, marketing, sales, and reimbursement

- Manufacturing processes is carried out under strict quality-control guidelines and regulations approved by FDA.
- The API may be made at one site and combined with the excipients at another location.
- Labels and product brochures are sent to the FDA for review

Medical Devices Product Development Process



Typical device development process

- For medical devices, product development process is highly variable depending on type of product, its predicate history with FDA and its risk classification by the FDA.
- Determine if the product is a medical device as per FDA?? - Medical devices are classified as those products intended to affect the structure of any function of the body and which does not achieve its primary intended purpose through chemical action and which is not depended upon being metabolized for the achievement of its primary intended purposes
- Development can range from a few months to a few years and may cost from a few hundred thousand to millions of dollars.

©

Schematic of device development value chain / process

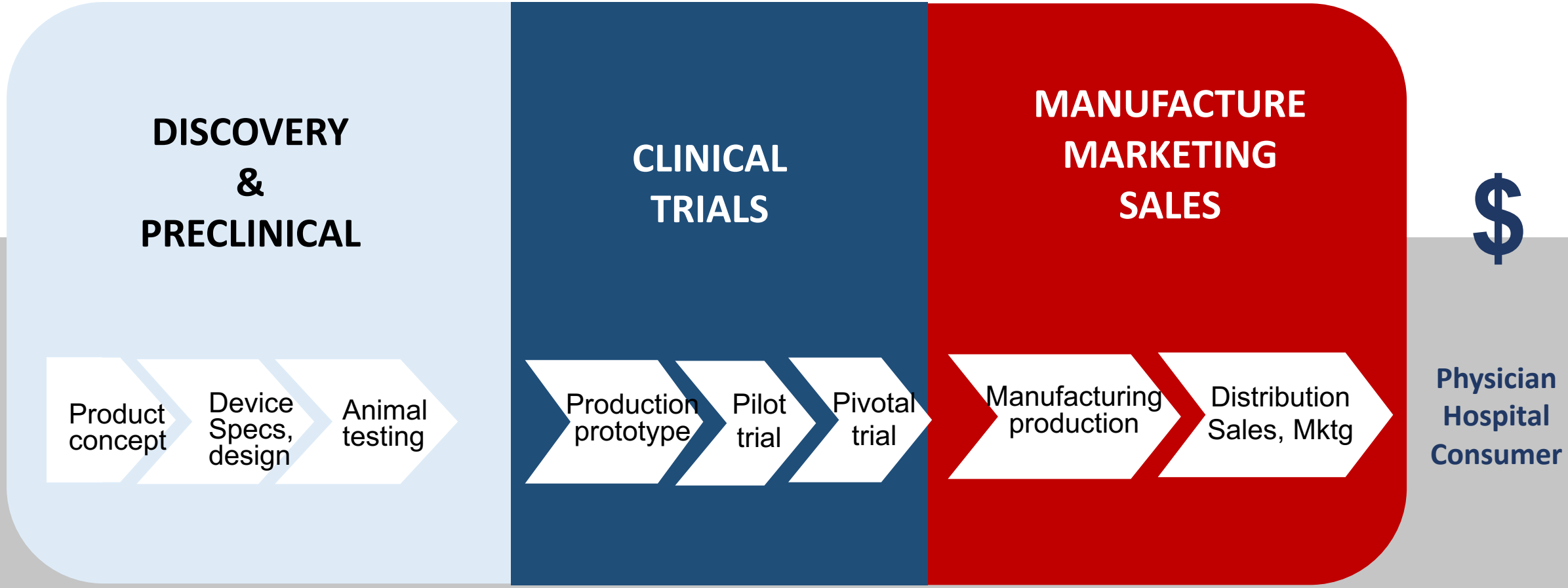


Figure 5.14

Discovery, feasibility, and optimization – design and preclinical testing

Product concept

- The idea for a product usually stems from an invention or discovery, or from examining the needs of caregivers in specific diseases, disorders, or treatment of trauma.
- Problems must be carefully analyzed to obtain the right product characteristics.
- The *indication* for the product and the *specific mechanism of action* are two key factors
- Market research and technology evaluation

Device design and specifications

- Controlled and regulated by the FDA
- Quality Systems Regulation Manual outlines the requirements
- The design process for devices also requires input from marketing, sales, manufacturing, and other corporate functions.
- Typical steps in device design are:
  - ✓ Identify the need and define the indication
  - ✓ Set design objectives/constraints
  - ✓ Devise alternative solutions and analyze
  - ✓ Evaluate solutions, make decisions, communicate through the Product Design Specifications doc (PDS)

