QUALITY AND REGULATORY COMPLIANCE IN BIOSCIENCE



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This text was compiled on 11/09/2026

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1: THE ORGANIZATION OF A BIOTECHNOLOGY COMPANY

Learning Objectives

After completing this chapter, you should be able to:

- Describe the roles of the major departments in a biotechnology company.
- Explain how a product moves from research into routine production.
- Distinguish the responsibilities of quality assurance, quality control, and regulatory affairs.
- Identify which teams should work together when a product or process problem occurs.

A research team has developed an enzyme that breaks down plant material. In a small flask, it works just as the scientists hoped. A food ingredient producer wants to try it, but first asks two practical questions. Can the company make enough for a trial? Will the enzyme work as well after it has been shipped and stored?

Answering those questions takes more than a discovery in the lab. Someone has to develop a production process, test the finished enzyme, and figure out how to ship it. Someone also has to work with the customer to agree on what the enzyme needs to do. This chapter follows that fictional enzyme to show how departments share the work and how their decisions affect product quality and regulatory compliance.

1.1: How Biotechnology Companies Are Organized

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1.1: How Biotechnology Companies Are Organized

Biotechnology companies use living organisms, cells, or biological molecules to develop products or provide services. One company might make an enzyme for food processing. Another might develop a diagnostic test, manufacture a medicine, or offer DNA sequencing as a service. The kind of product, the size of the company, and its stage of development all shape how it organizes the work.



In a small startup, one scientist may do both research and process development. The company might hire a contract manufacturer to produce its first commercial batches or send samples to an outside testing lab. A larger company may have several teams for each of those functions. Even when work is contracted out, the company needs to agree with its partner on who will do the work, what records must be kept, and who will review the results.

Who Makes Which Decisions

The organization chart shows who reports to whom. A project team shows how the work gets done across departments. For a customer trial, a project manager may bring together R&D, manufacturing, quality, and sales. Sales shares the customer's timeline, while manufacturing explains when a trial batch can be made. Quality identifies the evidence the company needs before the batch can be sent. Each group contributes to the schedule and has a different decision to make.

The same division of responsibilities matters when work goes outside the company. Before sending samples to a contract lab, the company and the lab agree on how samples will be labeled, which method the lab will use, and how it will report an unexpected result. A quality agreement can document who is responsible for activities such as testing, record retention, and reporting problems.

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1.2: Research and Development



Research and development (R&D) turns a problem or idea into a potential product. In the enzyme example, researchers compare several enzymes to see which one works best at the temperatures and pH used by the customer. They also develop an early test for enzyme activity and use it to see how much activity remains after storage. A promising result gives the team a reason to continue. The next experiments help the team learn whether the result is repeatable.

A **research associate** might prepare samples, run tests, and record results. A **scientist** might design experiments, interpret the data, and decide which candidate to study next. When the team hands a candidate to process development, it shares the methods, data, and known limitations so that the next team can build on the work.

Keeping Track of What Worked

An enzyme might look promising because it performs well in a clean laboratory solution. However, the customer's plant material may contain compounds that interfere with the enzyme. R&D can test the candidate in a sample that resembles the customer's material and include a control sample without added enzyme. Comparing the two helps the team judge whether the enzyme caused the observed change.

Research records explain how a result was obtained. Suppose two experiments give different readings. The team needs to know whether the samples came from the same source, whether the instruments were set up the same way, and whether the analysts followed the same steps. Recording those details also helps the next team repeat the work after a handoff.

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1.3: Process Development and Manufacturing

Process Development

Process development works out how to make the product consistently. For the enzyme, that may involve growing a microorganism in a bioreactor, recovering the enzyme, and preparing it for storage. The team studies conditions such as temperature, mixing, and oxygen supply to learn which ones affect yield or activity. Moving from a flask to a larger vessel is called scale-up. A setting that works in a flask may give different results in a tank because mixing and oxygen transfer change with scale.

Once the process is ready to move into production, the teams carry out a technology transfer. Process development shares the instructions, equipment needs, sampling steps, and what to watch for. Manufacturing staff may run trial batches with the development team and point out places where the instructions need clarification. An analytical development team, where present, also helps prepare test methods for routine use by the quality control lab.

Production involves several linked steps. Upstream processing includes growing the microorganism and producing the enzyme. Downstream processing includes recovering the enzyme and removing unwanted material. A change that increases the amount of enzyme made upstream may also increase the material that has to be removed downstream. Process developers look at the effect on the whole process before choosing a new setting.

During a trial run, operators may find that the larger tank takes longer to cool. The development team can use those observations to determine whether the process needs a different cooling step or additional monitoring. The transfer should capture the updated instructions, the evidence behind the change, and the training operators need before using the process routinely.



Manufacturing

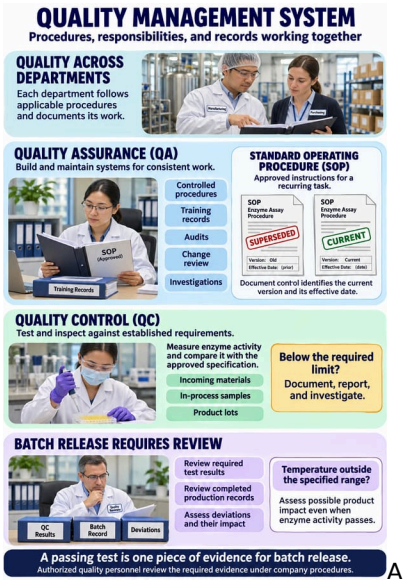
Manufacturing uses approved instructions to produce batches, also called lots. Operators prepare equipment and materials, run the process, collect samples, and record what happened. The batch record links a specific lot to the materials and equipment used, the steps performed, and any problems observed. A manufacturing technician who notices that the tank temperature moved outside the specified range records the event and reports it through the company's procedures. That information helps the company decide whether the batch can be used.

A shift begins with checks. Operators confirm that the equipment is ready, that materials have the right identity and status, and that the instructions apply to the product being made. During filling, staff may verify the container and label against the batch record. These checks can prevent a mix-up even when the enzyme itself meets every test requirement.

A supervisor coordinates the response when something unusual happens. If an operator notices a leak during filling, the immediate steps may include pausing the operation and identifying containers filled during the affected period. The operator records what was observed and when. Quality and manufacturing can then use those details to determine how much product may be affected.

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1.4: The Quality Department

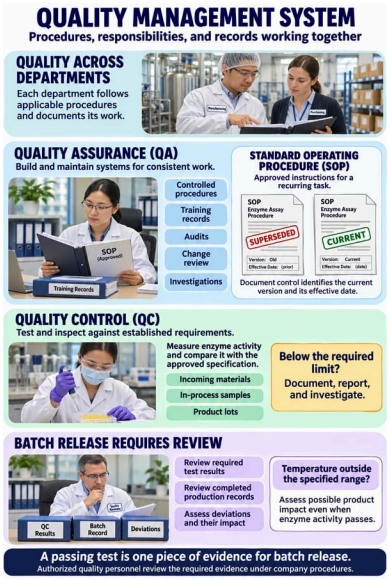


A **quality management system** (QMS) brings together the procedures, responsibilities, and records a company uses to manage quality. Manufacturing, purchasing, and other departments follow the procedures that apply to their work and document what they did. The quality department often includes two functions with different day-to-day responsibilities.

Quality assurance (QA) helps build and maintain the systems that support consistent work. **QA analysts** may oversee controlled procedures, training records, audits, change review, and investigations. A **Standard Operating Procedure (SOP)** gives approved instructions for a recurring task, such as cleaning a filling machine. If the instructions change, document control helps staff find the current version and know when to begin using it.

Quality control (QC) tests or inspects materials and products against established requirements. In the enzyme example, a **QC analyst** measures activity in a sample from each lot and compares the result with the approved specification. QC analysts may also check incoming materials or samples taken during production. If the activity result is below the required limit, the QC analyst documents and reports it so the company can investigate.

A passing test result is one piece of evidence for batch release. The authorized quality personnel review the required evidence under the company's procedures. That may include QC results, the completed batch record, and the status of any deviations. If the temperature went outside of the allowed specified range, the reviewer considers whether that event could affect the product even if the activity result meets the limit.



How QA Reviews a Change

Suppose the enzyme supplier wants to replace its current shipping box. QA helps make sure the proposal is documented and reviewed before use. Supply chain explains how the new box will be packed. Technical staff compare its ability to hold the required temperature under expected shipping conditions. If the change is approved, the relevant instructions and training are updated so staff know when to switch.

How QC Produces Reliable Results

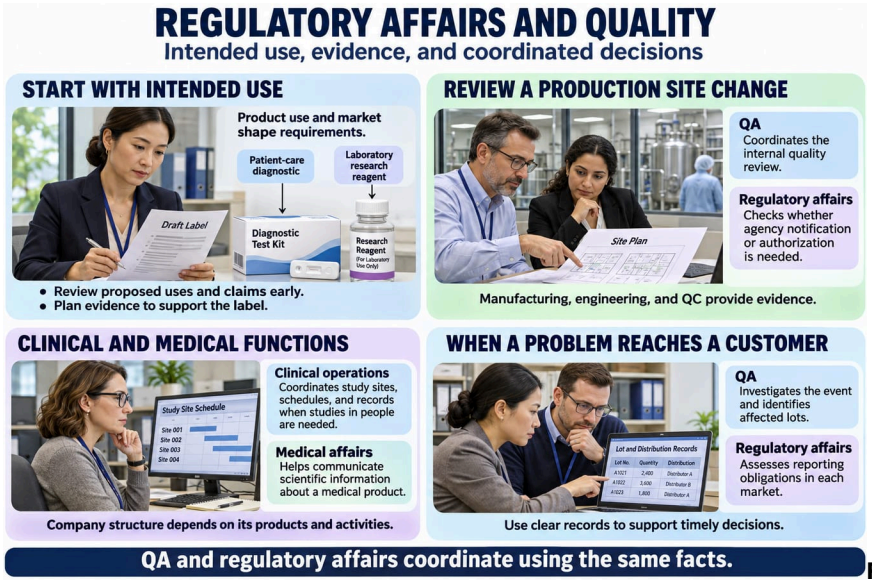
An activity result is useful only if the sample represents the lot and the method performs as expected. The QC analyst checks sample identity, follows the test method, and records the results and any problems. If a control included in the test fails, the analyst reports the issue and follows the laboratory's investigation procedure. Any repeat testing needs a documented reason and must follow that procedure.

Correcting a Problem and Preventing Recurrence

A batch may be placed on hold while a problem is investigated. The hold keeps it from being used or shipped during the review. If the investigation identifies a cause, the company can take corrective action to reduce the chance that the problem will happen again. For example, after finding that two similar labels were stored next to each other, the company might separate the labels and check subsequent batches to see whether the change reduced mix-ups.

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1.5: Regulatory Affairs and Product Studies



Regulatory affairs helps the company identify which rules apply to a product and what evidence it may need to provide to regulators. The intended use matters. A diagnostic test for patient care and a reagent sold for laboratory research can have different requirements. Depending on the product and market, regulatory affairs may coordinate submissions, communicate with agencies, review labeling, and assess the effect of proposed changes. If manufacturing proposes moving production to a new site, QA coordinates the internal review of how the move could affect quality. Regulatory affairs checks whether the company needs to notify an agency or obtain authorization before making the change. The two teams use evidence from manufacturing, engineering, and QC to make those assessments.

Some companies also have clinical affairs, clinical operations, or medical affairs teams. Clinical operations may coordinate study sites, schedules, and study records when a company needs to collect evidence in people. Medical affairs may help communicate scientific information about a medical product. Companies that make industrial enzymes or sell laboratory equipment may organize these responsibilities differently or have no clinical group.

Regulatory affairs often gets involved while a product is still being designed. If the commercial team proposes a new use for the enzyme, regulatory staff review how the use would be described and what evidence supports it. That discussion can change the development plan. For example, the team may need to study how the product performs under different processing conditions before using a new claim on its label.

QA and regulatory affairs also need the same facts when a problem reaches a customer. QA may investigate what happened and determine which lots were affected. Regulatory affairs evaluates whether the findings create a reporting obligation in the markets where the product was distributed. Clear records help both teams make timely decisions.

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1.6: Supply Chain and Facilities

Supply chain keeps materials and products moving. Purchasing works with technical and quality staff to choose suppliers.



Receiving checks that deliveries match orders and routes materials for inspection or testing as required. Warehouse staff track lot numbers and storage conditions. Shipping staff verify orders and use the specified packaging and transport conditions. These records support **traceability**. If a supplier reports a problem with a raw material, the company can identify which finished lots used it and where those lots went.

Engineering, facilities, and maintenance help keep equipment and buildings ready for use. Engineers may select and install a larger bioreactor. Maintenance technicians service pumps and replace worn parts. **Calibration** checks how an instrument's reading compares with a reference. If a temperature sensor reads incorrectly, the team documents what it found so manufacturing and quality staff can assess which batches may be affected.

Environmental health and safety (EHS) helps teams manage workplace hazards. Its work can include training staff to handle chemicals or biological materials, preparing for spills, and arranging safe waste handling. Information technology (IT) supports the systems that store records, track inventory, and control access to data. For example, an electronic lab system can help preserve who entered a result and when.

Managing Suppliers and Inventory

The least expensive material may become costly if it varies from shipment to shipment. Purchasing and technical staff can compare supplier information with the material specification, while quality staff help determine which suppliers and materials need closer oversight. If a supplier announces a change to how a material is made, purchasing routes the notice for review before the new material is used.

Keeping Equipment and Records Ready

Facilities staff may track maintenance dates, monitor storage areas, and respond to equipment alarms. If a cold storage unit fails overnight, warehouse staff identify what was stored there and facilities staff provide the alarm and repair records. Quality staff use those records and available stability information to assess the affected material. IT helps preserve access to the electronic records used in that review.

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1.7: Commercial Teams and Business Support



Marketing studies what customers need and helps explain where a product fits. Sales works with customers to understand their applications, arrange trials, and handle orders. Technical support helps customers use the product and documents problems. When several customers report low enzyme activity, technical support can collect the lot numbers and storage details and send them to the quality team for review.

Executive leadership sets priorities and decides where to invest. Finance tracks spending and helps teams budget for projects. Human resources supports hiring, onboarding, and employee development. Legal staff may review contracts and help protect intellectual property such as an enzyme design. Project managers coordinate schedules and decisions across departments, especially when one team needs another team's results before it can begin.

During a customer trial, sales may learn that the customer needs the enzyme to stay active for six months. That requirement gives R&D and quality teams a specific question to investigate. Marketing can use the approved evidence to describe the product's storage life, and technical support can explain how customers should store and handle it.

Business decisions can affect quality work directly. If production is growing, finance and leadership may need to fund more testing capacity, a backup storage unit, or additional operator training. Human resources and department managers work together to define the skills needed for new positions. The project manager helps coordinate when people, equipment, and instructions must be ready for the next production run.

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1.8: Example - A Shipment Arrives Warm



A customer calls to report that the enzyme shipment arrived warm. The technical support specialist asks for the lot number, when the package arrived, and whether it contained a temperature monitor. The specialist records the complaint and sends it to QA.

The supply chain team checks the shipping records and downloads the monitor data. QC can test a retained sample, a portion of the same lot kept by the company. A result from that sample can help assess the lot as manufactured. The shipping record and any suitable evidence from the affected shipment help assess what happened in transit. Process development checks what earlier studies showed about the enzyme's stability at the temperatures recorded.

QA coordinates the investigation and documents the decision about the affected product. If the team finds that the packing instructions allowed the wrong amount of coolant, it can revise the instructions, train staff, and check later shipments to see whether the change worked. Each department contributes a different piece of the evidence.

The investigation may also show that other shipments used the same packaging and route. The team can look for those shipments in the distribution records and check whether customers reported similar problems. If the evidence points to a wider issue, the company can expand the investigation and decide how to handle the other potentially affected lots.

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1.9: Chapter Summary

Biotechnology companies organize around the work needed to develop, make, test, and support a product. R&D develops promising candidates. Process development prepares a process for routine use, and manufacturing follows approved instructions to make and document each batch. QC produces test and inspection results, while QA oversees systems that help teams work consistently and investigate problems. Regulatory affairs helps identify requirements for a product and its intended use. Supply chain, facilities, EHS, IT, commercial teams, and business support all help keep the work moving. Clear handoffs and reliable records allow these teams to act on the same evidence when a problem occurs.

Key terms

Batch record	Batch release	Calibration
Corrective action	Deviation	Downstream processing
Environmental health and safety (EHS)	Process development	Quality agreement
Quality assurance (QA)	Quality control (QC)	Quality management system (QMS)
Regulatory affairs	Scale-up	Specification
Standard operating procedure (SOP)	Technology transfer	Traceability
Upstream processing		

Review questions

1. What are two factors that influence how a biotechnology company organizes its departments?

2. What does R&D do when it evaluates several candidates for a new enzyme product?

3. Why might a process that works in a small flask need changes before it can run in a large tank?

4. What information should process development share with manufacturing during technology transfer?

5. What information does a batch record capture, and how can it help during an investigation?

6. How do the daily responsibilities of QA and QC differ?

7. Besides QC test results, what information might be reviewed before a batch is released?

8. How can a product's intended use affect the work of regulatory affairs?

9. How do purchasing, receiving, and warehousing contribute to material traceability?

10. What does a calibration check tell you about a temperature sensor?

11. How do the responsibilities of sales and technical support differ?

12. What information can IT help preserve in an electronic lab record, and why does it matter?

Apply your knowledge

1. An enzyme performs well in a flask, but a trial batch in a larger tank produces much less active enzyme. Which teams should work together? Suggest two process conditions they should compare and explain why.

2. A manufacturing technician notices that the process temperature exceeded its limit for 15 minutes. The final QC result meets the enzyme activity specification. What should the technician record, and what evidence should quality staff review before deciding whether to release the batch?

3. A supplier reports a possible problem with a raw material shipped to your company last month. Identify the teams and records you would use to determine which batches may be affected and whether any reached customers.

4. A company sells a reagent for research. A customer asks if it can be used to guide patient treatment. Which teams should respond, what questions should they resolve first, and why does the proposed use matter?

