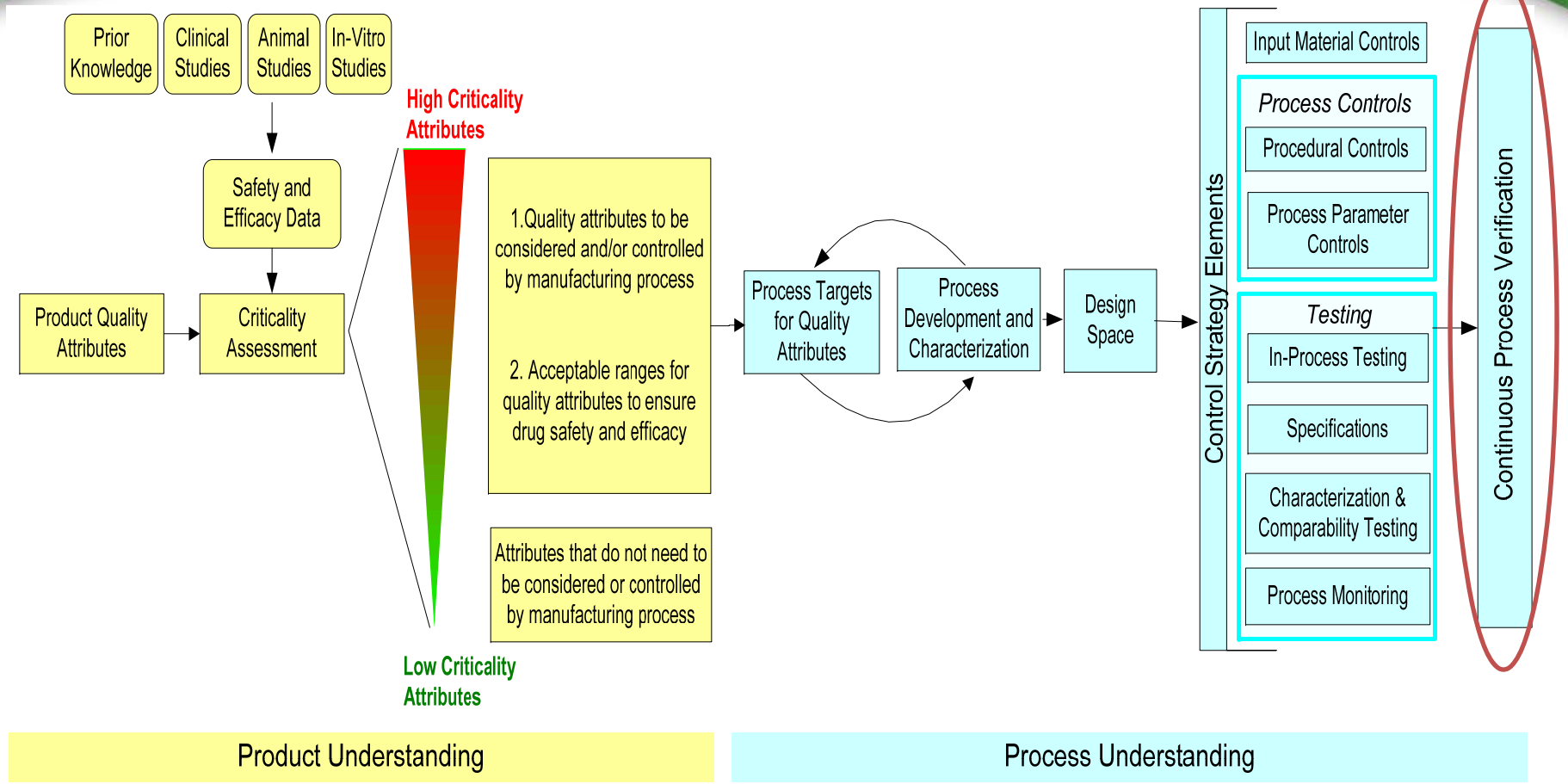
Validation

Chapter 4

Validation Exemplifies Process Understanding



FDA Definition

- "The process of *demonstrating*, through *documented evidence*, that a process, procedure, piece of equipment, analytical method, or facility will *consistently* produce a product or result that meets *predetermined* specifications and quality attributes."