Medical Device Design Process

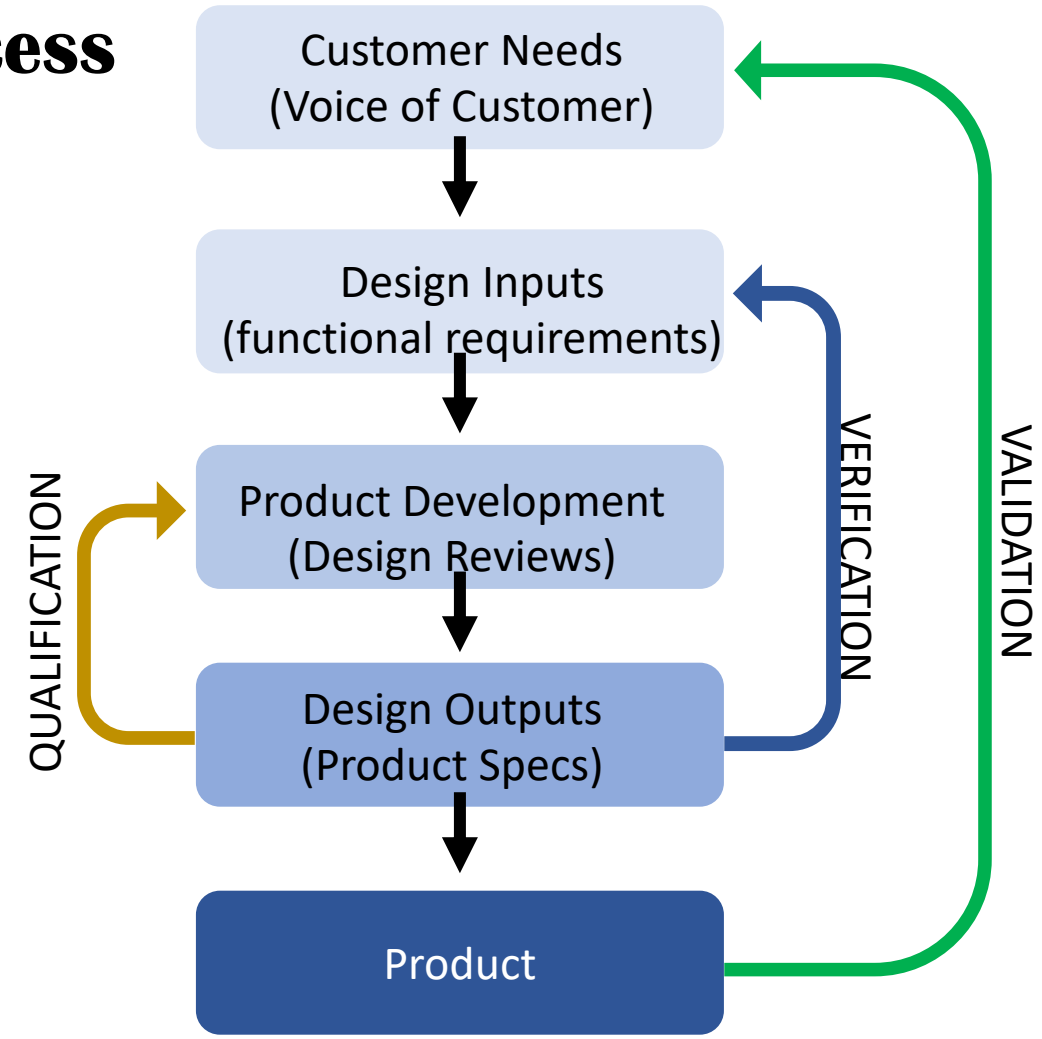


Figure 5.15

© 2022 S ır efal Mehta

Stages/Gates for Device Development

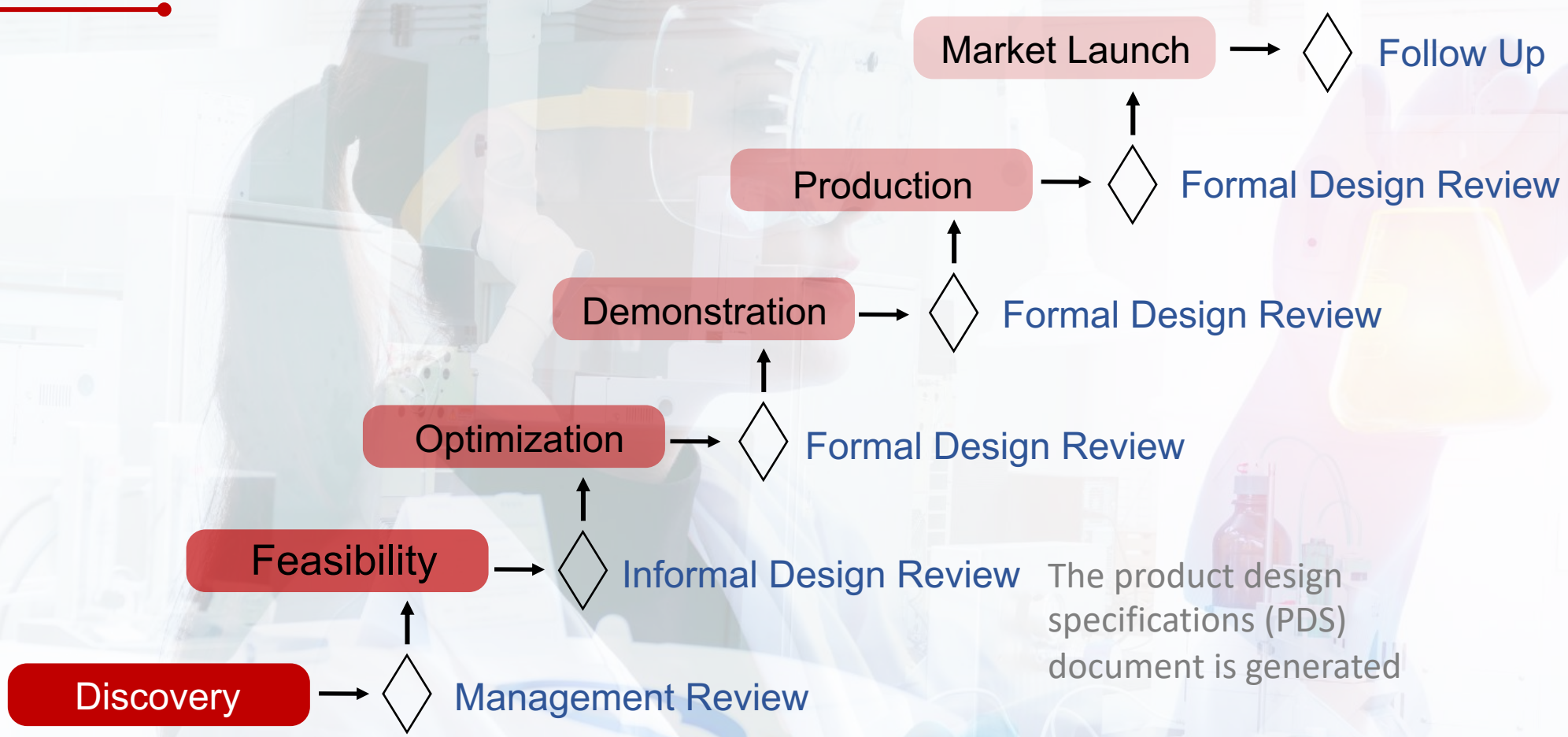


Figure 5.16

Animal and toxicity testing

- Device prototype is evaluated in animal models before the final production run.
- Specific biocompatibility and toxicology or safety tests will depend on the type of device.
- In general, biocompatibility/toxicology tests include the following:

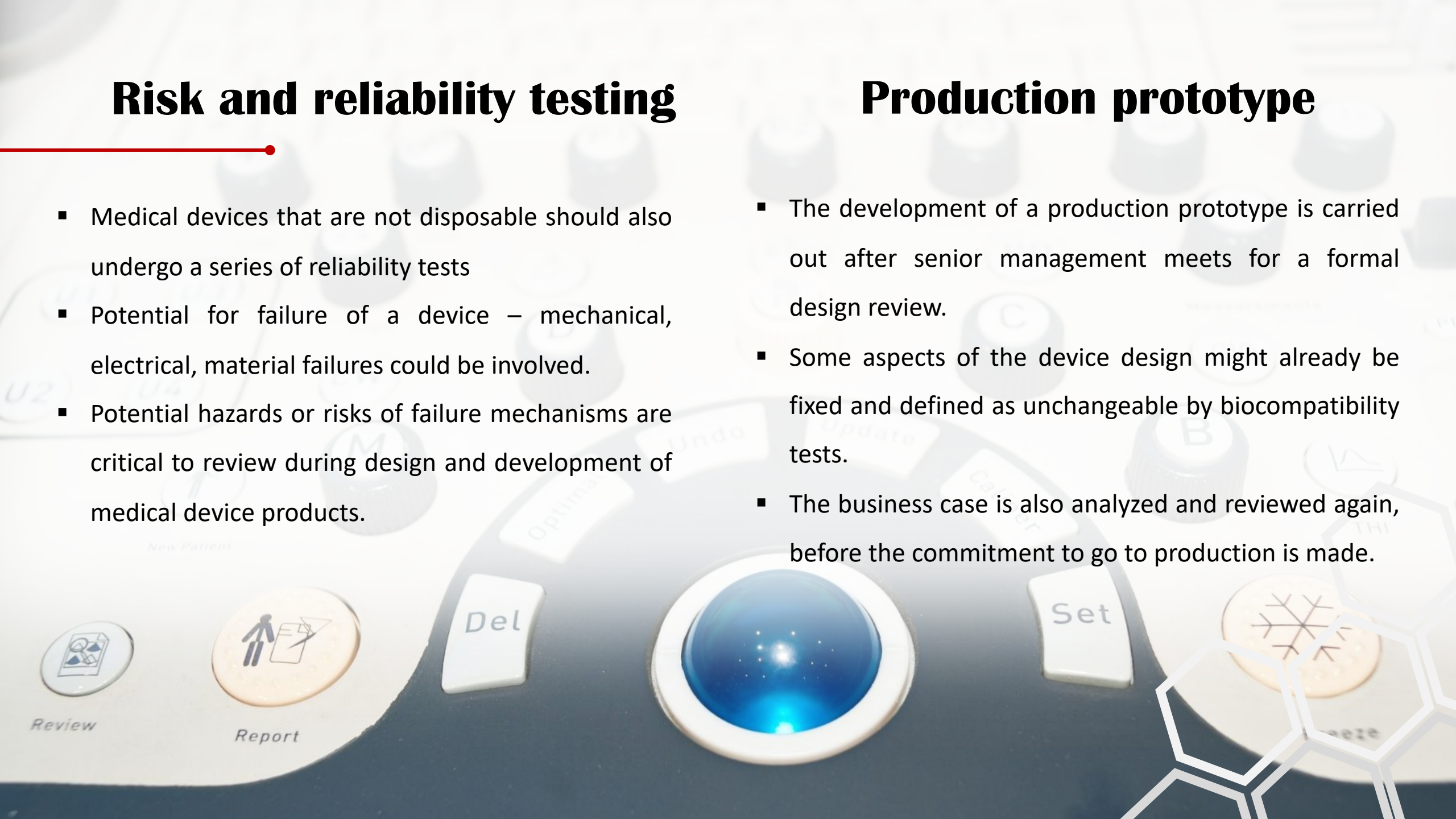
  - Acute, subchronic, and chronic toxicity
  - Irritation to eyes, skin, and mucosal surfaces
  - Sensitization
  - Hemocompatibility
  - Genotoxicity
  - Carcinogenicity
  - Effects on reproduction including developmental effects
  - Specific organ toxicity/effects as needed

Risk and reliability testing

- Medical devices that are not disposable should also undergo a series of reliability tests
- Potential for failure of a device – mechanical, electrical, material failures could be involved.
- Potential hazards or risks of failure mechanisms are critical to review during design and development of medical device products.

Production prototype

- The development of a production prototype is carried out after senior management meets for a formal design review.
- Some aspects of the device design might already be fixed and defined as unchangeable by biocompatibility tests.
- The business case is also analyzed and reviewed again, before the commitment to go to production is made.