5. Three customers report low enzyme activity after delivery. Retained samples from the same lots meet the specification. What information would you request from customers and shipping staff? Explain how that information could help you distinguish a shipping problem from another cause.

6. A small startup plans to hire a contract manufacturer for its first commercial batch. Draft a handoff that assigns responsibility for production instructions, testing, unexpected events, and the release decision. Name a record that would show each responsibility was carried out.

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2: UNDERSTANDING QUALITY

Learning Objectives

After completing this chapter, you should be able to:

- Define quality in products, services, and processes using biotechnology examples.
- Distinguish customer requirements, expectations, and fitness for use.
- Compare quality assurance, quality control, and quality improvement.
- Describe prevention, detection, correction, and corrective action.
- Explain how departments and employees contribute to quality.
- Classify quality costs and describe the human consequences of poor quality.
- Apply quality terminology to laboratory, manufacturing

A biotechnology company makes an enzyme that helps researchers prepare samples for genetic studies. One morning, a technician notices that a shipment was stored in a freezer different from the assigned location. The containers look normal, and the **customer** needs the shipment tomorrow. Should the team send it?

This hypothetical situation raises questions that appearance alone cannot answer. Did the actual storage conditions meet the **product**'s requirements? If not, for how long? What evidence would support a decision about suitability? Who has authority to decide what happens next? Using the wrong freezer is a **process** concern, but it does not by itself establish that the enzyme experienced unsuitable temperatures or lost activity.

Biotechnology uses organisms, cells, or biological materials to develop useful products and services. Its work supports research, patient care, agriculture, and environmental protection. **Quality** helps people trust both materials and information. This chapter introduces the terms used to define requirements, evaluate evidence, and assign responsibilities. Examples are hypothetical unless labeled as documented events.

2.1: Definitions of quality in products, services, and processes

2.2: Customer requirements, expectations, and fitness for use

2.3: Quality assurance, quality control, and quality improvement

2.4: Prevention, detection, and correction of problems

2.5: Quality responsibilities throughout an organization

2.6: Costs and consequences of poor quality

2.7: When a diagnostic result could not be trusted

2.8: Applying quality terminology in different workplace settings

2.9: Chapter summary

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2.1: Definitions of quality in products, services, and processes

Quality describes how well the characteristics of a product, **service**, or process meet requirements. A **requirement** is a need or condition that must be met. To assess quality, first identify the intended purpose and the relevant requirements. Then compare suitable evidence with those requirements. Price, attractive packaging, and new technology do not establish quality by themselves.



A **product** is an output provided to a user, such as an enzyme, a test kit, or a manufactured medicine. Product quality includes the properties needed for its intended purpose. An enzyme may need a defined level of activity, freedom from interfering contaminants, and enough stability to work throughout its labeled shelf life. A correct label and suitable packaging also matter because users depend on them to handle the product properly.

A **service** is work performed for another person or organization. A laboratory that tests water provides a service. Its quality depends on valid results, correct sample identification, clear reports, and delivery within the agreed time. A correct result sent to the wrong customer is still a serious quality failure.

A **process** is a set of related activities that turns inputs into outputs. Preparing a growth medium, testing a sample, and responding to a complaint are processes. Process quality concerns how well the work meets defined conditions and produces dependable outcomes. Clear instructions, suitable equipment, and reliable records help people repeat the work successfully.



These three views are connected. An enzyme is a product; filling its containers is a process; technical support is a service. A weakness in any one can affect the customer. Quality therefore includes both the final output and the work that makes it possible.

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2.2: Customer requirements, expectations, and fitness for use



A customer is a person or group that receives a product or service. An **external customer** is outside the organization, such as a research laboratory buying an enzyme. An **internal customer** receives work from another part of the same organization. For example, manufacturing is an internal customer of the group that prepares its approved production instructions.

Customer requirements state the conditions a product or service must meet to satisfy the customer's needs. **Customer expectations** are beliefs about what the customer will receive or experience. Some expectations are stated; others are assumed. An organization needs to understand them and translate relevant needs into clear commitments. Applicable safety, legal, and organizational requirements must also be considered, whether or not a customer mentions them.

Useful requirements are clear enough to guide action. "The enzyme should work well" leaves room for disagreement. A **specification** documents defined requirements, often including a test method and acceptance criteria. For a hypothetical enzyme, a specification might require at least 90 units of activity per milliliter by a stated method. An activity unit depends on the assay and its conditions, so results from different methods are not automatically comparable. The number is a teaching example, not an industry standard.

Fitness for use means suitability for the intended purpose under the expected conditions. A research enzyme may work well in one sample type but perform poorly in another. Meeting its stated specification does not prove it is suitable for every possible experiment. Understanding intended use helps the supplier define meaningful requirements and helps the customer select an appropriate product.

Customer satisfaction matters, but it cannot replace safety requirements or reliable evidence. A customer may request a shipment before required reviews are complete. Employees should explain the delay and follow the applicable release process. Meeting a delivery promise by bypassing a necessary check can place the customer at greater risk.

Requirements also need review when circumstances change. If customers will use a reagent in a different setting, the team should assess whether the existing evidence supports that use. A change in intended use can require different performance evidence, instructions, or regulatory review. The answer depends on the product and its context.

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2.3: Quality assurance, quality control, and quality improvement



Quality assurance (QA) consists of planned and systematic activities that provide confidence that quality requirements will be met. QA supports the way work is organized, performed, documented, and reviewed. Examples include managing approved procedures, reviewing training systems, and checking whether records support a decision.

Quality control (QC) focuses on fulfilling quality requirements through operational activities that include measurement, testing, and inspection. A QC analyst may measure enzyme activity, test a raw material, or monitor a production environment. These activities generate evidence for comparison with defined requirements. Testing may occur before, during, or after production; QC is broader than final-product testing alone.

Quality improvement uses evidence to make processes and their outcomes better. A team might reduce sample identification errors by redesigning labels and checking whether errors decrease. **Continuous improvement** is the ongoing practice of finding, evaluating, and sustaining such improvements. It includes small changes as well as larger projects.

QA, QC, and improvement describe related activities, not a universal departmental chart. QA builds confidence in how requirements are met. QC helps fulfill requirements and provides evidence about conformance. Improvement uses measurements, observations, and feedback to strengthen performance. Duties may overlap, and organizations assign them differently. The functions remain important even when one person performs several roles.

Quality activity	Main question	Enzyme example
QA	Can we have confidence in how the work is managed?	Review approved storage procedures and staff training.
QC	Does the evidence meet the defined requirements?	Measure activity using an approved method.

Quality activity	Main question	Enzyme example
Quality improvement	How can the process perform better?	Test a revised storage handoff and track error

A passing final test does not erase missing records or an uncontrolled production step. Tests usually examine selected properties in selected samples. They cannot reveal every possible problem. Confidence comes from suitable process controls, valid measurements, complete information, and appropriate review together.

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2.4: Prevention, detection, and correction of problems



Prevention means acting before a problem occurs to reduce its likelihood. Training staff before assigning a task and separating similar labels are preventive practices. **Detection** means finding a problem through observation, testing, or review. A barcode mismatch alert detects a possible identification error; it does not by itself explain why the mismatch occurred.

A **nonconformity** is a failure to meet a requirement. An incorrect container label or a missing required entry can be a nonconformity even when the material itself appears acceptable. A **correction** addresses the detected problem. Replacing a wrong label through an authorized, documented process is a correction.

Corrective action addresses the cause of a detected nonconformity to prevent it from happening again. Replacing one incorrect label is a correction. Changing a confusing label system after an investigation may be corrective action. Before choosing an action, examine the evidence about instructions, equipment, workload, training, communication, and individual decisions.

The first response may be **containment**, which limits exposure to a suspected problem while it is assessed. In the freezer scenario, staff could identify and hold the affected shipment under the applicable procedure. A hold prevents unintended use or shipment while evidence is reviewed; it does not establish that the material is damaged.

The team would document what happened, compare actual storage information with requirements, and assess the material using suitable evidence. Authorized personnel would decide its **disposition**, meaning what will be done with it. Any additional testing or rework should have a justified, authorized plan. Employees must preserve the original evidence rather than repeat testing until a favorable result appears.

After a corrective action, the team needs evidence that it worked. If freezer assignments were confusing, revised signs alone are not proof of success. Checking storage records and observing handoffs over an appropriate period can show whether the change reduced errors. The amount of follow-up should reflect the risk and nature of the problem.

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2.5: Quality responsibilities throughout an organization

Quality depends on connected responsibilities throughout an organization. The quality department provides expertise and oversight, while other departments carry out and check their own assigned work. Employees need clear duties, suitable training, and access to help when conditions differ from instructions.



Research and development identifies useful product properties and develops methods to make and evaluate them. Moving a process to larger equipment can change conditions such as mixing or temperature. Development teams must examine whether those changes affect performance. Successful work at a small scale is important evidence, but it does not guarantee successful manufacturing at a larger scale.

Manufacturing performs the production steps and records what actually happened. Purchasing communicates requirements to suppliers. Receiving staff verify incoming identities and conditions. Engineering and maintenance support reliable equipment and facilities. Shipping protects the material during delivery. Each group can prevent a problem that would otherwise reach another employee or a customer.

A **standard operating procedure** (SOP) gives approved instructions for a recurring task. Staff need the current version and enough training to use it correctly. **Traceability** is the ability to follow the history, use, or location of an item through records. A lot identifier links an enzyme shipment to production and testing records, helping the organization investigate a complaint or identify other affected units.

Authority must also be clear. **Product release** is the authorized decision that a product may be distributed or used for its intended purpose. QC results may support that decision, while quality personnel review other evidence. The exact authority depends on the organization and applicable requirements. Department names alone do not establish who can approve release.

Organizations differ in size and purpose. One person may perform several functions in a small company; a larger company may have separate groups. Using contractors does not remove the need to define responsibilities and assess their work. Formal regulatory obligations depend on the activity, product, and location. General good practices described here should not be read as identical legal requirements for every biotechnology workplace.

Accountability means being answerable for assigned responsibilities, including accurate work and honest reporting.



Managers support accountability through workable procedures, sufficient resources, and a fair response to concerns. Prompt reporting gives people a chance to limit harm and improve the process. Shared responsibility does not give everyone the same decision authority.



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2.6: Costs and consequences of poor quality

Poor quality uses resources that could support useful work. It can also harm people who never see the laboratory or production floor. A researcher may lose valuable samples. A patient may face delayed information. Employees may spend long hours investigating a preventable problem. Communities may bear the burden of wasted materials and disposal.

The **cost of quality** is a way to account for resources used to prevent problems, evaluate conformance, and respond to failures. **Prevention costs** include planning and training intended to avoid problems. **Appraisal costs** include inspection and testing used to evaluate quality. These categories describe the purpose of the expenditure, rather than whether it occurs in a department named QA or QC.

Internal failure costs arise from problems identified before the product or service reaches the customer. Examples include scrap, investigation of a failed batch, and authorized rework. **External failure costs** arise from problems identified after delivery, such as complaint investigations, replacements, and recall activities. In this textbook's convention, the two failure categories together are the **cost of poor quality**; all four categories make up the cost of quality.

In a hypothetical monthly review, an enzyme company spends $800 on preventive training, $1,200 on routine testing, $2,000 on material scrapped before shipment, and $3,000 on replacing failed customer shipments. Its listed cost of quality is $7,000. Its listed cost of poor quality is $5,000, the two failure categories combined. These totals do not measure every consequence, such as lost research time or reduced trust.

Reducing testing without understanding the risk may lower one visible expense while allowing more failures to escape. A sound improvement examines the whole outcome. The goal is dependable work that meets requirements with less waste, while retaining the evidence and controls needed for the setting.



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2.7: When a diagnostic result could not be trusted

A diagnostic test provides information that can influence a decision. The BD BACTEC MGIT 960 PZA Kit is used to assess whether cultured Mycobacterium tuberculosis is susceptible or resistant to pyrazinamide, a tuberculosis drug. These are classifications under defined test conditions, rather than guarantees of an individual patient's response. A falsely resistant result can make a useful drug appear unsuitable.

The concern did not begin with the 2025 recall. In August 2024, CDC alerted laboratories to affected kit lots that could intermittently produce falsely resistant results. The alert described complaint trends and internal raw-material testing and instructed laboratories to inspect inventory and destroy affected kits. In 2025, FDA listed a further recall, initiated by BD on May 20 and posted June 25.

The problem illustrates why a product's quality depends on its intended use. A laboratory needs more than an intact kit with a clear label. It needs a test whose performance supports the question being asked. When that performance is uncertain, the uncertainty can reach the people who rely on the report.

The word intermittent is important. A problem that appears only some of the time may be harder to recognize than a failure that occurs in every test. One acceptable result cannot, by itself, explain away a pattern of complaints. Customer feedback gives an organization evidence to examine alongside test results, manufacturing information, and the conditions in which the product is used.

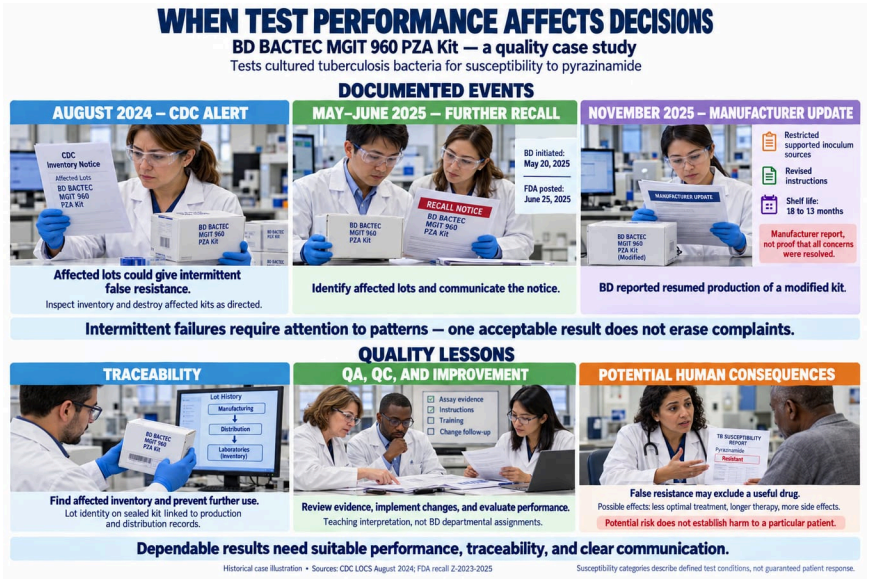
The recall response also depended on being able to identify particular material. A lot number connects a kit on a laboratory shelf with its production and distribution history. That connection gives traceability a practical purpose: staff can determine whether the notice applies to the material they have and pass the information to the people who need it. Finding affected inventory and preventing further use addresses the immediate problem while the broader response continues.

A later manufacturer communication, dated November 3, 2025, reported resumed production of a modified kit. It described restricted supported inoculum sources, revised instructions, and a shelf life reduced from 18 to 13 months. BD stated that the changes were intended to reduce the previously observed false resistance. This was the manufacturer's reported response, not independent proof that every possible performance concern had been resolved.

For a laboratory receiving revised instructions, the next task would be to put the change into practice. Staff would need the current instructions, training suited to the change, and a clear way to identify the applicable product. This is a teaching implication, not a documented account of a particular laboratory's actions. Issuing a revised document and confirming that people can use it are separate steps.

The case brings QA, QC, and improvement together. Testing provides evidence about performance. Quality oversight helps organize the review of that evidence, control instructions, and support decisions. Improvement requires evaluating whether a change produces the intended result. These connections describe the quality functions students are learning, not BD's internal departmental assignments.

The potential human consequences explain why these steps matter. CDC warned that omitting pyrazinamide because of a false resistance result could lead to a less optimal regimen, longer treatment, and greater risk of medication side effects. That warning describes a possible consequence; it does not establish that a particular patient was harmed. The case connects dependable performance with traceability, complaints, and communication, while keeping documented events separate from teaching interpretation.



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2.8: Applying quality terminology in different workplace settings



The documented case brings several terms together. To apply them elsewhere, start by naming the product, service, or process. Identify the requirement and available evidence, then describe what the action is intended to do: prevent a problem, detect it, limit exposure, correct it, or address its cause. Several terms may apply to one event, but each describes a different part of the response.

In a research laboratory, a mislabeled tube is a nonconformity if it fails the sample identification requirement. Holding the tube while its identity is investigated is containment. A correct-looking test result cannot establish sample identity. The laboratory needs evidence connecting the result to the right sample.

In manufacturing, an operator notices an unusual equipment reading and reports it before continuing. The observation supports detection. An investigation may show that the instrument needs repair, that the process changed, or that the reading was misunderstood. The observation alone does not prove which explanation is correct.

In a testing service, reports repeatedly arrive after the promised date. The laboratory might produce technically valid results and still fail the delivery requirement. A team can review where reports wait for review, test a revised handoff, and measure whether delivery improves without reducing review quality.

In customer support, staff may receive several complaints that an enzyme loses activity after delivery. Those complaints are evidence worth investigating, but they do not establish the cause. The team should connect the complaints with lot records, transport information, storage instructions, and test data. Careful language keeps an observation from becoming an unsupported conclusion.

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2.9: Chapter summary

Quality describes how well a product, service, or process meets requirements. In biotechnology, quality includes dependable product performance, valid laboratory results, accurate labels, suitable storage, and clear communication. A product's appearance or price alone cannot establish its quality. Decisions require evidence that can be compared with defined requirements.

Customer requirements and expectations help organizations understand what users need. A specification documents defined requirements, often including test methods and acceptance criteria. Fitness for use means that a product or service is suitable for its intended purpose. A reagent may meet its specifications yet be unsuitable for a different experiment or sample type.

Three related activities support quality. Quality assurance (QA) provides confidence through planned activities such as managing procedures, reviewing records, and overseeing training systems. Quality control (QC) uses testing, measurement, and inspection to help fulfill quality requirements. Quality improvement uses evidence to strengthen processes and outcomes. These activities work together, and their responsibilities may overlap.

Organizations also need to distinguish different responses to problems. Prevention reduces the likelihood of a problem, while detection identifies a problem that has occurred. Containment limits exposure while a concern is investigated. A correction addresses the detected problem; corrective action addresses its cause to prevent recurrence. After making a change, the organization should check whether it worked.