Validation

- Documented evidence that
  - the facility, equipment, and utilities all perform as expected
  - the analytical methods used in the quality control laboratory perform as expected
  - each step of the production process contributes to a final product that meets all of the quality attributes and specifications

Validation

- Validation is an external check on the performance of a system and ultimately the entire manufacturing process
  - If the process performs properly, it should produce a product that meets predetermined specifications
  - If it does not perform properly, a step in the process exists that is either inadequately understood or is not performing as designed.

Demonstration and Documentation

- Validation also forces the biomanufacturer to examine assumptions about equipment, materials, procedures, and the entire production process
  - one can *assume* that material placed in an autoclave will be sterilized if the autoclave is working properly
  - But how can that person *know* that the autoclave is working properly or that it sterilizes the material to meet the necessary established standard if it *is* working properly?

Validation Evolution

- Validation remains a time-consuming and expensive process
- It is improved from the old mindset *validate anything that moves and don't move anything that is validated*
- The current approach incorporates process understanding and risk assessment towards an elimination or reduction of those risks

Validation Evolved

- Product and process knowledge culminate in validation activities
  - Documentation that the controlled processes result in products with desired quality attributes
- To this end, biomanufacturers should
  - Understand the sources of variation
  - Detect the presence and degree of variation
  - Understand the impact of variation on the process and ultimately on product attributes
  - Control the variation in a manner commensurate with the risk it represents to the process and product

Demonstrating Process Parameters

- Temperature-mapping studies to ensure that all areas within the vessel achieve the desired temperature
- The mixing rate of the material needs to be documented to prove that as the solution is mixed it maintains its temperature.
- Testing under worse-case scenarios
  - Maximum volume, lowest mixer setting, partially-operable heater, other plausible mechanical issues
- Verification that if specifications are met at the limits of the ranges, the specifications will assuredly be met at the normal operating range
  - All with no impact on product quality!

Risk-based Validation

- Risk analysis is a formal analytical activity
  - Identify
  - Assess
  - Manage
- Risks considered in this process are related to
  - Product
  - Patient
  - Employees of the biomanufacturer

Identifying Systems

- Develop a comprehensive list of all systems in the manufacturing operation, categorized by functional area
  - facility, equipment, and utility systems
  - analytical equipment systems
  - computerized systems
  - cleaning systems

Systems Impact Assessment (SIA)

- The Systems Impact Assessment (SIA) is a process to determine which systems should be subject to qualification, which evaluates the impact that a system has on product quality
- Each identified system is then categorized as one of the following
  - Direct Impact (DI) system
  - Indirect Impact (ID) system
  - No Impact (NI) system