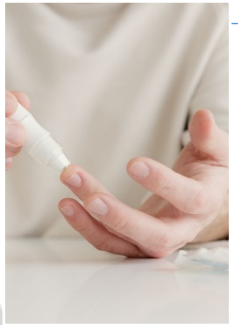


Special considerations for device clinical trial design

Clinical trials

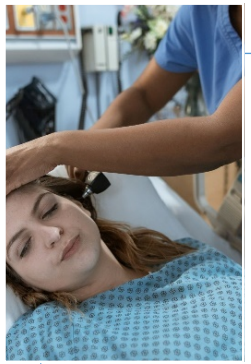
Device trials

- Typically have a short safety or biocompatibility study (comparable to Phase I trials in drugs) and a pilot efficacy or feasibility study (Phase II in drug trials) followed by a larger pivotal clinical study (Phase III in drug trials) that compares the safety and efficacy of the new device to the current standard of care.



Randomized trials

- Patients are randomly assigned to only one device or treatment regimen.
- Since a placebo group cannot usually be included, some trials have no choice but to compare results against historical data.



Crossover study

A patient sequentially receives more than one device or treatment regimen in the clinical trial and effectively serves as their own control.

© 2022 Shreefal Mehta

Clinical trial objectives

- The purpose of the study is explained in terms of its goals scientifically.
- Objectives should provide support for the intended use of the device, including any desired labeling claims.
- Claims can be supported statistically by formal hypothesis testing or by point estimates with corresponding confidence intervals.
- Hypothesis should be formulated with extreme care and specificity to effectively evaluate a particular type of intervention.
- A question such as “Is my device safe and effective?” is far too general to be meaningful.

© 20 Shreefal Mehta

Control groups

- Every clinical trial intended to evaluate an intervention is comparative, and a control exists either implicitly or explicitly.
- The safety and effectiveness of a device is evaluated through the comparison of differences in outcomes (or diagnosis) between the treated patients and the control patients.
- There are many types of control groups.

(i) No treatment

(ii) Placebo control

(iii) Active treatment control

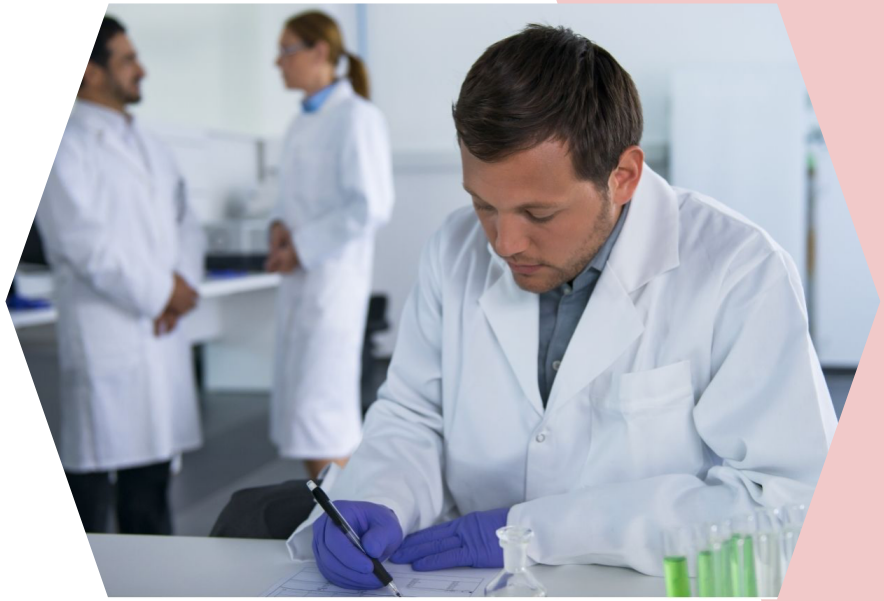
(iv) Historical control

(v) Subject as own control

© 2021 Shreefal M

Device manufacturing

- Manufacturing a medical device has to be done in accordance with FDA guidelines (cGMP) and regulations
- These guidelines are known as current good manufacturing practices (cGMP) and each facility that is certified by the FDA is regularly inspected.

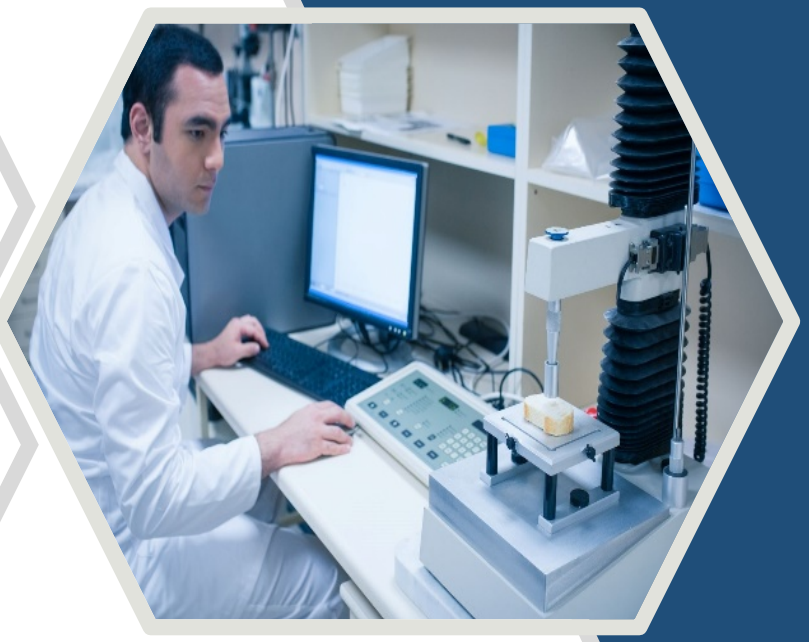


Keeping records for the FDA

- All clinical trials and preclinical studies must be carefully documented for review by the FDA.
- Records are maintained in four different formats
  - DMR : The device master record
  - DHF : Design history file
  - DHR : Device history record
  - TDF : Technical documentation file

© 2022 Shreefal Mehta

Diagnostics Product Development Process



Typical diagnostics development process

- In vitro diagnostics are developed in two stages –front-end investigative or exploratory research
- The discovery is validated in in-vitro studies
- Include analysis of various stratification markers from tissue or serum samples.
- Further assay development and optimization
- The development of a commercial test method
- Larger companies may choose to first configure the assay on their already commercialized test instrument platform.