Quality depends on employees throughout an organization. Management provides resources and establishes responsibilities. Other functions develop products, purchase materials, perform production, maintain equipment, test samples, review records, and communicate with customers. Approved instructions, honest reporting, traceable records, and clear decision authority help these groups work together. A passing test alone does not replace the other evidence needed for a release decision.

The cost of quality includes prevention, appraisal, internal failure, and external failure costs. Under this chapter's convention, internal and external failure costs together make up the cost of poor quality. Financial totals capture only part of the impact. Poor quality can also waste research samples, delay decisions, increase employee workload, and reduce trust.

The documented diagnostic-kit example shows why dependable performance, customer complaints, lot records, and communication matter. Quality problems can affect the people who rely on laboratory information. Careful investigations must distinguish what the evidence establishes from what remains uncertain.

Key terms

Quality	Requirement	Specification
Product	Service	Process
Customer	Internal customer	External customer
Customer requirements	Customer expectations	Fitness for use
Quality assurance	Quality control	Quality improvement
Continuous improvement	Prevention	Detection

Nonconformity	Containment	Correction
Corrective action	Disposition	Product release
Standard operating procedure	Traceability	Accountability
Cost of quality	Prevention costs	Appraisal costs
Internal failure costs	External failure costs	Cost of poor quality

Review questions

1. What does quality mean when evaluating a biotechnology product or service?

2. What is the difference between a product, a service, and a process? Give one biotechnology example of each.

3. How does an internal customer differ from an external customer?

4. What is a specification, and how does it help employees evaluate quality?

5. What does fitness for use mean?

6. How do QA, QC, and quality improvement contribute to dependable work?

7. What is the difference between prevention and detection?

8. How does correction differ from corrective action?

9. How do standard operating procedures and traceability support quality?

10. What are the four cost-of-quality categories? Which two make up the cost of poor quality?

Apply your knowledge

1. A shipment with uncertain storage conditions

An enzyme shipment is found in the wrong freezer. The containers look normal, but the team has not confirmed the actual storage temperature. The customer needs the enzyme tomorrow. Describe an appropriate response that includes containment, evidence gathering, customer communication, and decision authority. Explain why neither the freezer location nor the containers' appearance establishes whether the enzyme is suitable for use.

2. A passing result with missing information

A batch meets its enzyme activity specification, but a required production record is incomplete. Explain what the passing result establishes and what remains uncertain. Identify additional information and review needed before authorized personnel decide whether to release the batch.

3. A recurring labeling problem

Three employees select an outdated label template during the same month. A supervisor suggests reminding everyone to be

more careful. Identify two conditions the team should investigate. Propose a corrective action based on one possible finding, and explain how the team could check whether the action reduced errors.

4. Calculating quality costs

A laboratory spends $700 on preventive training, $1,100 on routine quality checks, $1,600 on work repeated because of errors found before reporting, and $2,500 on correcting errors after reports reach customers. Classify each expense. Calculate the listed cost of quality and cost of poor quality. Identify one consequence these totals do not capture.

5. Meeting a specification versus meeting a need

A researcher buys an enzyme that meets its stated specifications but plans to use it with a sample type the supplier has not evaluated. Explain why meeting specifications does not establish fitness for this new use. Describe what the researcher and supplier should clarify and what evidence could support a decision.

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3: QUALITY PHILOSOPHIES AND IMPROVEMENT FRAMEWORKS

Learning Objectives

After completing this chapter, you should be able to:

- Describe how inspection, prevention, and organization-wide improvement contribute to modern quality management.
- Explain Shewhart's contributions and apply the plan-do-check-act cycle to a biotechnology problem.
- Interpret Deming's 14 points and connect them to leadership decisions.
- Distinguish quality planning, quality control, and quality improvement in Juran's trilogy.
- Explain how Ishikawa's approach supports employee participation and investigation of possible causes.
- Evaluate Crosby's prevention approach and the responsible use of a zero-defects expectation.
- Compare quality philosophies and select useful applications for biotechnology work.
- Distinguish a management philosophy, an improvement framework, and an individual quality tool.

A process map helps show how work fits together within a system. **Quality philosophies** help leaders decide how to manage that work, support employees, and respond when performance falls short.

A biotechnology company supplies cell culture medium to research laboratories. During the past month, several customers have reported that bottle labels are difficult to read. The company replaces the affected bottles, but similar complaints arrive the next week. Shipping staff check every label again. Supervisors remind employees to be more careful. The problem continues.

What should the company do next? It could examine label printing over time, ask employees what makes the labels difficult to check, clarify what customers need, or redesign the labeling process. Each response reflects a way of thinking about quality. The choice matters because repeated inspections and reminders may leave the conditions causing the problem untouched.

This hypothetical situation introduces the work of five influential quality thinkers: Walter Shewhart, W. Edwards Deming, Joseph Juran, Kaoru Ishikawa, and Philip Crosby. Their approaches differ, but each offers a way to move beyond repeated corrections. Their ideas help explain how leaders, employees, and evidence can work together to protect customers and improve performance.

3.1: Development of modern quality management

3.2: Shewhart's contributions and the PDCA improvement cycle

3.3: Deming's management philosophy and 14 points

3.4: Juran's trilogy- planning, control, and improvement

3.5: Ishikawa's contributions to participation and cause analysis

3.6: Crosby's prevention approach and zero-defects philosophy

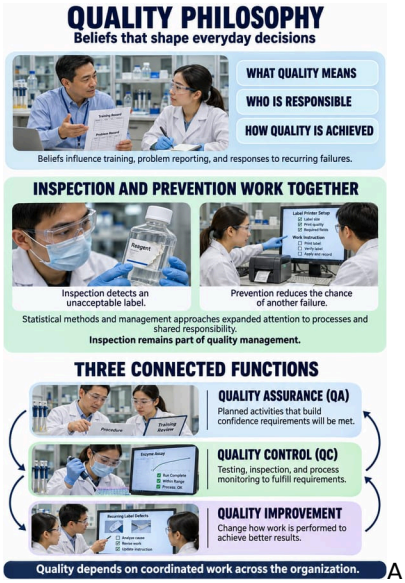
3.7: Comparing philosophies and selecting useful applications

3.8: Distinguishing management philosophies from individual tools

3.9: Chapter Summary

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3.1: Development of modern quality management



A quality philosophy is a set of beliefs about what quality means, who is responsible for it, and how it should be achieved. It influences everyday decisions, including whether managers invest in training, how employees report problems, and whether an organization studies recurring failures.

Inspection has long helped separate acceptable products from unacceptable ones. It remains important, but finding a damaged label does not prevent the next damaged label. During the twentieth century, statistical methods and management approaches strengthened attention to process behavior, **prevention**, and organization-wide responsibility. These approaches developed alongside one another; inspection did not simply disappear as newer ideas emerged.

Modern quality management includes several connected functions. **Quality assurance**, or QA, focuses on planned activities that provide confidence requirements will be met. **Quality control**, or QC, focuses on fulfilling requirements through operational activities, including testing, inspection, and process monitoring. **Quality improvement** changes how work is performed to achieve better results. These functions support one another.

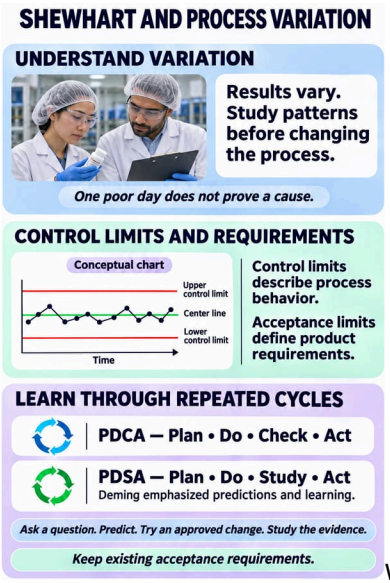
For the medium company, QA may establish how label changes are reviewed and employees are trained. QC may check that the printed batch number is correct and readable. Improvement may involve studying why labels smear and evaluating a more reliable printing setup. The goal is dependable work that serves the people using the product.

Prevention means acting to reduce the likelihood of a problem before it occurs. Clear label requirements and a reliable printing process help protect customers before bottles leave the company. A **regulation** is an enforceable rule issued under legal authority; a quality philosophy guides management thinking. Following a philosophy does not, by itself, demonstrate regulatory compliance. Applicable requirements depend on the product and activity.

An **improvement framework** provides an organized structure for examining performance and making changes. A **quality tool** supports a specific task, such as recording defects or organizing possible causes. A philosophy influences the questions an organization asks; a framework helps organize the work; tools help answer particular questions.

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3.2: Shewhart's contributions and the PDCA improvement cycle



Walter A. Shewhart helped establish a scientific approach to quality control. His work connected statistical reasoning with industrial decisions, and he is especially associated with the **control chart**. **Variation** means differences among repeated results. Some differences are expected in a process; others may signal that conditions have changed.

A control chart displays process results over time with a center line and statistically derived limits. It helps users evaluate process behavior. Those limits describe process behavior and are different from the acceptance limits set for a product. A chart does not automatically prove that every result meets customer requirements.

Imagine that the medium company records the proportion of unreadable labels each day. Staff must respond to unacceptable labels under the approved procedure. To improve the process, the team also examines the longer pattern and relevant changes in materials or equipment. One unusually poor day does not by itself prove a special cause or identify who caused it. Adjusting settings after every fluctuation can make the process less predictable.

Shewhart's work influenced later learning cycles. **Plan-do-check-act**, or PDCA, organizes a repeating process of planning a change, trying it, examining results, and deciding what to do next. Deming emphasized **plan-do-study-act**, or PDSA, with particular attention to comparing results with predictions and building knowledge. The cycles are related, but their names should not be treated as interchangeable when describing Deming's teaching. Neither name means that Shewhart alone invented the modern PDCA form.

A useful cycle begins with a question and a prediction. For example: Will a different approved printer setting reduce smearing without making batch numbers harder to read? Define an unreadable label consistently and compare unreadable labels with the total examined under comparable handling conditions. The worked example below is hypothetical. The trial needs the applicable approvals, and its improvement target does not replace existing acceptance requirements.

If the trial does not improve results, the team should review what was tested and what the evidence supports. The result may prompt investigation of storage conditions or label materials, but it does not prove either caused the problem. Revise the question and plan another justified test. A limited trial also cannot establish long-term performance by itself.

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3.3: Deming’s management philosophy and 14 points

W. Edwards Deming emphasized management’s responsibility for the system in which people work.



His 14 points address purpose, leadership, cooperation, learning, and the conditions needed for quality. The following numbered list paraphrases the points; it is not a quotation.

1. Maintain a lasting purpose centered on improving products and services.

2. Adopt management practices that make quality a central responsibility.

3. Build quality into work instead of depending on final inspection.

4. Minimize total purchasing cost; move toward a single supplier for each item through long-term trust.

5. Keep improving production and service systems.

6. Provide training for the work people perform.

7. Lead by helping people and processes perform better.

8. Remove fear that prevents honest communication.

9. Enable cooperation across departments.

10. Replace workforce slogans and unsupported demands with practical system improvement.

11. Replace quotas and management by numerical targets with leadership.

12. Remove barriers to pride in work, including annual merit ratings and management by objectives.

13. Support education and continued personal development.

14. Involve everyone in changing the organization.

These points need careful interpretation. Reducing dependence on inspection does not cancel required testing or release checks. Deming’s single-supplier recommendation is a historical management position; a biotechnology organization must evaluate supplier qualification, continuity of supply, and applicable requirements. His criticism of numerical management does not make measurement unnecessary. Measurable objectives should support learning and sound decisions, rather than become quotas pursued at the expense of quality.



For the medium company, a poster telling employees to produce perfect labels adds little if the printer frequently smears or the purchasing specification permits unsuitable label stock. Managers need to provide usable materials, clear requirements, and a process employees can follow. Staff members should still follow approved instructions, document their work, and report problems promptly.

Consider a supervisor who praises only the number of bottles labeled per hour. Employees may feel pressure to continue when print quality becomes uncertain. A better response would examine both dependable output and the conditions that support it. Production, purchasing, maintenance, and QC may all need to participate. This is a hypothetical application of Deming's ideas, rather than a practice attributed to a particular company.

Removing fear does not remove accountability. An employee who identifies an error should be able to report it without being discouraged or humiliated. Leaders must then examine the evidence, address behavior fairly, and improve conditions that make errors more likely. Open reporting gives the organization information it would otherwise lose.

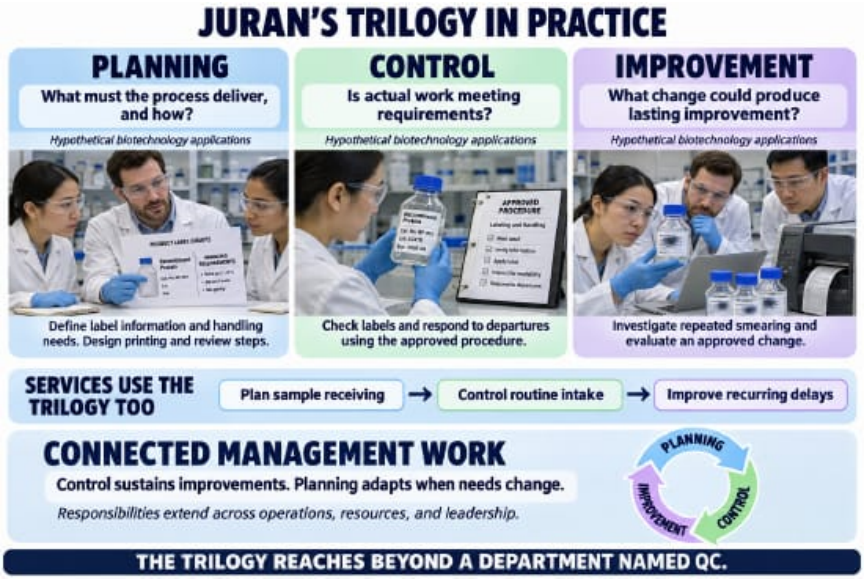
Deming's points form a connected management approach. Selecting only a convenient point, such as training employees, while keeping conflicting incentives can weaken the result. Training cannot compensate for every equipment, staffing, or communication problem.

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3.4: Juran's trilogy- planning, control, and improvement

Joseph M. Juran's **quality trilogy** describes three related management processes: **quality planning**, quality control, and quality improvement. Each addresses a different question. What should the process accomplish? Is it performing as intended? How can it achieve a better level of performance?

Quality planning identifies customers, determines their needs, and designs products and processes to meet those needs. Quality control evaluates actual performance against established goals and responds to differences. Quality improvement changes the process to overcome recurring limitations. Restoring a process after a disruption is important, but it may only return performance to the previous level.



In the medium company, planning includes deciding which information customers need on a label, how readable it must be, and how it will remain attached during expected handling. Employees need a practical way to determine whether those requirements are met. A vague instruction to make labels look good is difficult to apply consistently.

Control includes checking print settings, verifying required information, and following an established response when labels do not meet requirements. If the printer runs out of ink, correcting that immediate problem may restore normal operations. It does not necessarily resolve smearing that has occurred for months.

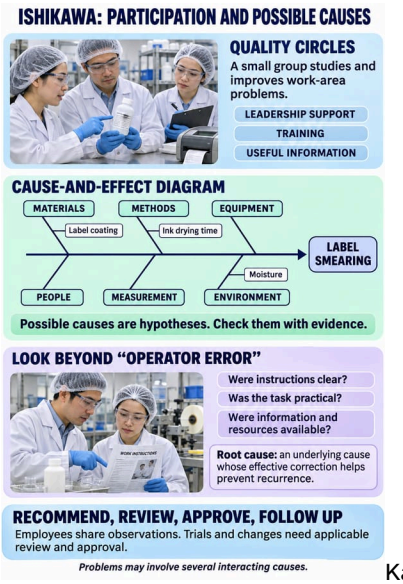
A **chronic problem** is a recurring problem that continues under the usual way of working. Improvement may require examining label materials, handling conditions, equipment capability, and work instructions together. A team that only replaces rejected labels can remain busy while the underlying loss continues.

The trilogy also applies to services. A laboratory plans how to receive samples, controls routine intake, and improves a recurring delay. These management processes are broader than the work of a department named QC. Planning involves customer needs, operations, resources, and leadership decisions throughout the organization.

Once improvement establishes a better way of working, control helps sustain it. Planning may also need revision as customer needs, materials, or services change. The trilogy describes connected management work, rather than three steps performed only once.

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3.5: Ishikawa's contributions to participation and cause analysis



Kaoru Ishikawa supported broad participation in quality and helped develop the **quality circle** movement. A quality circle is a small group of employees, typically from the same work area, who meet to study and improve work-related problems. Leadership support, training, and access to useful information help make participation effective. Broader investigations may also bring together people from different departments.

Ishikawa is also associated with the **cause-and-effect diagram**, often called a fishbone diagram. This tool organizes possible causes of a clearly stated problem. It helps a team consider several explanations, but it does not establish which explanation is correct. Evidence is needed to distinguish a possible cause from a supported conclusion.

For the label problem, operators may notice that smearing increases after cleaning. Purchasing staff may know that the label material changed. Maintenance staff may identify wear in the printer. A manager who hears only one department's explanation may miss an important relationship. Participation helps bring these different observations together.

A team could organize possible causes under headings such as materials, methods, equipment, people, measurement, and environment. These headings are prompts, not mandatory categories. Under materials, the team might list label coating. Under methods, it might list the time allowed for ink to dry. Under environment, it might list moisture during handling. All remain hypotheses until checked.

A **root cause** is an underlying cause that, when addressed effectively, helps prevent recurrence of a problem. Some problems involve several interacting causes. Writing operator error at the end of an investigation often leaves important questions unanswered: Were instructions clear? Was the task practical? Did the operator have the necessary information and resources?

Employees should contribute observations without being asked to make changes beyond their authority. A quality circle may recommend a trial, but the proposal still needs the applicable technical review and approvals. Meaningful participation combines employee knowledge with clear responsibility, evidence, and follow-up.