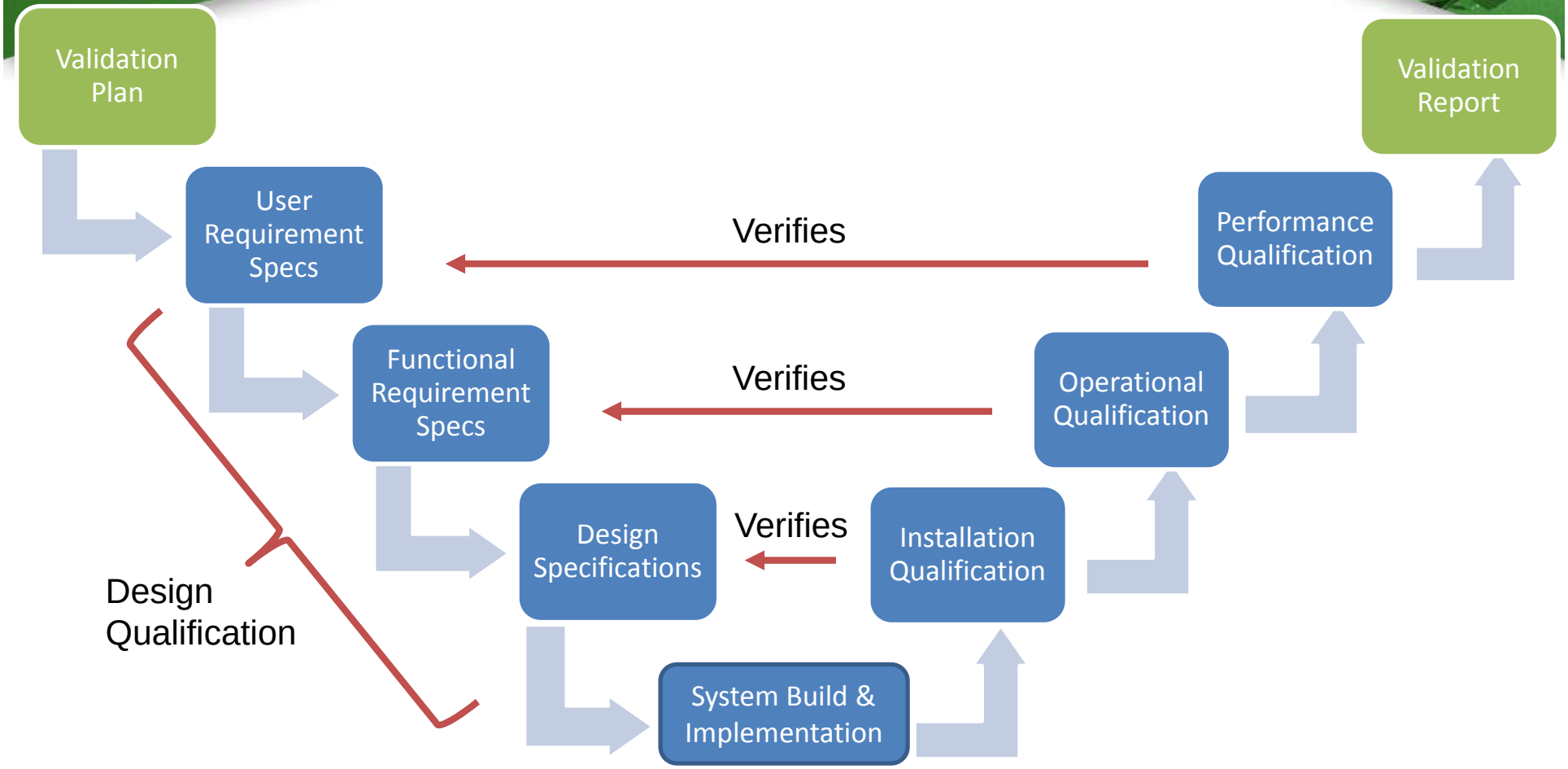
Risk-based SIA

- Conducted by a multi-disciplinary team consisting of representatives from engineering, validation, operations, quality assurance, etc
- With the traditional approach toward validation, every system is qualified and validated
- With the risk-based approach, qualification activities are limited to Direct Impact Systems (DI)

Risk assessment

- patient safety: risk of a patient being physically harmed
- product quality: risk that the product quality profile (identity, strength, quality, or purity) will be negatively impacted
- compliance: risk of a regulatory enforcement action (e.g., FDA, EMA, etc.) or the delay of a product approval

GAMP V-Model


Validation Plan
User Requirement Specs
Functional Requirement Specs
Design Specifications
System Build & Implementation
Installation Qualification
Operational Qualification
Performance Qualification
Validation Report
Verifies
Verifies
Verifies
Design Qualification