© 2022 S ır efal Mehta

Schematic of diagnostics development process

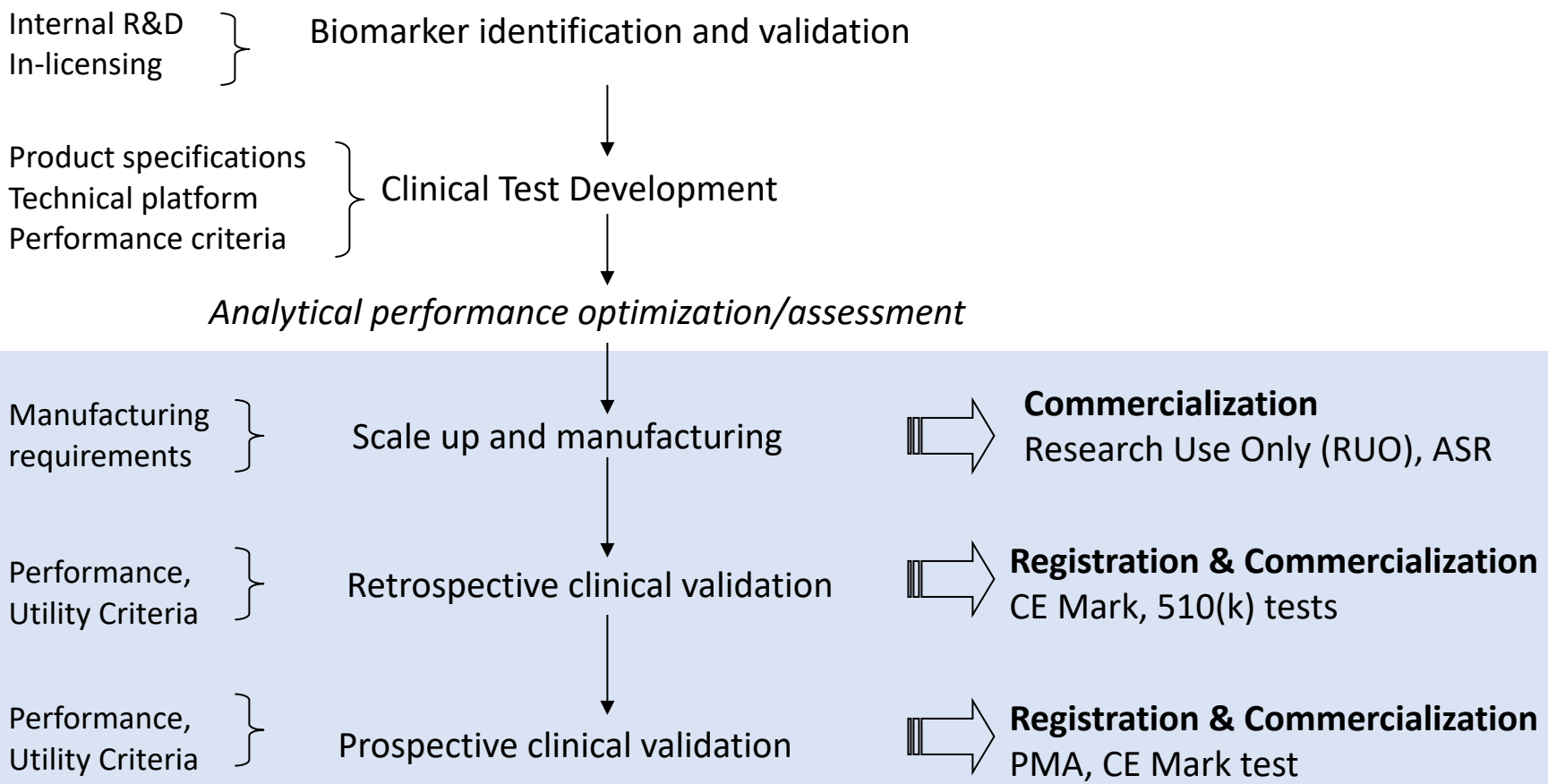
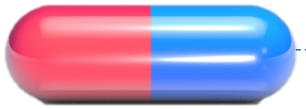


Figure 5.12

Stage 1



Gate 1

Biomarker discovery and validation

Stage 2

Gate 2

Clinical test development

Stage 3

Gate 3

Analytical assessment optimization

Stage 4

Gate 4

Scale-up, manufacturing, and early sales as nonregulated test (ASR/LDT)