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3.6: Crosby's prevention approach and zero-defects philosophy



Philip B. Crosby defined quality in terms of **conformance** to requirements and promoted a preventive management culture. His **zero-defects philosophy** treats zero defects as the performance standard rather than accepting a routine allowance for failures. It emphasizes clear requirements and prevention. This standard is not evidence that a process has no risk or can never produce a defect.

Conformance means meeting established requirements. A label with the wrong batch number does not become acceptable because its color and appearance are attractive. Before judging conformance, however, the organization must define what is required and give employees a dependable way to meet that requirement.

A responsible teaching application is to pair high expectations with practical support. For



the medium company, prevention could include verifying the correct label template before printing and preventing outdated templates from being selected. These are hypothetical examples, not practices documented in Crosby's biography.

A zero-defects expectation should never become a reason to hide errors, alter records, or punish honest reporting. An organization needs accurate information about failures to improve. It should also avoid claiming that an ambitious expectation proves a process is capable of meeting it. Capability must be evaluated using evidence.

The **cost of poor quality** is the loss associated with failures and the work needed to address them. It includes internal and external failure costs. Examples include avoidable repeat testing caused by errors, discarded materials, replacement shipments, and failure investigations. Planned replicate tests are not failure costs simply because a measurement is repeated. Prevention

can reduce losses, but each proposed investment still needs evaluation.



Crosby and Deming should not be collapsed into one message. Crosby promoted zero defects as a performance expectation; Deming explicitly rejected workforce exhortations demanding zero defects. When comparing them, examine both the expectation and the management behavior behind it. A demand for perfect results without changing inadequate conditions offers employees little help.

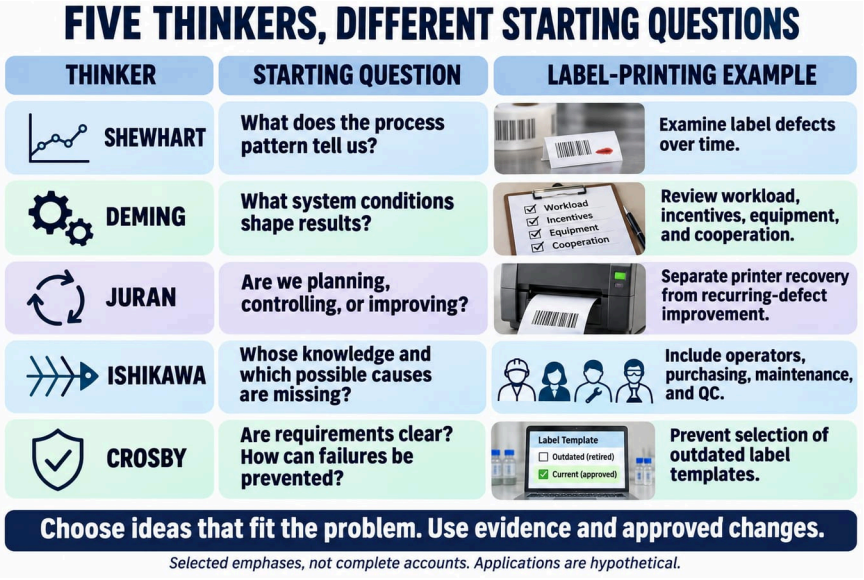
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3.7: Comparing philosophies and selecting useful applications

The five thinkers offer different starting questions. Shewhart directs attention to process behavior and variation. Deming asks how management decisions shape the system. Juran distinguishes designing performance, maintaining it, and improving it. Ishikawa broadens participation and possible-cause analysis. Crosby emphasizes clear requirements and prevention. These are selected emphases, not exclusive contributions or complete accounts of their work.

A team should select ideas that address the problem it faces. If no one agrees on what a readable label means, requirements need clarification. If requirements are clear but the process behaves unpredictably, evidence about variation is useful. If employees know about a recurring problem but feel unable to speak, a new chart alone will not address the barrier.

A combined response might clarify requirements, include the employees doing the work, examine time-based data, and test an approved change. Combining ideas is useful when their roles are clear. It becomes confusing when every idea is treated as an interchangeable slogan.



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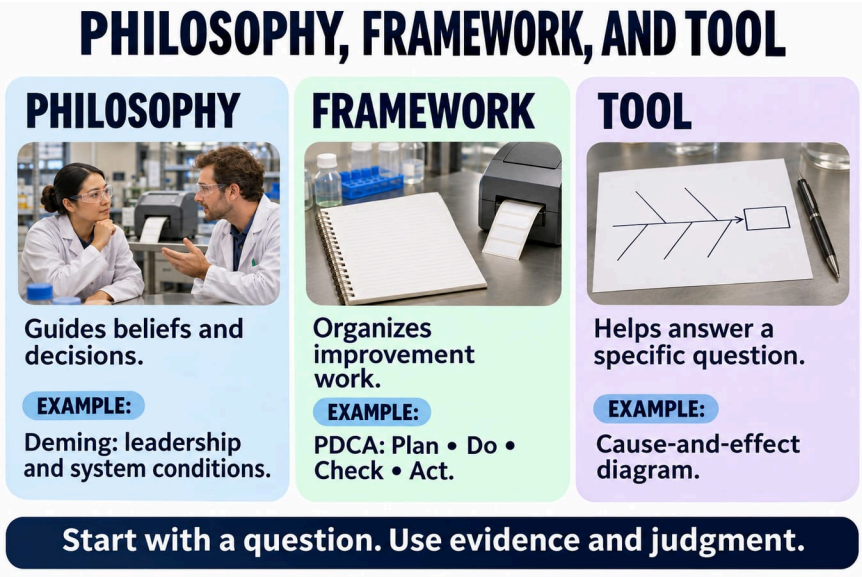
3.8: Distinguishing management philosophies from individual tools

A philosophy describes broad beliefs about managing quality. A framework organizes improvement work or organizational assessment. A tool helps perform a specific activity. These levels are connected, but they are not interchangeable. A fishbone diagram is not a complete management philosophy, and completing a PDCA form does not prove that learning occurred.

For example, an organization may value broad participation, use PDCA to organize a label-printing trial, and use a cause-and-effect diagram to plan its investigation. It may then use a control chart to examine process behavior. The tools serve the question being asked; they do not make decisions without human judgment.

An organization can use a sophisticated tool poorly. A control chart built from inconsistent measurements may mislead the team. A cause-and-effect diagram completed only by managers may overlook practical conditions. A successful trial may not last if instructions, training, resources, and follow-up are missing.

Choose the question first. Then select the approach, gather suitable evidence, decide within the appropriate authority, and check the result. In biotechnology, changes may affect scientific validity, product quality, or customer use. Improvement work must operate within applicable requirements and the organization's approved change process.



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3.9: Chapter Summary

Modern quality management extends beyond finding defects. It includes designing dependable processes, supporting employees, checking results, and learning from evidence. QA, QC, and improvement work together to protect the people who rely on biotechnology products and services.

Shewhart helped establish statistical quality control and attention to process variation. Learning cycles such as PDCA and PDSA organize investigation and action. Deming's 14 points emphasize management responsibility, cooperation, education, and conditions that allow good work. Juran's trilogy distinguishes planning, control, and improvement. Ishikawa supports participation and organized cause analysis. Crosby emphasizes conformance to requirements and prevention.

These approaches share interests while retaining meaningful differences. A high expectation is useful when people have clear requirements and capable processes. Employee participation is useful when observations lead to evidence and action. A philosophy, framework, or tool should be chosen for its purpose and judged through its application, not its name alone.

Key Terms

Quality philosophy	**Quality assurance**	**Quality control**
Quality improvement	Prevention	Regulation
Improvement framework	Quality tool	Variation
Control chart	Plan-do-check-act	Plan-do-study-act
Quality trilogy	Quality planning	Chronic problem
Quality circle	Cause-and-effect diagram	Root cause
Zero-defects philosophy	Conformance	Cost of poor quality

Review Questions

1. Why do modern quality systems combine inspection, prevention, and improvement?

2. How do QA, QC, and quality improvement contribute to dependable biotechnology work?

3. What was Shewhart's contribution to quality control, and what question can a control chart help answer?

4. Describe the four stages of PDCA. What does the word study emphasize in PDSA?

5. Choose three of Deming's 14 points and explain how they could affect a biotechnology laboratory.

6. Why might a production quota interfere with dependable quality? How can managers use measures to support learning

instead?

7. Distinguish planning, control, and improvement in Juran's trilogy.

8. How does restoring normal operation differ from reducing a chronic problem?

9. What contributions did Ishikawa make to participation and cause analysis?

10. Why does a cause-and-effect diagram require follow-up evidence?

11. Explain Crosby's conformance and prevention concepts. How could a zero-defects demand be misused?

12. Distinguish a philosophy, a framework, and a tool, using one example of each.

Apply Your Understanding

1. A culture-medium supplier receives repeated complaints about unreadable labels. Supervisors propose more inspections and a poster telling employees to be careful. Use two quality philosophies to evaluate that response. Propose actions, identify who should participate, and state what evidence would help assess the result.

2. A laboratory proposes a new sample submission form to reduce missing information. Design a PDCA cycle with a specific prediction, an authorized trial, measures, and a decision after review. Explain what the team should learn if missing information does not decrease.

3. A freezer failure interrupts testing. Staff transfer materials according to the approved procedure and assess whether affected materials remain suitable. A separate investigation finds that freezer alarms have been unreliable for months. Use Juran's trilogy to distinguish immediate control from the work needed to improve the system. What planning decisions also deserve review?

4. A manager announces that no documentation errors will be accepted, but employees receive conflicting instructions and cannot access the current form. Compare a responsible prevention approach with a demand for perfection. Explain how leaders can maintain accountability while supporting honest reporting and clear requirements.

5. In the Donor Alliance story, staff meetings, measurement, leadership practices, and reported outcomes appear together. Identify two connections to this chapter's philosophies. Explain why the account does not prove that one meeting format caused the reported transplantation outcome. What additional evidence would help evaluate a particular improvement?

6. Your team lists printer wear, label material, moisture, and drying time as possible causes of smearing. Another team member says the fishbone diagram has solved the problem. Explain what the tool has accomplished and what remains unknown. Select an improvement framework and propose the next evidence-gathering step.

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4: QUALITY PLANS AND ORGANIZATIONAL RESPONSIBILITY

Learning Objectives

After completing this chapter, you should be able to:

- Define a quality plan and describe how its scope guides work across an organization.
- Connect quality objectives with an organization's mission, vision, and strategy.
- Translate a requirement into activities, responsibilities, acceptance criteria, and records.
- Explain contributions from management, operations, quality, purchasing, and support functions.
- Evaluate whether training, resources, documentation, and communication support a plan.
- Interpret performance measures and propose suitable review schedules.
- Describe how to assess, approve, communicate, and verify changes to a quality plan.

A **quality plan** identifies who acts, what resources are needed, what evidence must be kept, and who makes decisions. These connections help people work together before a gap reaches the customer.

A biotechnology company is preparing to sell a new enzyme kit for research laboratories. Development staff have evidence that the enzyme performs its intended activity under the conditions studied. Manufacturing has prepared larger batches, and sales staff are answering customer questions. Then a shipping employee asks: Who selects and approves the packaging that will protect the enzyme during delivery?

Development expected shipping to select packaging. Shipping expected approved instructions. Quality control (QC) has an activity test, but the organization has not defined the transport evidence or approval needed before shipment. Useful work has been completed, yet the **handoff** between responsibilities remains unclear. Successful activity testing alone does not establish that a packaging configuration will protect the product in transit.

This hypothetical situation shows why quality needs a plan. A successful product depends on people agreeing about requirements, actions, evidence, and decisions before a gap becomes a customer's problem. This chapter explains how a quality plan turns shared intentions into coordinated work. Unless identified as a documented event, examples and numerical targets are hypothetical teaching examples, not regulatory requirements.

4.1: Purpose and scope of a quality plan

4.2: Connecting quality objectives to organizational strategy

4.3: Translating requirements into responsibilities and activities

4.4: Example of translating one requirement

4.5: Contributions from management, operations, quality, purchasing, and support functions

4.6: Training, resources, documentation, and communication

4.7: Performance measures and review schedules

4.8: Updating a quality plan when requirements or processes change

4.9: Example - When a bottle shortage challenged laboratory planning

4.10: Chapter summary

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4.1: Purpose and scope of a quality plan



A **quality plan** describes the activities, resources, responsibilities, controls, and timing used to meet quality requirements for a defined product, service, process, or project. It answers practical questions: What must be achieved? Who will do the work? When will it occur? What evidence is needed? Who reviews and approves it? What happens when a requirement is not met? ASQ describes quality plans as linking objectives with the practices, resources, and activities needed to achieve them.

The **scope** defines what the plan covers and where its boundaries lie. A plan for an enzyme kit might cover incoming materials through production, testing, storage, shipment, and complaint handling. It should identify the kit and intended use clearly. If development studies are covered by another plan, the connection should be stated so that important work does not fall between the two.

A **quality management system** (QMS) is the connected policies, processes, responsibilities, and resources an organization uses to direct and manage quality. It provides common practices, such as **document control** and training. A quality plan applies the relevant practices to a defined need and can refer to existing procedures instead of copying them. The plan and QMS should agree; the plan does not replace the wider system.

A plan also differs from a standard operating procedure. A procedure explains how to perform a recurring task. The quality plan identifies which procedures apply, who performs the tasks, when checks occur, and what records support decisions. A test procedure alone cannot answer all the questions about staffing, supplier approval, shipping, or release authority.

The level of detail should match the work and its **risk**. For the potential harms considered here, risk involves both the likelihood of an unwanted event and the seriousness of its consequences. A temperature-sensitive product may need controls different from those for a stable research supply. Risk-based planning uses evidence to select suitable controls while retaining applicable requirements; it does not justify removing an inconvenient check without assessment.

A useful plan is accessible and workable. Staff should be able to locate their responsibilities without searching through unrelated material. A short plan that refers to controlled procedures may be more useful than a long document that repeats instructions and becomes outdated.

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4.2: Connecting quality objectives to organizational strategy



An organization's **mission** describes its purpose and the people or needs it serves. Its **vision** describes a desired future. **Values** express principles that guide behavior. These statements influence quality when they shape decisions about resources, priorities, and acceptable conduct.

For the enzyme company, a mission might be to provide dependable tools that help researchers obtain useful results. Its vision might be to become a trusted supplier for teaching and research laboratories. Values might include honest reporting and respect for customers' time. These statements become meaningful when employees have the time and support to act on them.

Organizational strategy is the overall approach used to reach important goals. A strategy to expand sales can create pressure to increase output quickly. Quality planning connects that goal with the conditions needed to protect performance, such as sufficient testing capacity, trained staff, and reliable supplies. Growth should include the resources that make dependable delivery possible.

A **quality objective** is a defined result the organization intends to achieve in relation to quality. It should be specific enough to evaluate. For example: "Reduce the proportion of shipments with documented temperature excursions from a verified 6% **baseline** to 2% or less during the final month of the next quarter, while obtaining usable records for every shipment that requires **monitoring**." The figures are hypothetical planning targets.

An objective needs an owner, an evaluation period, and consistent measurement rules. Here, a temperature excursion means a departure from approved transport limits. The 2% target measures progress across shipments; it does not permit an excursion in any particular shipment. Each exception still needs assessment. The team must also track missing records so that incomplete monitoring does not make performance look better.

Targets can create unintended pressure. A team rewarded only for rapid shipment may avoid reporting a temperature problem. A balanced plan pairs delivery measures with measures of product condition and **record** completeness. Honest reporting must remain valuable even when it reveals that a target has been missed.

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4.3: Translating requirements into responsibilities and activities

Once the objective and scope are clear, identify the source of each important requirement. Sources may include intended use, customer agreements, development evidence, internal policies, and applicable regulations. Distinguish mandatory requirements from preferences and improvement targets. A customer preference cannot authorize staff to ignore an applicable safety or regulatory obligation.

Next, the team translates each requirement into work that can be assigned and checked. **Acceptance criteria** are the conditions that must be met for a result, material, or activity to be considered acceptable. They should be established before the decision, using a suitable scientific or business basis. An improvement target describes a desired change; an acceptance criterion governs a particular evaluation. They serve different purposes.

A **process owner** is the person responsible for overseeing a defined process's ongoing performance and coordinating needed changes. The owner helps resolve gaps and arranges follow-up within their authority. Performing a task, reviewing its evidence, and authorizing a decision may belong to different people. Naming an owner does not transfer every technical or release approval to that person.

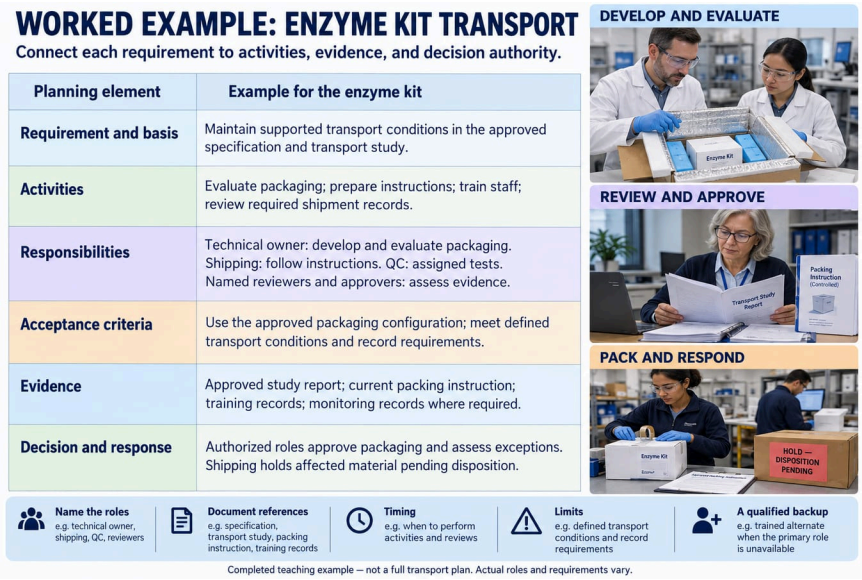
A **handoff** occurs when work, material, information, or responsibility passes from one person or group to another. Define the sender, receiver, required information, and how receipt is confirmed. A batch may enter storage while it is still awaiting release, provided its identity, status, and permitted handling remain clear. A handoff must not make material appear approved merely because it has moved to another location.