Stage 5

Gate 5

Retrospective clinical trials, registration through 510(k) and commercialization

Stage 6

Gate 6

Prospective clinical trials, registration, and commercialization

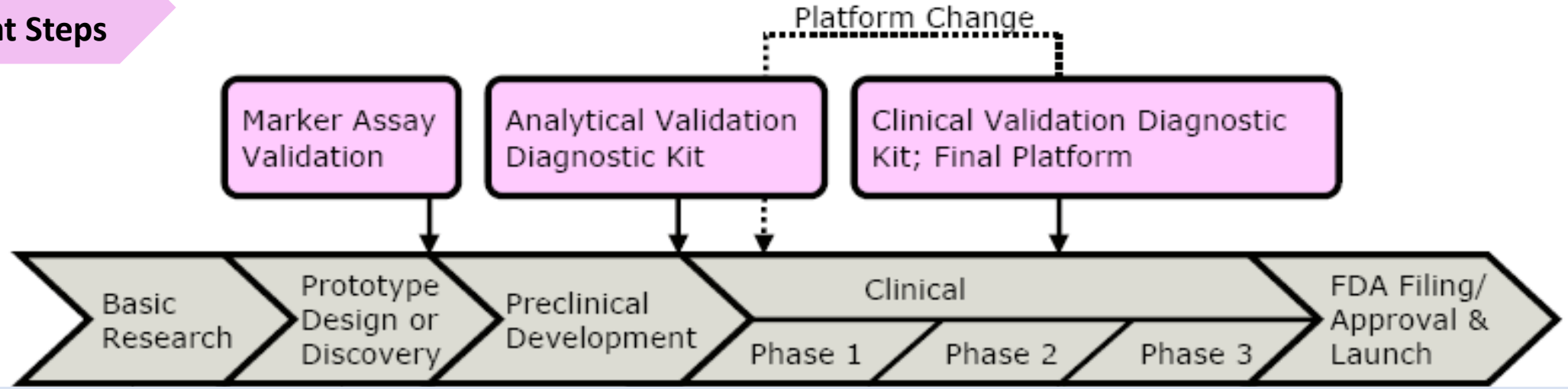
Statistical analysis of results from studies supports the claims of efficacy and correlation to clinical outcome.
FDA approval of 510(k) or PMA for marketing.

Stages and gates for diagnostic development

© 2022 Shreefal Mehta

Co-development of diagnostics and therapeutics

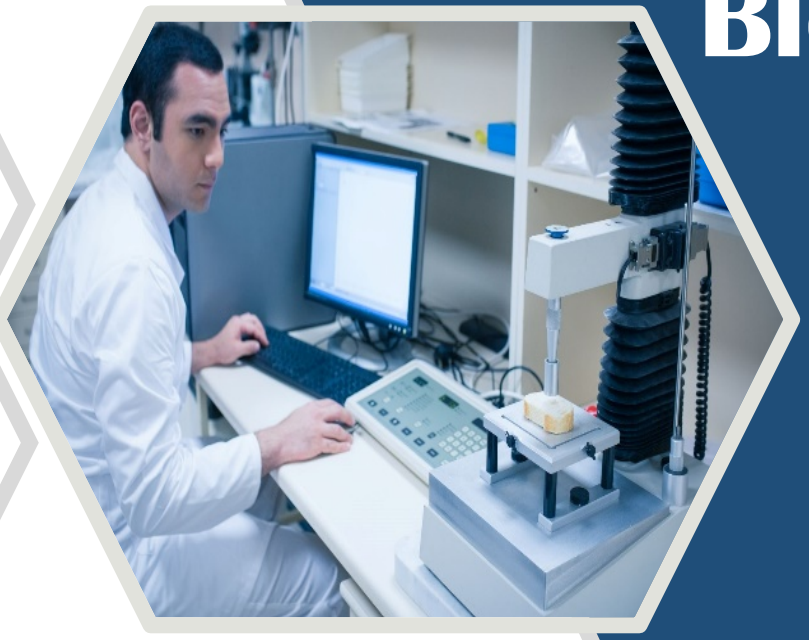
Diagnostic Development Steps



Drug Product Development Steps

Figure 5.13

General Considerations for Managing Bio-Medical Product Development



Some key dos and don’ts with respect to biomedical product development:

DO

DON’T

© 2022 Shreefal Mehta

Some key dos and don’ts

DON’T	carry out extensive studies for alternate diseases/indications once a product has entered formal clinical development for a particular chosen indication
DO	obtain appropriate insurance for the human clinical trials
DON’T	forget to put the adequate ethical controls and regulatory certifications
DO	carry out a failure mode and effects analysis
DON’T	Forget to include effective information security and privacy controls.

© 2022 Shreefal Mehta

Some key dos and don’ts

DO	design with empathy for the users
DO	consider, as a start up, putting your quality system in place as you go through the design process
DO	write product specifications with the test in mind
DON’T	Turn on your quality system too late.

© 2022 Shreeraj Mehta

Project management tools – Gantt charts and critical path

- It makes it easy to visually check timelines
- Check job allocations per person so that all team members and management are unequivocal about the tasks and timeline responsibilities.
- Progress can be easily tracked against Gantt charts and the software

© 2022 Shreefal Mehta

Project management tools – Gantt charts and critical path

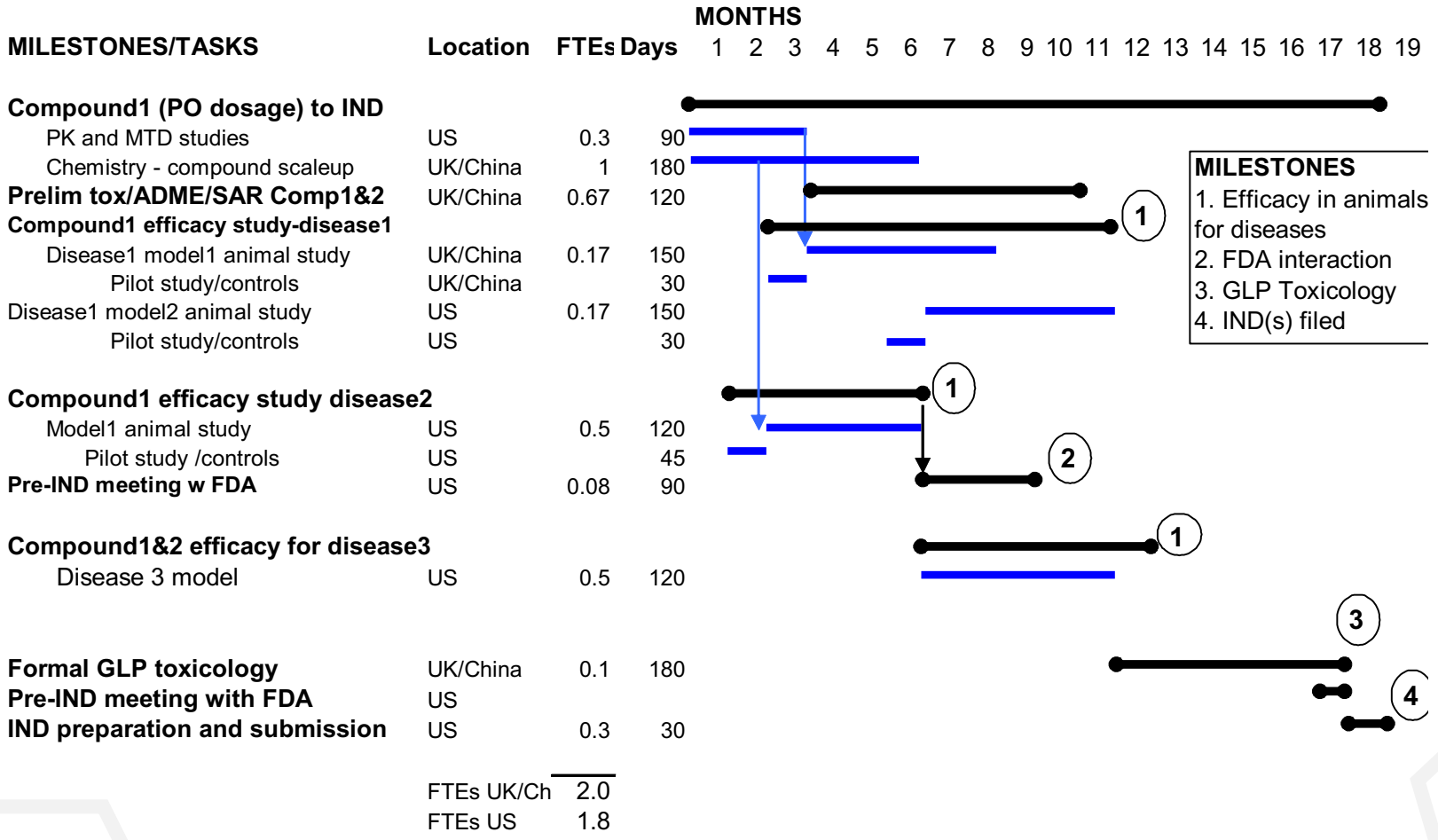


Figure 5.17

© 2021 Shreefal M

Team composition

- Multidisciplinary teams must be formed
- In biomedical product development, there is a need to get input from sales and marketing, reimbursement, regulatory affairs, finance, and general management throughout the development process.
- With progression into advanced preclinical stages, a regulatory affairs and manufacturing person might be added into the team to help prepare for the first interactions with the FDA.
- During clinical stage studies, a clinical physician, regulatory affairs, biostatisticians, and manufacturing might be part of the project team

© 2022 Shre

Team composition example for drug product development

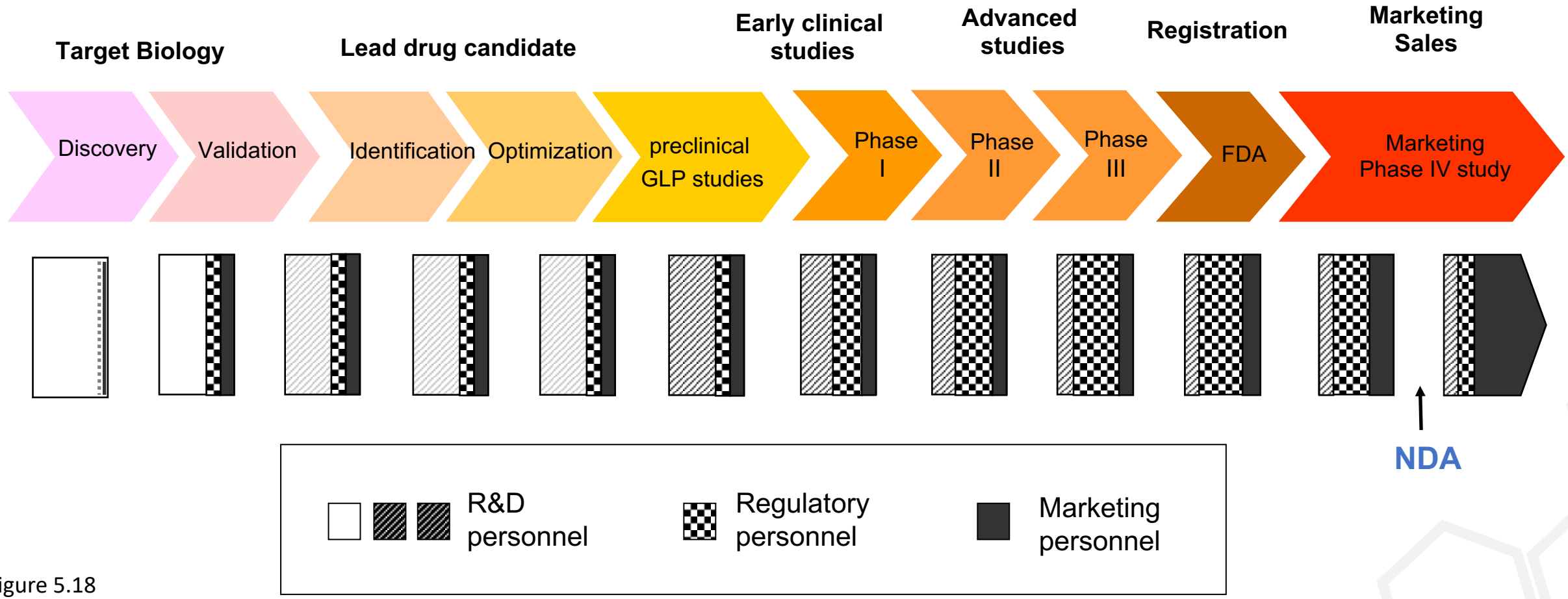


Figure 5.18

Composition of a product development team in drug development path. Device development teams will have similar configurations/ composition.