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4.4: Example of translating one requirement

Suppose the enzyme kit must remain within transport conditions supported by suitable studies. The plan references the approved conditions, packaging configuration, and supporting evidence. It also assigns who develops the packaging proposal, evaluates it, approves it, and uses it. The following matrix connects the requirement to that work.



This matrix is a completed teaching example, not a full transport plan. The actual plan would identify roles, document references, timing, and limits precisely. It should also name a backup when a key decision-maker is unavailable. A responsibility that depends on one absent employee can become a predictable source of delay.

The opening question now has a practical answer: a designated technical owner develops and evaluates the packaging proposal; the named approving roles review the evidence; trained shipping staff use the approved configuration. The exact roles vary by organization. Writing “QA is responsible for quality” would leave these steps unclear.

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4.5: Contributions from management, operations, quality, purchasing, and support functions

Management approves priorities, provides resources, and defines decision authority. Leaders also set expectations for reporting. If staff are told to follow procedures but given schedules that make this impossible, the quality plan needs management attention. Employees should not have to choose between documenting work honestly and meeting an unrealistic deadline.

Operations includes the groups that perform the core work, such as manufacturing or laboratory testing. These staff help identify practical limits that may be missed during planning. Their contribution includes following approved instructions, recording actual conditions, and reporting when work cannot proceed as planned.

Quality assurance (QA) supports planned activities that provide confidence requirements will be met. QC focuses on fulfilling requirements through operational activities, including measurement, testing, and **inspection**. Development supplies knowledge about product performance and process design. These functions help establish sound controls together; specifications need a suitable basis regardless of which department prepares them.

Purchasing turns technical needs into clear supplier requirements and agreements. Receiving checks incoming identity, condition, and required records. Engineering, maintenance, and information technology help keep equipment and electronic systems fit for their assigned purpose. Customer support reports patterns that may reveal unmet needs or product problems.

Escalation means bringing an issue to someone with the authority or expertise to address it. The plan should state which situations require escalation and who is contacted. For example, a missing transport record may require a hold and quality review rather than an informal decision by the packer.

Organizations may combine roles, especially when they are small. Contractors may also perform testing, maintenance, or shipping. The plan must still establish who supplies requirements, reviews results, and follows up on problems. Exact responsibilities and required independence depend on the work and applicable rules; a department title does not settle them.



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4.6: Training, resources, documentation, and communication



Assigning responsibilities is only the beginning. A plan can fail when people lack the ability or resources to carry out their assigned work. **Competence** is the ability to apply knowledge and skills to achieve intended results. A training record may show attendance, reading, practice, or a performance assessment. Its meaning depends on what was evaluated; a signature alone does not establish readiness. Training should fit the task. Reading a revised contact list may be sufficient for one change. A new packing method may require demonstration, supervised practice, and an observed performance check. The plan should identify who evaluates readiness and what happens if additional practice is needed.

Resources include staff time, equipment, space, approved materials, reliable software, and access to expertise. A plan that requires temperature monitoring needs suitable devices, a method for reviewing their records, and staff available to respond. Budgeting only for the devices leaves part of the work unsupported.

Document control manages how instructions are reviewed, approved, issued, revised, and withdrawn from routine use. Employees need the current approved version where they work. Superseded versions may need to be retained for history or other requirements, but they should be clearly identified and protected from accidental use. A plan should identify who maintains its references to controlled instructions.

A **record** is a type of document that preserves evidence of an activity or result. An instruction describes what should happen; a completed record documents what was observed or done. For example, a packing instruction guides the work, while a completed packing record identifies the shipment and provides evidence about its preparation. Both need control, but completed records should preserve the history rather than be silently updated to match later instructions.

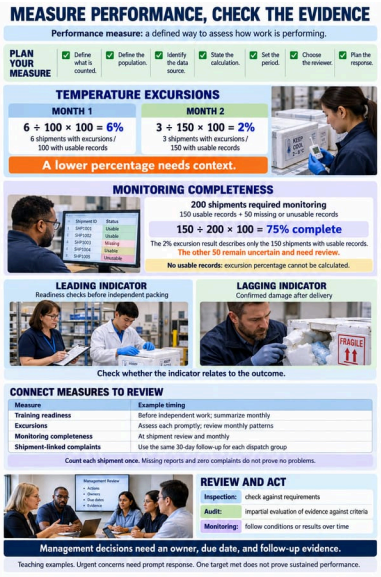
Data integrity means keeping information complete, consistent, and accurate throughout its use and retention. Record what actually happened and preserve original evidence. An inconvenient temperature reading needs assessment. Follow the approved correction process so that a later reader can understand what changed and why.

Communication planning identifies what information must reach whom, when, and through which channel. Routine summaries may be reviewed at scheduled meetings, while an urgent concern needs the defined immediate reporting route. Sending a message does not establish that it was understood. Acknowledgment confirms receipt; repeating key details and obtaining confirmation checks understanding. Neither alone proves that the assigned work is complete. For the enzyme company, the plan could require shipping staff to contact the designated quality reviewer before moving a held shipment. Customer support would receive the approved delivery update so that it can give customers accurate information. This links technical decisions with respectful communication about delays.

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4.7: Performance measures and review schedules

A **performance measure** is a defined way to assess how a process or plan is working. A baseline is the



starting performance used for comparison. Specify the population, what is counted, the data source, calculation, evaluation period, reviewer, and response to a concerning result. These details connect the plan's objectives with evidence that can guide a decision.

Consider the percentage of monitored shipments with a temperature excursion. If 6 of 100 monitored shipments had an excursion, the result is 6 ÷ 100 × 100 = 6%. If 3 of 150 had an excursion the next month, the result is 2%. The percentage decreased, but the team still needs to check whether monitoring coverage and the definition of an excursion stayed consistent.

Missing records matter. Suppose the second month included 200 shipments requiring monitoring, but only 150 had usable records. The 2% figure describes those 150 shipments, not all 200. Monitoring completeness is 150 ÷ 200 × 100 = 75%. The 50 shipments with missing or unusable records remain uncertain and need the required review. If there are no usable records, an excursion percentage cannot be calculated.

A **leading indicator** tracks an activity or condition expected to help prevent a later problem, such as readiness checks before staff pack independently. A **lagging indicator** describes a result that has already occurred, such as confirmed damage after delivery. These labels depend on the outcome being studied: training completion is a completed activity, but may be used as a leading indicator of future packing performance. The relationship must be checked; completion alone does not prove an improvement.

These schedules are teaching examples. The appropriate frequency depends on the risk, workload, history, and applicable requirements. A quarterly review should not delay an urgent response. The plan should name event-based triggers as well as calendar dates.

The complaint example links reports to the shipments they concern and uses a fixed follow-up period. Reports received this month may concern earlier shipments, so simply dividing this month's complaint count by this month's shipment count can be misleading. A zero count also does not prove that no problems occurred.

An inspection checks an item or activity against defined requirements. An **audit** systematically evaluates recorded evidence against stated criteria and requires an impartial reviewer. It may examine a product, process, or management system. The reviewer need not always come from outside the organization. Monitoring follows selected conditions or results over time. These approaches answer different questions and can support one another.

During **management review**, leaders assess the continuing suitability and performance of the quality system and decide on actions or resources. Decisions need an owner, due date, and follow-up evidence. A product meeting its specification is also different from a process showing statistical stability over time. A target being met once does not establish sustained performance; Chapter 6 examines that distinction.

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4.8: Updating a quality plan when requirements or processes change



A plan needs review when its assumptions change. Triggers include a new supplier, revised customer use, an equipment change, repeated complaints, audit findings, or a change in applicable requirements. A scheduled review is useful even when no problem has been reported, because silence does not prove that the plan remains suitable.

Change control is a defined process for evaluating, approving, carrying out, and documenting changes. An **impact assessment** examines how a proposed change could affect connected activities and outcomes. Replacing a shipping container may influence temperature protection, packing instructions, storage space, supplier checks, and customer information.

A sound change process follows a clear sequence:

1. Describe the proposed change and the reason for it.

2. Identify affected requirements, risks, people, records, and procedures.

3. Determine the evidence, resources, and approvals needed before use.

4. Obtain the required approvals and complete implementation preparations, including necessary training and communication, before the effective date.

5. Implement the approved change, verify completion, assess its effectiveness over a suitable period, address problems, and retain the change history.

The plan should state the effective date and how staff distinguish old from new arrangements. Materials in storage or transit may need separate assessment. For an urgent temporary change, define its controls, authorization, duration, review date, and conditions for ending it. Preserve the applicable records and prior versions. Urgency does not remove the need for a controlled response.

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4.9: Example - When a bottle shortage challenged laboratory planning

In June 2024, a warning about a routine laboratory supply raised an important question: How would laboratories keep testing if deliveries slowed? BD Life Sciences had notified users on June 11 that some BD BACTEC blood culture media bottles could face intermittent supply delays. On July 10, CDC shared the warning with clinical laboratory professionals and directed them to FDA recommendations for prioritizing and conserving the bottles.

The concern centered on a small item with an important purpose. Blood culture testing helps clinical teams investigate bloodstream infections. The bottle is part of the path from a patient's blood sample to information used in care. Without a dependable supply, laboratories could need to reconsider how they organized their work. The situation shows how a supplier problem can reach far beyond a purchasing office.



On July 10, BD explained that its supplier was providing fewer vials than needed. In its public statement, the company described several efforts to reduce delays: helping the supplier with manufacturing expertise, using air shipments, and changing manufacturing schedules to speed production. It also reported that a former supplier of glass vials would restart production to help cover the gap. These were measures reported by BD; the statement did not independently establish how well each measure worked.

By March 14, 2025, the public guidance had changed. FDA announced that the blood culture media bottle shortage had resolved and that its conservation recommendations were no longer needed. That announcement described the national status reported on that date; it did not establish that every laboratory had the same inventory or delivery experience.

The notices document a supply disruption and a later announcement that it had resolved. They also raise planning questions for laboratories: How should purchasing, laboratory staff, clinical leaders, and quality personnel coordinate during a shortage? The following discussion applies the chapter concepts to that question; it does not describe one laboratory's documented actions.

A laboratory facing such a disruption would need reliable answers to practical questions. How many usable bottles are available? Which deliveries are confirmed? Who reviews that information? Who may approve a temporary change, and what evidence is required? An inventory count is useful only when people know how to act on it.

Purchasing could gather delivery updates while laboratory operations checked inventory and expected use. Designated clinical and laboratory leaders would make decisions within their authority, with quality personnel supporting controlled instructions and records. These are proposed responsibilities, not documented assignments at a specific laboratory.

A quality plan would give those connections a clear structure. It could name the person responsible for reviewing supplies, identify the conditions that trigger escalation, and explain how staff receive approved updates. Any proposed substitute would need

assessment before use. Availability alone would not show that an alternative was suitable for the laboratory's equipment and methods.

A simple estimate can support this proposed planning. If a laboratory had 600 usable bottles and used 100 per day, with no new deliveries, 600 ÷ 100 would suggest about six days of supply. This is a hypothetical estimate, not a clinical recommendation or a guarantee of coverage. Bottle types, expiration dates, demand, and deliveries could change the estimate and the needed response.

The aim would be appropriate testing and patient care. A target to conserve supplies must remain tied to that purpose and to authorized clinical and laboratory decisions. Counting fewer bottles alone would not establish that the plan was successful.

When supply improved, a laboratory using temporary arrangements would need to check its own conditions before ending them. Authorized staff could confirm supplies, approve the return to routine instructions, and communicate an effective date. Superseded temporary instructions would be removed from routine use while preserving their history.

A quality plan needs to support both disruption and recovery. It connects reliable information with named responsibilities, decision authority, and follow-up. The public notices establish what CDC, BD, and FDA reported. A local laboratory would need its own records to evaluate whether its response worked.

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4.10: Chapter summary

A quality plan turns requirements into coordinated work for a defined product, service, process, or project. It identifies the activities, resources, responsibilities, controls, timing, and evidence needed to meet those requirements. Its scope states what the plan covers and how it connects with other work. The plan applies relevant parts of the organization's quality management system (QMS) and refers to approved procedures rather than creating conflicting instructions.

Quality planning connects an organization's mission, vision, values, and strategy with everyday decisions. A useful quality objective states an intended result clearly enough to evaluate. It needs an owner, a time period, and consistent measurement rules. An improvement target describes desired progress across a process; acceptance criteria define what must be met in a particular evaluation. Meeting an overall target does not excuse an individual shipment or result that fails a requirement.

Each requirement must lead to assigned activities and clear decision authority. A process owner coordinates ongoing performance, while other people may perform tasks, review evidence, or approve decisions. Handoffs should identify who sends and receives the work, what information must accompany it, and how receipt is confirmed. Escalation routes direct concerns to someone with the authority or expertise to respond.

Management, operations, development, quality personnel, purchasing, and support functions all contribute to the plan. Assigning a task is not enough: employees also need time, equipment, approved materials, usable instructions, and appropriate training. Competence means being able to apply knowledge and skills to achieve the intended result. A signature showing that someone read a procedure does not, by itself, demonstrate readiness to perform a complex task independently.

Document control helps employees use current approved instructions and keeps outdated versions from accidental use. Completed records preserve evidence of what was actually done or observed. Data integrity requires information to remain complete, consistent, and accurate. Communication should reach the right people at the right time, with checks of receipt and understanding where needed. Receiving a message does not establish that the work was completed.

Performance measures help teams judge whether a plan is working. Their meaning depends on clear definitions, suitable baselines, reliable data, and consistent calculations. Missing records must remain visible because they can make performance appear better than the evidence supports. Leading indicators track conditions or activities expected to help prevent later problems; lagging indicators describe outcomes that have already occurred. Scheduled reviews support routine oversight, while urgent concerns require prompt action through defined reporting routes.

Quality plans need controlled updates when suppliers, equipment, intended uses, requirements, or other conditions change. Change control includes an impact assessment, required evidence and approvals, staff preparation, implementation, and follow-up. The documented blood culture bottle shortage illustrates why supply information, assigned responsibilities, authorized temporary arrangements, and recovery planning matter. A plan remains useful when people keep it aligned with actual conditions and verify that its actions produce the intended results.

Key terms

Quality plan	Scope	Quality management system
Standard operating procedure	Risk	Mission
Vision	Values	Organizational strategy
Quality objective	Acceptance criteria	Process owner

Handoff	Escalation	Competence
Document control	Record	Data integrity
Performance measure	Baseline	Leading indicator
Lagging indicator	Inspection	Audit
Monitoring	Management review	Change control
Impact assessment	Improvement target	Effective date

Review questions

1. What is a quality plan, and what information should it include?

2. How does a quality plan differ from a QMS and a standard operating procedure?

3. Why does a quality plan need a clearly defined scope?

4. What is the difference between an organization's mission and its vision?

5. What information makes a quality objective measurable?

6. How does an acceptance criterion differ from an improvement target?

7. What should be defined when work or information passes from one department to another?

8. Why does a signed training record not always establish competence?

9. How does a completed record differ from an instruction?

10. What is the difference between a leading indicator and a lagging indicator?

11. Why must a team consider missing records when interpreting a performance measure?

12. What are the main steps in change control?

Apply your knowledge

1. Planning for growth

An enzyme supplier plans to double its monthly output. QC staff already work at full capacity, and shipping instructions were designed for smaller orders. Propose one measurable quality objective that supports dependable growth. Identify three responsibilities or resources that need review, and explain how each would help protect product quality or customer needs.

2. An unclear handoff

Shipping receives a batch with no documented release status. Manufacturing says the batch is probably ready, and a customer is

waiting. Describe the immediate response, the evidence needed, and the roles that should make and communicate the decision. Propose a handoff improvement that would reduce the chance of this problem recurring.

3. Interpreting incomplete monitoring data

A company dispatches 100 shipments that all require temperature monitoring. Usable records are available for 80 shipments, and 4 of those records show an excursion. Calculate the excursion percentage among shipments with usable records and the monitoring completeness percentage. Explain what remains unknown and why the team cannot treat the missing records as evidence of acceptable temperatures.

4. Evaluating a packaging change

A new supplier offers lower-cost packaging that looks identical to the approved packaging. Purchasing wants to use it next week. Describe an impact assessment that considers product protection, supplier requirements, instructions, training, records, and affected departments. Explain what evidence and approvals are needed before use and how the team should check performance after implementation.

5. Responding to a supply interruption

Use the documented blood culture bottle shortage as a starting point. A hypothetical laboratory has 600 usable bottles and uses about 100 per day. With no new deliveries and unchanged use, estimate its days of supply. Identify three quality-plan elements the laboratory should review during the interruption and one review needed before ending temporary arrangements. Explain who should coordinate information and authorize decisions, and why the estimate alone cannot establish that patient testing needs will be met. Distinguish your proposed response from the events documented in the chapter.

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5: SYSTEMS, PROCESSES, AND SIPOC

Learning Objectives

After completing this chapter, you should be able to:

- Distinguish a system from a process using biotechnology examples.
- Explain how connected processes influence the quality of a final product or service.
- Identify suppliers, inputs, process steps, outputs, and customers in a SIPOC diagram.
- Define process boundaries and describe measurable input and output requirements.
- Create and interpret a SIPOC diagram for a biotechnology process.
- Evaluate handoffs and feedback between departments.
- Predict unintended consequences of a change and select measures that assess the whole system.

Chapters 2 and 3 examined quality planning, responsibilities, and employee participation. Those responsibilities often connect across departments. This chapter shows how to examine the **system** around a task and map the people, materials, information, and results that the work depends on.

A biotechnology company makes an enzyme used in research laboratories. **Customers** depend on it to carry out their experiments. Recently, orders have arrived late even though production reports that it finishes every batch on schedule. The **quality control** laboratory reports that testing also meets its schedule. Shipping employees say that they send orders as soon as they receive permission.

The schedules measure only part of the work. Production counts a batch as complete before its sample submission is checked. QC measures testing time after it receives a complete submission. Shipping measures dispatch time after release is authorized. A closer review finds missing sample information and a gap between the product transfer and the availability of its release record. Customers experience those waiting periods even when the department measures exclude them.