© 2022 Shreefa Agenta

How to get your project funded in a larger organization

Communicate, communicate!

Communications must cover the elements listed below

- ✓ The art of persuasion
- ✓ Establish credibility
- ✓ Illuminate advantages
- ✓ Provide evidence
- ✓ Connect emotionally
- ✓ Show commitment
- ✓ Understand and adjust to audience

Stakeholders

Carry out a formal or informal stakeholder analysis to prepare to communicate more effectively

List all stakeholders

Prioritize stakeholders

Considerations in preparing to deal with stakeholders

- How can you help the high-power, high-interest stakeholders do their job better with your project?
- Use the opinions of the most powerful stakeholders
- Win more resources
- Anticipate what people's reaction to your project
- What financial or emotional interest do they have
- What motivates them
- What is their current opinion
- Who influences their opinions generally
- If they are not likely to be positive, what will win them

Outsourcing product development

Outsourcing can add value to a company

- If the company is never going to build the capability to do cGMP (FDA-regulated process) manufacturing
- If the company does not have animal facilities
- Need for speed
- Complexity

Outsourcing brings in expertise to the project that is not present in the company.

© 2024 Shreefal Mehta

Outsourcing product development (contd.)

Strategic business model for planning internal and external development

	R&D	FDA Process & Clinical Trials	Manufacturing	Marketing & Sales	
				US	International
Do It Yourself					
Strategic Partners/ Licenses					

Figure 5.21

© 2022 Shreefal Mehta

Outsourcing product development (contd.)

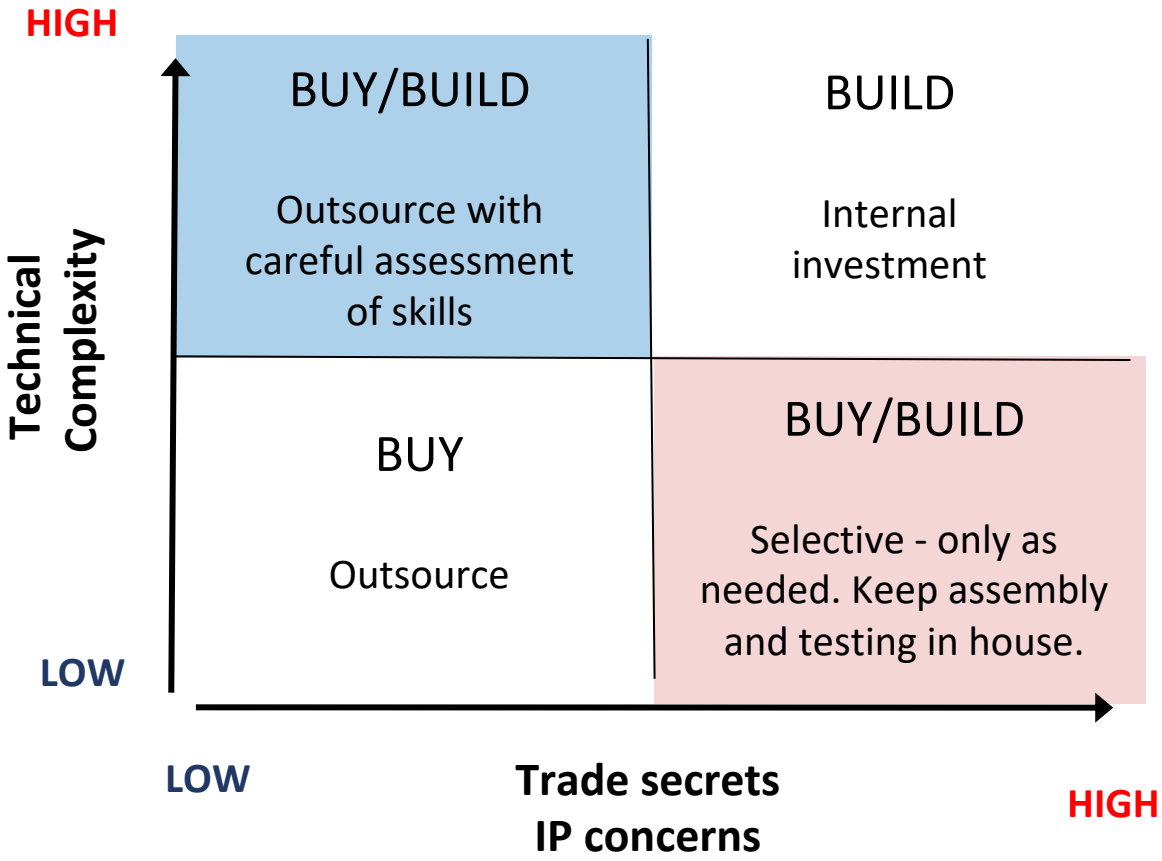
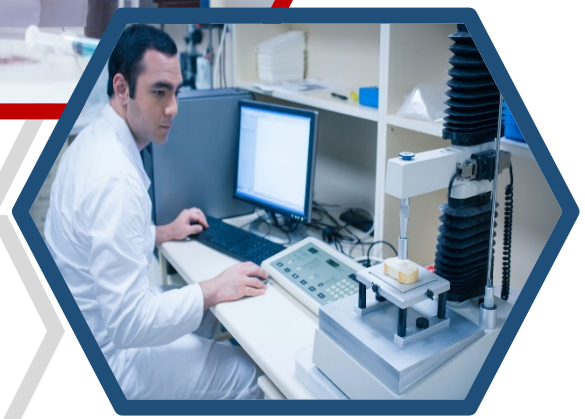


Figure 5.22

Strategic choices between outsourcing (buying) vs building it internally

© 2022 Shreefal Mehta



www.shreefalmehta.com/csbtbook

Thank you…

© 2022 Shreefal Mehta