This hypothetical situation shows why quality requires a view of connected work. A local measure can look satisfactory while the customer still receives a late order. SIPOC helps the team describe those connections before deciding where and how to improve the **process**.

5.1: Distinguishing a system from a process

5.2: Relationships among processes within a system

5.3: SIPOC- suppliers, inputs, process, outputs, and customers

5.4: Defining process boundaries and requirements

5.5: Creating and interpreting a SIPOC diagram

5.6: Handoffs, feedback, and interactions among functional areas

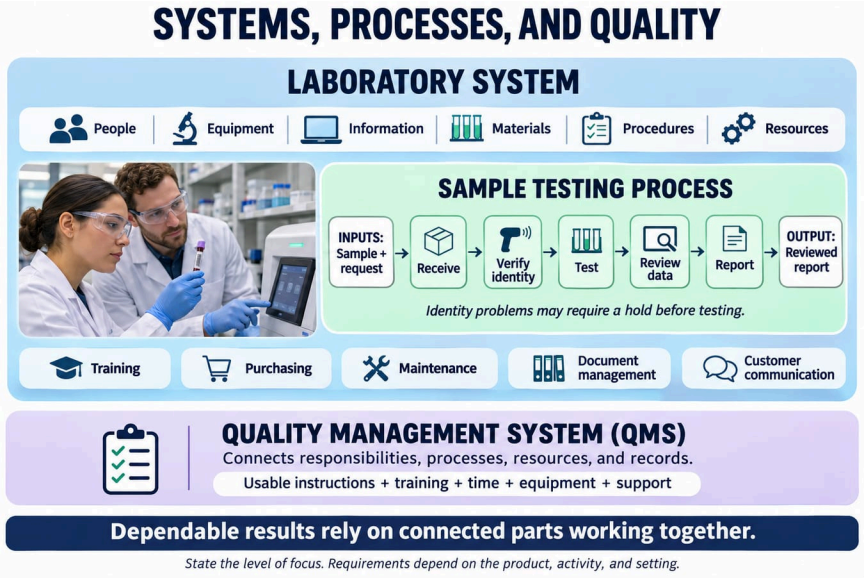
5.7: A decision that depended on the manufacturing system

5.8: Recognizing unintended consequences of local improvements

5.9: Chapter summary

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5.1: Distinguishing a system from a process



A **system** is a set of connected parts that work together toward a purpose. In a biotechnology company, those parts include people, equipment, information, materials, procedures, and resources. Their relationships matter as much as the parts themselves. A trained analyst cannot produce a dependable result if the sample label is wrong or the instrument is not working properly.

A process is a connected series of activities that uses **inputs** to produce **outputs**. Receiving a laboratory sample, confirming its identity, performing a test, reviewing the data, and reporting the result form a testing process. The larger laboratory system also includes training, purchasing, equipment maintenance, document management, and communication with customers.

The difference depends partly on the level being examined. Sample testing can be treated as one process within a laboratory system. If the team examines testing more closely, it can describe a testing system containing several smaller processes. The team should state its level of focus so that everyone is discussing the same work.

A **quality management system**, or QMS, organizes the responsibilities, processes, and resources used to manage quality. Its purpose is to help an organization consistently meet applicable requirements and improve its work. A QMS connects what people are expected to do with the evidence showing what actually happened. Written procedures alone do not make an effective system; people also need usable instructions, training, time, equipment, and support.

System design depends on the work and its requirements. A research laboratory and a medicine manufacturer may organize their work differently. Both need appropriate controls, resources, and evidence. Specific legal or certification requirements depend on the product, activity, and setting. A general example in this chapter should not be read as an identical **requirement** for every biotechnology workplace.

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5.2: Relationships among processes within a system



Processes rarely operate alone. The output of one process often becomes the input of another. Purchasing obtains a reagent, receiving checks and stores it, production uses it, and quality control tests the resulting product. A problem early in this chain can affect work much later.

These connections create **interdependence**, meaning that the performance of one part depends on other parts. If purchasing orders the correct chemical but the wrong grade, production may need to stop. If a storage unit fails overnight, a scheduled test may no longer have suitable materials. The employee who discovers the problem may be far from the activity where it began.

The quality functions introduced in Chapter 1 help support these relationships. **Quality assurance** (QA) focuses on planned activities that provide confidence requirements will be met. Quality control (QC) focuses on fulfilling requirements through operational activities, including testing and inspection. **Continuous improvement** uses evidence to strengthen performance over time. These functions connect prevention, detection, and learning, with responsibilities defined for the organization.

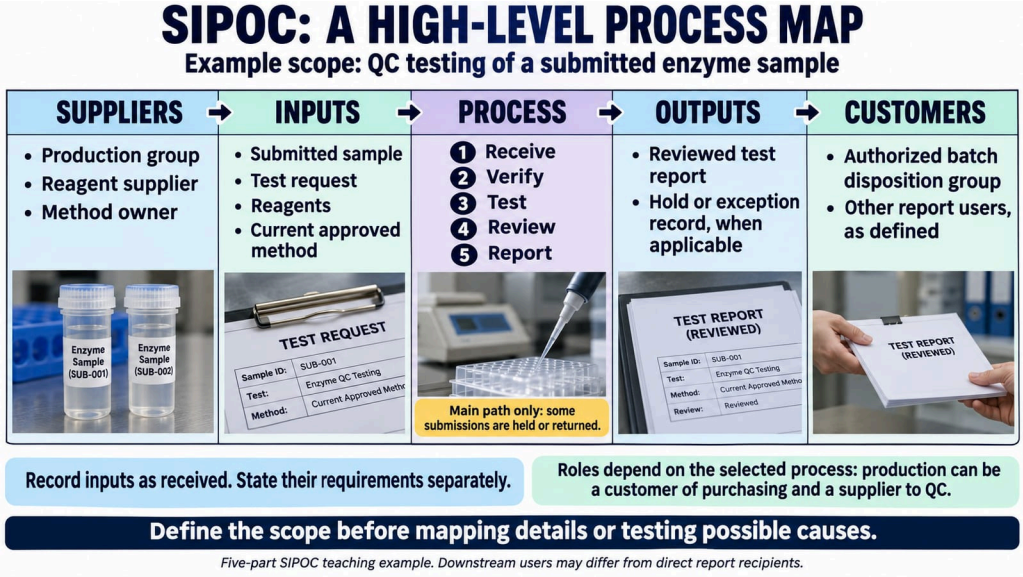
For the enzyme company, QA may help define the information required on a sample submission form. QC checks the enzyme against established specifications. An improvement team studies repeated sample delays and changes how the form is completed and checked. These activities support each other, but one cannot replace all the others.

A **process owner** is the person responsible for overseeing a defined process's ongoing performance and coordinating needed changes. The owner may coordinate work across departments and help resolve gaps, while acting within assigned authority. Identifying an owner should make follow-up clear without transferring every technical or release approval to that person.

When investigating a problem, follow the movement of material and information. Ask what the next person needs, whether that need is clearly stated, and whether the previous process provides it. This approach supports accountability while avoiding the assumption that the last person handling the work caused the failure.

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5.3: SIPOC- suppliers, inputs, process, outputs, and customers



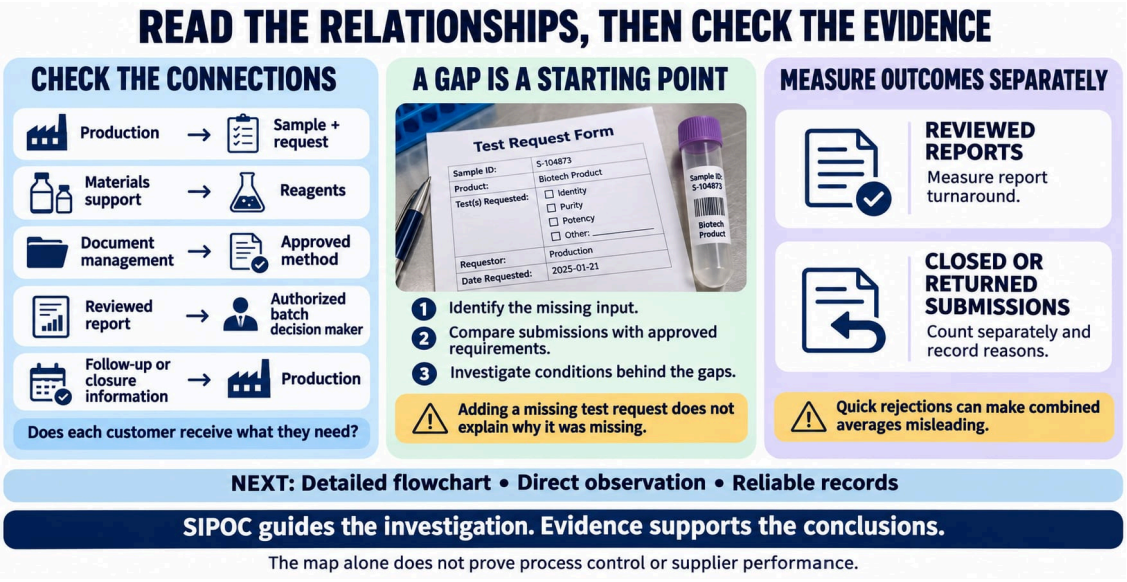
Five-part SIPOC teaching example. Downstream users may differ from direct report recipients.

A **SIPOC diagram** is a high-level map of a process and its main relationships. SIPOC stands for **suppliers**, inputs, process, outputs, and customers. It helps a team describe the work under investigation before developing a detailed map or testing possible causes. ASQ uses these five elements and also describes an extended version that adds constraints and measures. This chapter uses the five-part form.

Suppliers are people or organizations that provide something the process needs. They can be outside the company, such as a reagent manufacturer, or inside it, such as a production group that supplies samples to a testing laboratory.

Inputs are the materials, information, or resources that enter or support the selected process. A test may need a submitted sample, a test request, suitable reagents, and a current approved method. Record what arrives in the current process, then state the requirements separately. A submitted sample may be an input even when it arrives with an identification problem.

The process column summarizes the main activities connecting inputs to outputs. Use action words such as receive, verify, test, review, and report. Include the main path



The map alone does not prove process control or supplier performance.

without implying that every submission reaches testing. A detailed flowchart can later show decisions, holds, returns, and other exceptions.

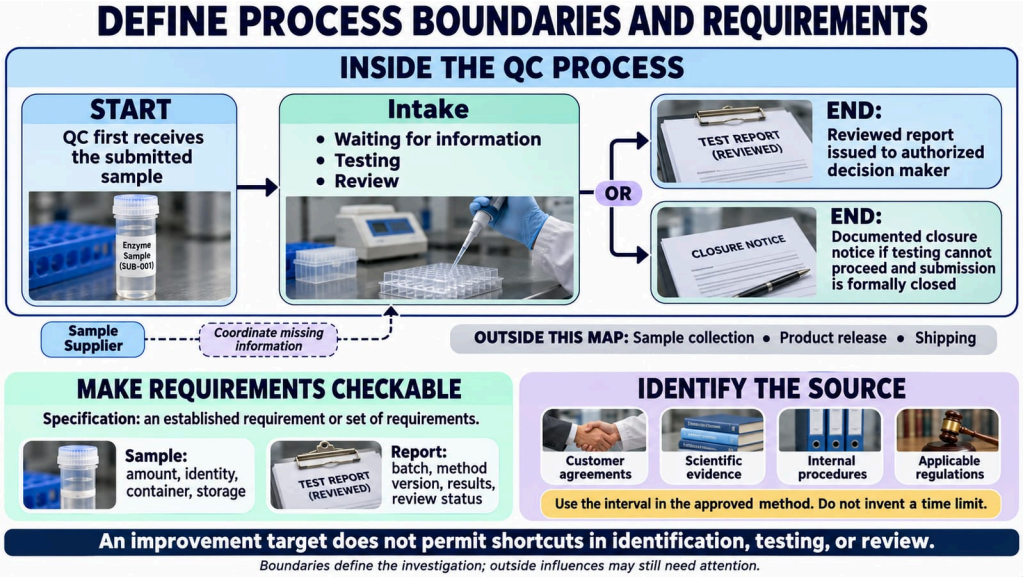
Outputs are the products, services, information, or decisions produced by the process. A laboratory output could include a reviewed test report. A receiving process may produce an accepted material record or a record showing that a delivery was placed on hold.

Customers are the people or organizations that receive or use the outputs. An **internal customer** works within the organization, while an **external customer** is outside it. For a QC testing process, the next customer may be the authorized group that makes a batch disposition decision. Patients or research users may be affected farther downstream, even when they do not directly receive the laboratory report.

A person or organization can occupy different roles on the same map or on different maps. Production receives materials as an internal customer of purchasing and supplies samples to QC. Define each role in relation to the selected process and the particular input or output, rather than assigning a department permanently to one column.

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5.4: Defining process boundaries and requirements



A **process boundary** identifies where the selected process begins and ends. Without clear boundaries, one team member may study the time needed to run a test while another measures the time from sample collection to final approval. Both measurements can be correct, but they answer different questions.

For the enzyme company, the selected process starts when QC first receives a submitted sample. It normally ends when QC issues a reviewed report to the authorized decision maker. If testing cannot proceed and the submission is formally closed under the applicable procedure, it ends with a documented closure notice. This boundary includes intake problems and waiting for missing information. Product release and shipping remain outside the map, although they use its outputs.

A requirement states a condition that an input, activity, or output must meet. A **specification** defines an established requirement or set of requirements, often including acceptance limits. A sample requirement might identify the needed amount, label information, container, and storage conditions. A report requirement might identify the batch, method version, results, and review status.

Requirements should be clear enough to check. “Send the sample promptly” leaves room for disagreement. “Record the collection and receipt times and deliver within the interval defined by the approved method” provides a clearer expectation. The actual interval must come from the applicable method or justified procedure. It should not be invented to make a diagram look complete.

When defining requirements, identify their source. Customer agreements, scientific evidence, internal procedures, and applicable regulations may all contribute. Distinguish a justified acceptance requirement from an improvement target. A report-turnaround target does not authorize shortcuts in identification, testing, or review.

Boundaries limit the investigation, but they should not prevent the team from examining important outside influences. If a report is late because samples repeatedly arrive without labels, the team needs to involve the sample supplier. Mark the connection and coordinate the response rather than silently expanding the project to cover the whole company.

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5.5: Creating and interpreting a SIPOC diagram



Begin with the current process. Create a SIPOC with people who perform the work and people who supply or receive its outputs. A supervisor may know the procedure, while an analyst knows where submissions wait. Compare their accounts with observation and records. Keep a proposed future process separate so that an intended improvement is not mistaken for current practice.

1. State the process purpose and the question being investigated.

2. Agree on the starting and ending events.

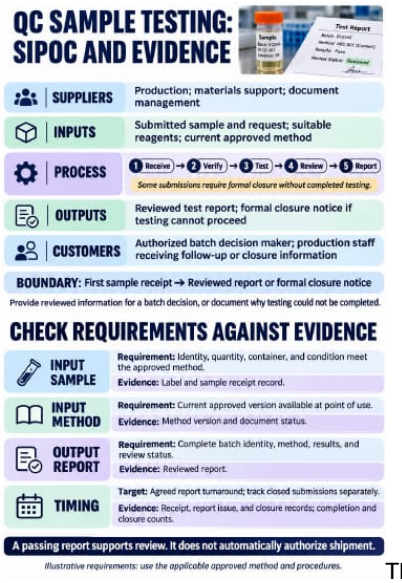
3. Describe the process in a few major steps.

4. Identify the outputs and the customers who use them.

5. Confirm what those customers require.

6. Identify the necessary inputs and their suppliers.

7. Check the map against actual work and revise it with the people involved.



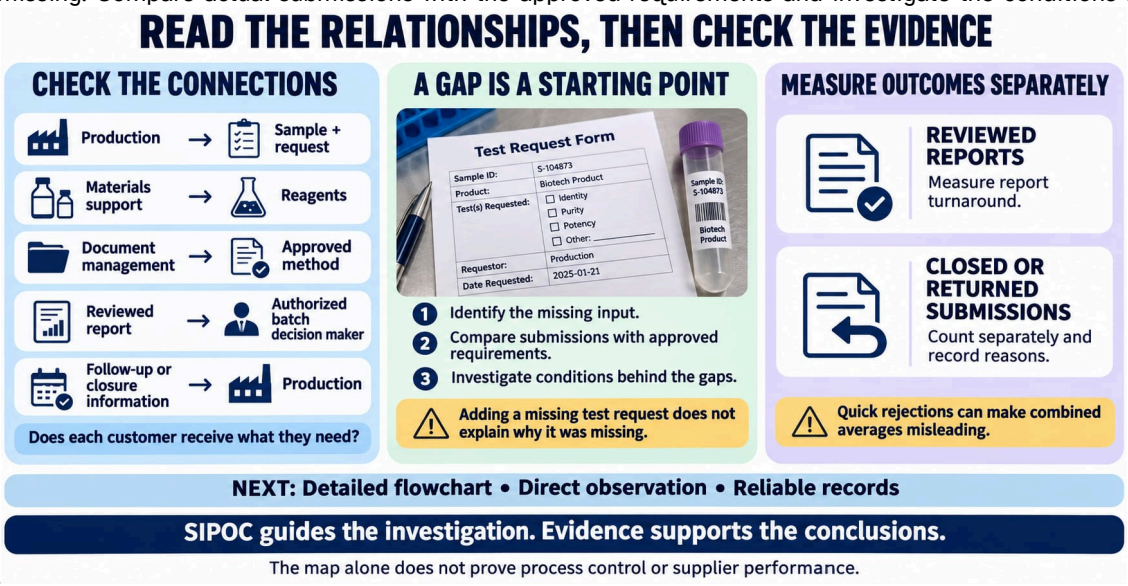
The following completed SIPOC summarizes the hypothetical enzyme testing process. The columns describe the same overall process; entries at the same height are not separate pathways. The normal sequence is shown in the process column. The exception output represents formal closure when testing cannot proceed, rather than an informal message while a submission remains open.

Process boundary: first receipt of a submitted sample through issue of a reviewed report or formal closure notice. Purpose: provide reviewed test information for a batch decision, or clearly document why the requested testing could not be completed. A passing report supports review; it does not automatically authorize shipment.

Read the map by checking relationships. Does each important input have an identified supplier? Does each output have a customer? Does the process produce what that customer needs? A missing entry can signal unclear responsibility or a requirement that has never been discussed.

For example, production supplies the sample and request; materials support provides reagents; document management supplies the current approved method. The authorized batch decision maker receives the report, while production receives relevant follow-up or closure information. These connections explain the lists in the five-column map.

Suppose an initial draft omits the test request. Adding it identifies information the laboratory needs; it does not establish why requests are missing. Compare actual submissions with the approved requirements and investigate the conditions associated with the gaps.



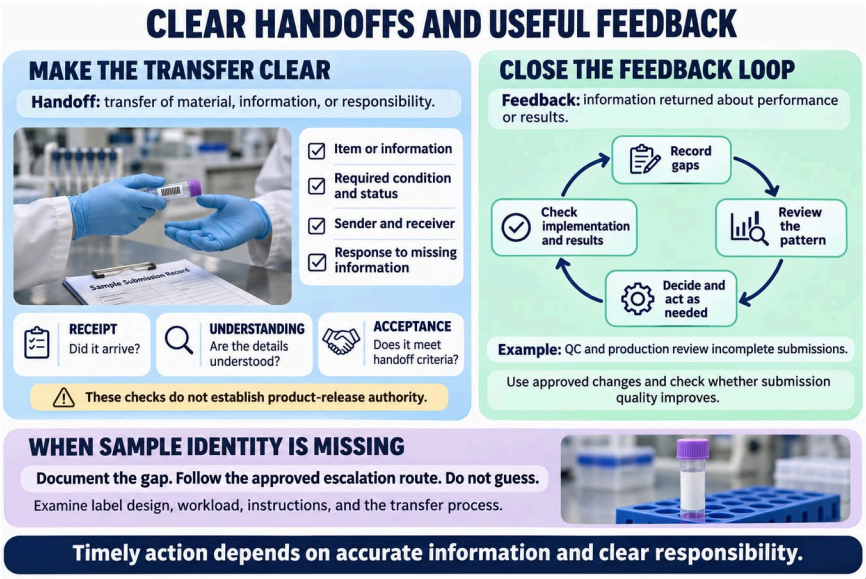
SIPOC does not show every task, decision, exception, or possible cause of failure. It also does not prove that a process is controlled or that a supplier performs well. A detailed flowchart, direct observation, and reliable records may be needed next. The

map guides the investigation; evidence supports the conclusions.

Measure different outcomes separately. Report turnaround describes submissions that produce reviewed reports. Closed or returned submissions need their own counts and reasons. Combining quick rejections with completed reports could make average completion time look better while fewer customers receive usable results.

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5.6: Handoffs, feedback, and interactions among functional areas



A **handoff** occurs when material, information, or responsibility moves from one person or group to another. Common biotechnology handoffs include a supplier sending materials to receiving, production delivering samples to QC, and quality staff providing a disposition decision to shipping. Each transfer needs both a sender and a receiver who understand what is required.

An effective handoff identifies the item or information, its required condition and status, the sender, the receiver, and the response to missing information. Receipt, understanding, and acceptance are different checks. Acknowledging a file confirms receipt; checking its details helps confirm understanding; acceptance means it meets the relevant handoff criteria. None of these alone establishes product-release authority.

Feedback is information returned about performance or results. A **feedback loop** connects it to review, a decision or action when needed, and a later check. QC might record incomplete submissions and review the pattern with production. If a change is approved, the team would check both whether it was introduced and whether submission quality improved.

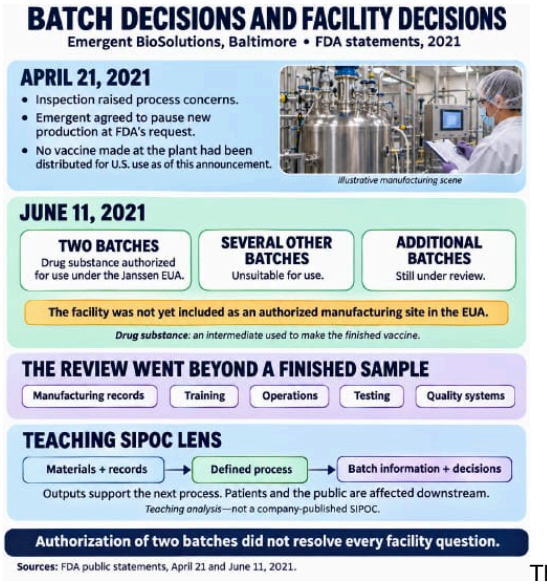
A useful feedback loop supports timely action without hiding failures. The analyst should document a missing sample identity and follow the approved escalation route. The analyst should not guess the identity to keep work moving. Management should also ask whether the label design, workload, instructions, or transfer process contributed to the problem.

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5.7: A decision that depended on the manufacturing system

Public FDA statements from April and June 2021 describe separate decisions about manufacturing conditions and individual batches at Emergent BioSolutions. The account below follows those events. The SIPOC interpretation is a teaching analysis, rather than a map published by the company.

In spring 2021, COVID-19 vaccine manufacturing carried urgent public expectations. At Emergent BioSolutions in Baltimore, work intended to support the Johnson & Johnson vaccine reached a pause. On April 21, FDA reported that its inspection had raised concerns about the facility's processes. At the agency's request, Emergent agreed to stop new production while potential quality issues were addressed.



The review reached beyond a finished sample. FDA described examining manufacturing records, training, operations, production, testing, and quality systems. Existing material would need additional evaluation before possible distribution. FDA also stated that vaccine manufactured at the plant had not been distributed for use in the United States as of that announcement.

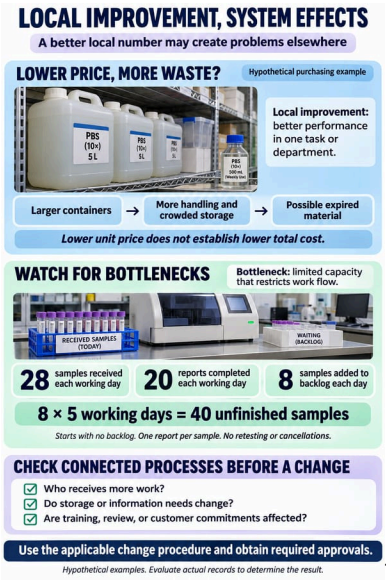
The review then produced different decisions. On June 11, 2021, FDA authorized two batches of vaccine drug substance for use under the Janssen emergency use authorization (EUA), after reviewing facility records and manufacturer quality-test results. Drug substance is an intermediate used to make the finished vaccine. Several other batches were unsuitable, and additional batches remained under review. FDA was not yet ready to include the facility itself as an authorized manufacturing site in the EUA.

Permission to use the two batches did not mean that all facility questions were resolved or that all batches were acceptable. FDA described its decision in the context of its evidence review and the COVID-19 public health emergency. The batch decisions and the facility decision answered related but distinct questions.

Through a teaching SIPOC lens, materials and records are inputs to defined manufacturing or review processes; batch information and disposition decisions become outputs used by the next process. The exact map depends on its boundary. Patients and the public are affected downstream. The case illustrates why production, testing, documentation, and authority must connect. It does not establish that Emergent used SIPOC or that a diagram alone would have prevented the problems.

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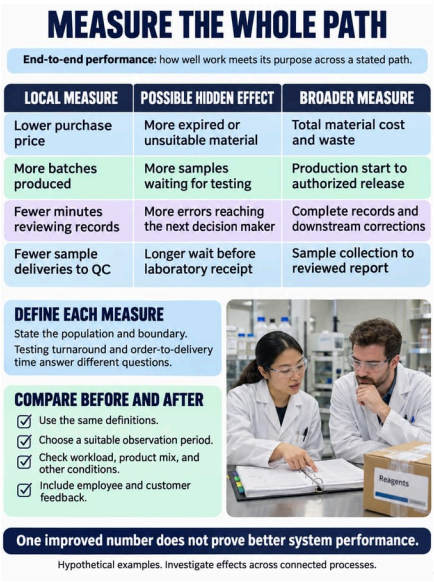
5.8: Recognizing unintended consequences of local improvements



The same system view matters when a team proposes a change. A **local improvement** makes one task or department perform better according to a selected measure. It may benefit the larger system, but that needs evaluation. An **unintended consequence** is an effect that was not the intended purpose of the change. Faster or cheaper work can create delays, extra work, or new risks elsewhere.

Imagine that the enzyme company asks purchasing to lower material costs. Purchasing selects larger containers because their price per unit is lower. Production uses only a small amount each week. Repeated opening increases handling, storage becomes crowded, and unused material reaches its expiration date. The purchase price improves while total waste may rise. This is a hypothetical example; the team would need actual records to determine the result.

A **bottleneck** is a step whose limited capacity restricts the flow of work. If production increases output while QC capacity stays the same, more samples may wait for testing. Production can report success even as customers wait longer. The system benefits only when the increased activity supports usable output at the pace the whole process can handle.



Consider a laboratory that starts with no backlog. It receives 28 samples but completes only 20 reports each working day. Assume each sample needs one report, with no retesting or cancellations. Eight samples remain

unfinished each day, so the backlog grows to 40 after five working days. Receiving more samples has increased waiting work without increasing completed reports.

Before approving a change, examine the connected processes. Ask who will receive more work, whether information or material needs will change, and whether the change affects storage, training, review, or customer commitments. In a controlled process, use the applicable change procedure and obtain required approvals before implementation.

Select measures that reveal the broader result. **End-to-end performance** describes how well work meets its purpose across a stated path. For the enzyme company, useful measures may include order-to-delivery time, complete and correct orders, avoidable repeat work, waste, and shipment-linked complaints. Define the population and boundary for each measure; a narrower testing turnaround measure answers a different question from order-to-delivery time.

Compare performance before and after a change using the same definitions and a suitable observation period. Check whether workload, product mix, or other conditions also changed. A short improvement in one number does not by itself show that the change caused better system performance. Include feedback from employees and customers who experience the effects.

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5.9: Chapter summary

A system brings connected people, equipment, materials, information, procedures, and resources together to achieve a purpose. A process is a series of activities that uses inputs to produce outputs. A laboratory testing process operates within a larger system that also supports training, purchasing, maintenance, and communication. The level being examined matters: a process in one map may contain several smaller processes in a more detailed study.

Processes are interdependent because the output of one often becomes an input to another. A missing sample identifier, unsuitable reagent, or delayed approval can affect work far beyond the place where the problem began. Department measures may leave these connections hidden. Production, QC, and shipping can each meet their own schedules while customers still wait because no department's measure includes the time between them. A system view follows both materials and information across those gaps.

SIPOC stands for suppliers, inputs, process, outputs, and customers. A SIPOC diagram provides a high-level view of a selected process and its relationships. Suppliers provide the materials, information, or resources the process needs. The process uses those inputs to produce outputs for customers. Suppliers and customers may be internal or external, and the same department can have different roles depending on the process being studied.

A useful SIPOC begins with a clear purpose and process boundaries. The starting and ending events determine what work and waiting time are included. The team should identify actual inputs and outputs, then state the requirements that make them suitable. An input does not stop being an input because it fails a requirement. Maps should describe current practice accurately, with proposed future changes kept separate. Employees who perform, supply, and receive the work should help check the map against observations and records.

A SIPOC diagram guides investigation but does not establish the cause of a problem, prove supplier performance, or show every decision and exception. Detailed flowcharts and reliable records may be needed next. The documented Emergent example illustrates why manufacturing conditions, records, testing, and decision authority must connect. A decision about a particular batch answers a different question from a decision about a facility. The account does not establish that the company used SIPOC or that a diagram would have prevented its problems.

Handoffs need clear expectations about identity, condition, status, required information, and responsibility. Receipt, understanding, and acceptance are different checks, and none automatically authorizes product release. Feedback becomes a useful loop when information leads to review, action when needed, and a later check of the result. A process owner helps coordinate performance and changes across the selected process while working within assigned authority.

A local improvement must be evaluated for its effects on the larger system. Lower purchase prices can increase waste, and faster production can create a backlog when testing capacity does not increase. A bottleneck limits the flow of work. End-to-end measures, such as order-to-delivery time, help reveal whether customers benefit. Teams should use consistent definitions, examine other changes in workload or conditions, and consider employee and customer feedback before concluding that an improvement worked.

Key terms

System	Process	Quality management system
Interdependence	Quality assurance	Quality control
Continuous improvement	Process owner	SIPOC diagram

Suppliers	Inputs	Process boundary
Outputs	Customers	Internal customer
External customer	Requirement	Specification
Handoff	Feedback	Feedback loop
Local improvement	Unintended consequence	Bottleneck
End-to-end performance	Acceptance criteria	Backlog

Review questions

1. What is the difference between a system and a process?

2. What does interdependence mean in a biotechnology workplace?

3. What does each letter in SIPOC stand for?

4. How does an input differ from an output?

5. How can one department be a supplier in one process and a customer in another?

6. Why should a team define a process's starting and ending events?

7. Give two input requirements and two output requirements for a laboratory testing process.

8. Why should a SIPOC describe current work separately from proposed changes?

9. What can a SIPOC diagram help a team understand, and what does it leave unresolved?

10. What information should be clear when material or records pass between departments?

11. How does a feedback loop differ from simply collecting information?

12. What is a bottleneck, and how can it affect the customer?

Apply your knowledge

1. Mapping incomplete sample submissions

A QC laboratory receives 50 sample submissions, but 15 lack the requested test or collection time. Define a process boundary that includes intake and waiting for missing information. Create a SIPOC with all five elements, identify one requirement that needs review, and name the people who should help check the map. Explain why identifying a missing input does not establish the cause of the problem.

2. Finding a capacity constraint

A laboratory starts with no backlog, receives 28 samples each working day, and completes 20 reports each working day. Assume one report per sample and no retesting or cancellations. Calculate the number of unfinished samples after five working days. Propose two ways to investigate the capacity constraint and select an end-to-end measure that would help show whether customers receive reports sooner.

3. Resolving conflicting status information

Shipping receives a box labeled ready, but the electronic batch record says review pending. Describe the response needed before shipment under the organization's approved process. Propose a handoff that defines the sender, receiver, required status evidence, and escalation route. Explain why receiving the box does not establish that release has been authorized.

4. Evaluating a lower purchase price

Purchasing proposes a supplier whose price per unit is 12% lower, but the supplier delivers only in larger containers. Identify three connected processes that might be affected. Describe the evidence needed to assess storage, handling, material suitability, and waste. Select two broader measures that would help determine whether the proposal benefits the system rather than only the purchasing budget.

5. Closing a feedback loop

A laboratory adds automatic reminders for incomplete sample submissions. The next month, missing information decreases, but analysts spend more time resolving duplicate requests. Design a feedback loop to assess the change. Identify who should participate, what evidence should be collected, and how the team should compare results before and after implementation. Explain how you would judge whether customers receive better service overall.

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6: VARIATION AND PROCESS PERFORMANCE

After completing this chapter, you should be able to:

- Describe sources of variation in biotechnology processes and measurements.
- Distinguish common-cause variation from special-cause variation.
- Explain process stability and the limits of predicting future performance.
- Distinguish specification limits from control limits and interpret a result against both.
- Select an appropriate response to evidence of different sources of variation.
- Explain how unnecessary adjustments can increase variation in a stable process.
- Use process data to propose an improvement and evaluate whether it lasts.

Shewhart's attention to process behavior and Deming's warning against unsupported adjustments help explain how to respond to **variation**. The aim is to choose actions that fit the evidence while protecting the people who rely on biotechnology products and services.

A biotechnology technician checks bottles on a research-reagent filling line. The **target** volume is 10.00 mL. The first three results are 9.98, 10.03, and 10.01 mL. The technician wonders whether to adjust the filler after every measurement so that the next bottle lands exactly on target.

Later, a bottle measures 10.28 mL. It is still within the company's approved fill-volume range, but it falls beyond the upper limit on the established individual-fill **control chart**. Should the technician ignore it because it passes the volume requirement, adjust a setting immediately, or follow the procedure for investigating a chart **signal**?

This hypothetical situation raises two different questions: Does the measured bottle meet its requirements, and is the process behaving as expected? Quality work requires both questions. In this chapter, you will learn how variation helps explain repeated results, when it calls for investigation, and why reacting to every small difference can make performance worse.

6.1: Why repeated process results differ

6.2: Common-cause and special-cause variation

6.3: Process stability and predictable performance

6.4: Distinguishing specification limits from control limits

6.5: Responding appropriately to different sources of variation

6.6: A children's medicine recall brings variation into focus

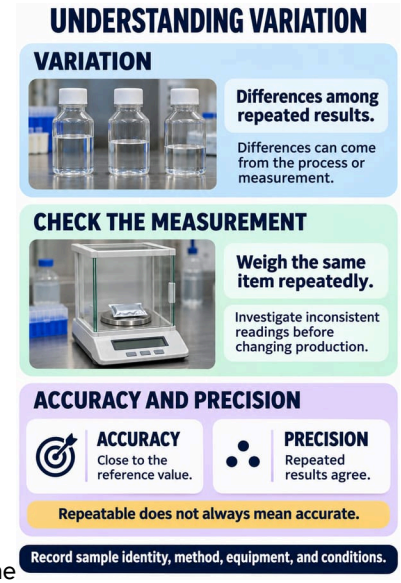
6.7: Risks of adjusting a stable process unnecessarily

6.8: Using variation knowledge to guide improvement

6.9: Chapter summary

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6.1: Why repeated process results differ



Variation **means** differences among repeated observations or results. Bottles filled by the same machine do not contain exactly the same measured volume. Repeated measurements of one sample can also differ. Understanding those differences helps a team decide whether to maintain the current settings, investigate a change, or plan an improvement.

In biotechnology, variation can arise from materials, equipment, methods, people, environmental conditions, and measurement. Different raw-material lots may behave differently. Temperature can influence a reaction. Mixing conditions can affect how evenly material is distributed. A sample collected from an unrepresentative location may give a misleading picture of the batch.

A **measurement system** includes the instrument, method, reference materials, software, people, and conditions used to obtain a result. Some observed differences come from the process, while others arise during measurement. Before changing production settings, check whether the measurements are reliable enough for the decision.

Imagine that an analyst repeatedly weighs the same sealed reference item and obtains inconsistent results. The changing values cannot be explained by production filling different bottles because the item being weighed is unchanged. The team should examine the balance, handling, environment, and method. This hypothetical check does not identify a cause by itself, but it helps focus the investigation.

Accuracy describes closeness to an accepted reference value. **Precision** describes agreement among repeated results under stated conditions. A balance can give nearly identical readings each time and still read consistently high. Good repeatability therefore does not, by itself, prove accuracy.

Biological systems add another layer. Cells from different cultures may grow at different rates even when staff follow the same procedure. Some differences may be expected; others may reflect a change in culture condition or handling. The presence of biology does not make every difference acceptable. Teams still need defined requirements, suitable methods, and evidence about expected performance.

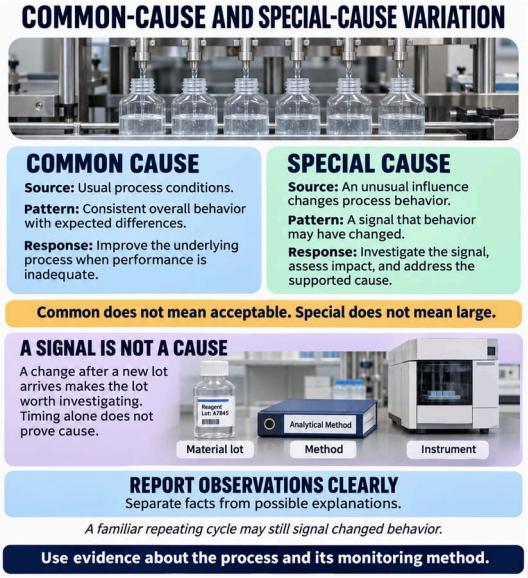
Record conditions that may help explain results, including time, sample identity, equipment, method version, material lot, and relevant operating settings. A number without its context is harder to interpret. Avoid combining unlike products or test methods into one dataset simply because they share a unit of measurement.

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6.2: Common-cause and special-cause variation

Common-cause variation comes from the usual collection of conditions built into a process. Individual results differ, but their overall pattern can remain reasonably consistent. **Special-cause variation** arises when an unusual influence changes that pattern. These categories help guide investigation and response.

Common does not mean harmless, small, or acceptable. A filling process may routinely vary more than customers can tolerate. Special does not necessarily mean a large numerical difference. A modest but sustained shift can be important when the process previously varied within a narrow range.



For the hypothetical filling line, common causes might include the combined small differences in valve timing and routine operating conditions. A damaged seal or a newly introduced setup error might produce a special cause. These are possible explanations, not labels that can be assigned from an equipment name alone. Their classification depends on evidence about the particular process.

A condition should not be called a common cause merely because it happens often. For example, a daily rise and fall in room temperature could produce a repeating cycle in fill results. Such a cycle can signal a problem on a standard chart even though it is familiar. The team should investigate and improve the conditions or justify a monitoring method that accounts for them. A sudden heating-system failure presents a different investigation. Classification depends on the process and monitoring approach.

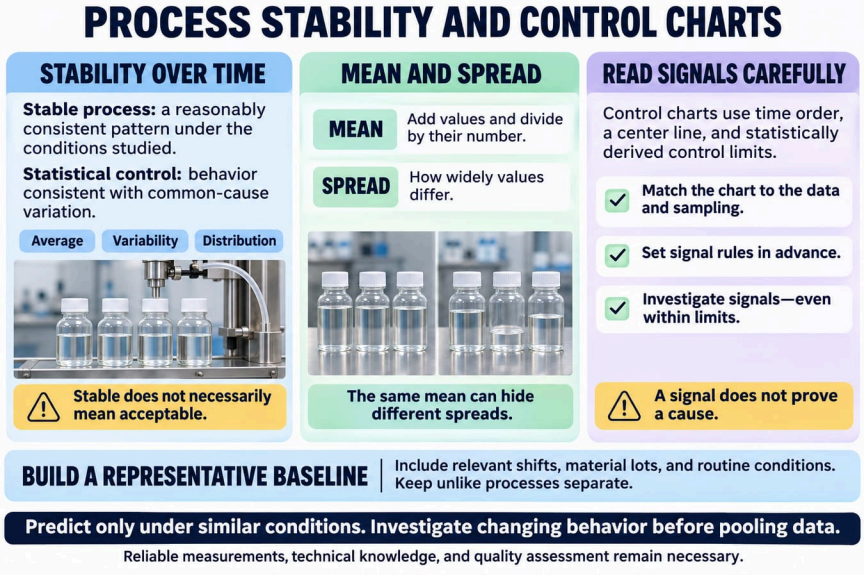
A signal does not identify its cause automatically. If a result changes after a new reagent lot arrives, the timing makes the lot worth investigating. It does not prove that the lot caused the change. A method revision, instrument problem, or sample-handling change may have occurred at the same time.

Employees contribute valuable observations, especially about events near a signal. They should report what they observed and distinguish facts from possible explanations. The aim is to understand the process and protect the people who depend on its output, while holding individuals responsible for their actual decisions and actions.

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6.3: Process stability and predictable performance

A **stable process** has a reasonably consistent pattern of results over time under the conditions studied. **Statistical control** means that the pattern is consistent with common-cause variation. NIST describes stability through a consistent average, variability, and distribution over time. This supports predictions under similar conditions, while leaving room for future changes.



The mean is the arithmetic average: add the values and divide by their number. **Spread** describes how widely values differ. Two processes can have the same mean but very different spreads. A filler alternating between low and high volumes may average 10.00 mL while producing bottles that are individually unsuitable.

Stability supports conditional prediction. If relevant conditions remain the same, the established pattern provides a basis for estimating future behavior. It does not guarantee the next exact value or rule out a future failure. A stable process also can perform poorly in a consistent way.

A control chart plots a process measurement or summary in time order and compares it with a reference pattern. The chart includes a center line and appropriate **control limits** derived using process data and a suitable statistical method. Some charts monitor individual values; others monitor subgroup averages, ranges, or proportions. Select a chart that matches the data and sampling design.

A team looks for defined signals: patterns that warrant investigation under the chosen chart rules. Examples include a point beyond a control limit or a sustained pattern on one side of the center line. A signal can occur while every point remains inside the limits. Establish suitable rules in advance. A signal is evidence to investigate, rather than proof of a particular cause, and a chart can occasionally signal when no process change has occurred.

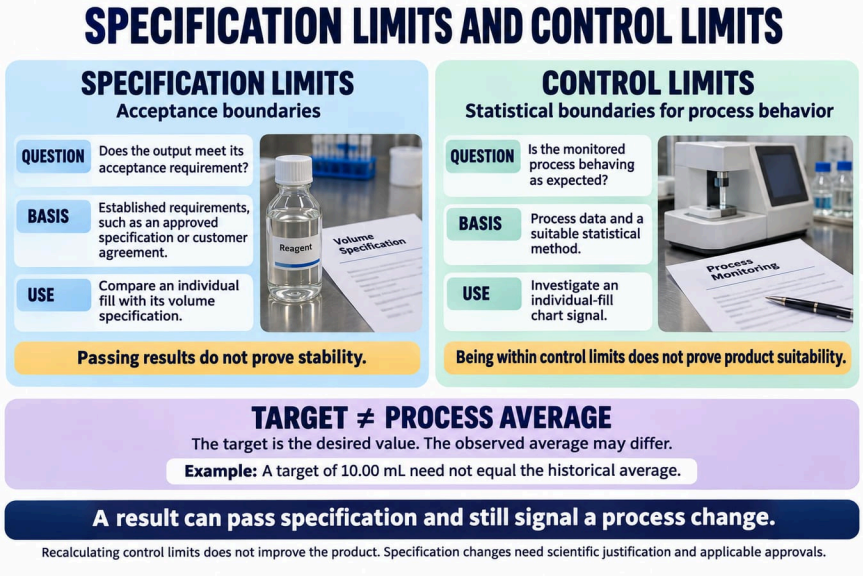
A short sequence that looks quiet does not establish long-term stability. Baseline data should represent relevant shifts, material lots, and routine operating conditions for the defined process. Keep unlike processes separate. The sampling frequency and relationships between successive measurements also affect interpretation. An apparent pattern may reflect how samples were collected rather than a change in production.

An **unstable process** shows statistical evidence that its monitored behavior is changing. Combining changing conditions into one average can hide important information. Investigate before using pooled data to predict future performance. A chart supports judgment; technical knowledge, reliable measurement, and a quality assessment remain necessary.

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6.4: Distinguishing specification limits from control limits

Specification limits are established acceptance boundaries for a product or measured characteristic. They come from applicable product requirements, such as an approved specification or customer agreement. Control limits are statistical boundaries used to assess process behavior. They are calculated for the particular chart statistic and monitoring approach.

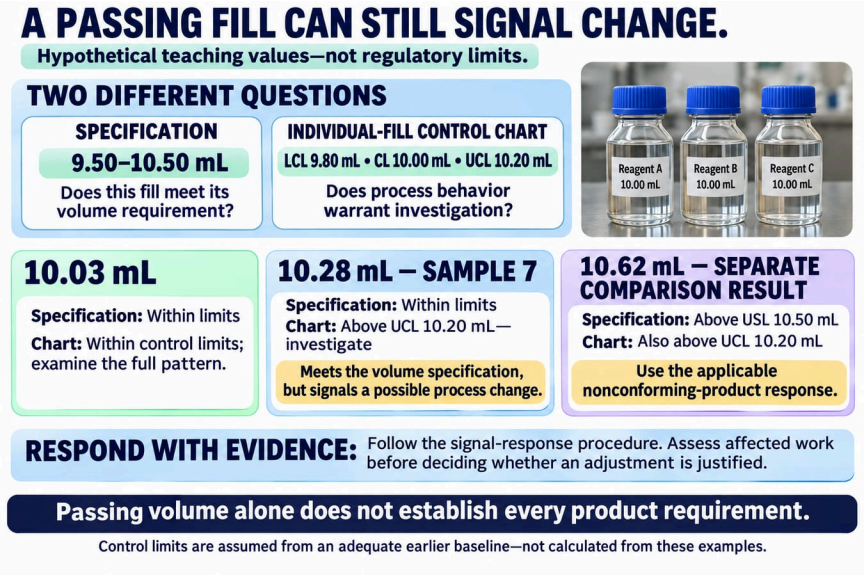


A target is the desired value. It is not necessarily the same as the observed process average. A team may aim for 10.00 mL while its historical average is slightly different. The target, specification limits, and control limits answer different questions and must be labeled clearly.

An individual result can meet its specification and still signal a process change. Conversely, a stable process can produce values outside specification if its usual spread is too wide or its average is poorly positioned. Recalculating control limits does not improve the product. Revising a specification needs separate scientific justification and the applicable approvals.

Worked example comparing two kinds of limits

The following numbers are hypothetical teaching values, not regulatory limits. Assume the company has an approved individual-fill specification of 9.50–10.50 mL. An established chart of individual fills has a center line of 10.00 mL, a lower control limit of 9.80 mL, and an upper control limit of 10.20 mL. Those chart limits are assumed to come from an adequate earlier baseline; they are not calculated from the few values shown here.



The 10.28 mL result at sample 7 meets the volume specification but signals a possible change in the process. Follow the signal-response procedure and assess affected work before deciding what adjustment, if any, is justified. The separate 10.62 mL result in the comparison table also fails the volume requirement and needs the applicable nonconforming-product response. A passing volume alone does not establish that a bottle meets every other product requirement.

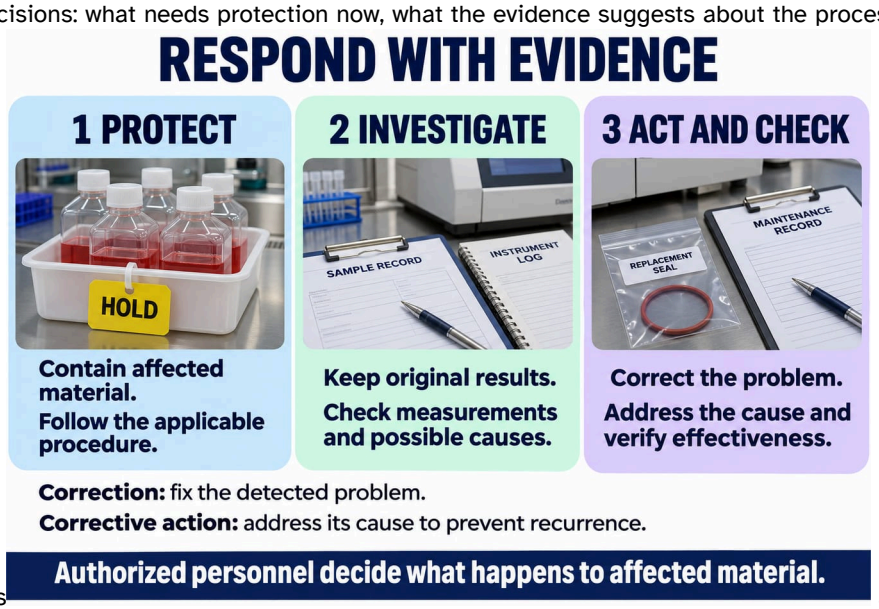
Process capability describes how well a stable process can meet its specifications. It depends on both the location and spread of results relative to requirements. Formal capability calculations have assumptions and data needs. This chapter introduces the concept without asking you to calculate an index from a small illustrative dataset.

Compare like with like. Control limits for subgroup averages describe averages, not the expected range of individual bottles. A narrow average chart cannot establish that every individual bottle is acceptable. The unit, sampling plan, and plotted statistic must be clear before comparing results with any limits.

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6.5: Responding appropriately to different sources of variation

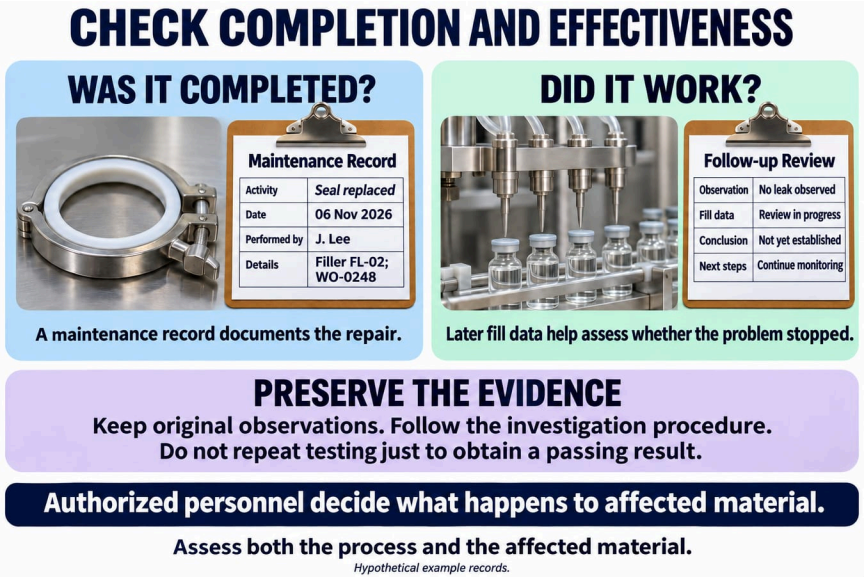
An appropriate response separates three decisions: what needs protection now, what the evidence suggests about the process, and what change is justified. **Containment** is an immediate action that limits the possible spread or use of affected material while the situation is assessed. It may include identifying material, placing it on hold, or pausing work under an approved procedure.



Containment protects affected work while a concern is assessed. Correction addresses the detected problem; **corrective action** addresses its cause to prevent recurrence. Holding bottles does not repair a damaged seal. Replacing the seal does not establish which earlier bottles were affected. The investigation must assess both the process and the material.

For a suspected special cause, preserve the data and examine conditions around the signal. Confirm sample identity and measurement validity. Review equipment events, material changes, maintenance, and setup records. Involve the people who performed the work. Record supported findings separately from hypotheses, and assess whether other batches or time periods may be affected.

If the process appears stable but regularly misses its purpose, repeated local corrections may not help. The team may need to redesign part of the process, improve equipment capability, strengthen material controls, or change a method. Such work generally needs coordination and planned evaluation, rather than asking one operator to compensate indefinitely.



After a change, check whether it was completed and whether it worked. For example, a maintenance record may verify that a seal was replaced, while later fill data help show whether the problem stopped. Authorized personnel must separately decide what to do with affected material.

In pharmaceutical manufacturing, FDA's 2011 process-validation guidance recommends continued process verification: ongoing collection and evaluation of information to help determine whether the process remains controlled. The guidance addresses drug and biological-product manufacturing; it is not a universal rule for every research laboratory. Guidance recommendations also must be distinguished from binding requirements.

Do not discard an inconvenient result or repeat testing until a passing value appears. Follow the applicable investigation procedure and retain original observations. An unusual result may reflect a measurement problem, a manufacturing change, or another cause. Each explanation needs evidence, and the product decision must remain with the authorized personnel.

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6.6: A children's medicine recall brings variation into focus

This historical account follows FDA inspection observations, a company recall statement, and later FDA testimony about McNeil's



2010 recall. The events are documented; the explanation of their connection to variation is a teaching analysis.

From April 19 to April 30, 2010, FDA investigators examined McNeil Consumer Healthcare's Fort Washington, Pennsylvania, facility. It made medicines for infants and children. A caregiver measuring a dose depended on the medicine having the stated strength and meeting its other quality requirements. Inside the facility, investigators were examining the manufacturing controls meant to support that expectation.

The investigators recorded concerns about evaluating manufacturing changes, mixing, and controls for processes associated with variability in finished medicine. They also identified gaps in tracking and trending products, components, and complaints. These findings appeared in the Form FDA 483 issued April 30. The form records inspection observations, rather than a final agency determination of compliance.

The concern soon reached families' medicine cabinets. In a May 1 statement, Johnson & Johnson reported that McNeil had announced a voluntary recall the previous night. Some recalled infants' and children's products might contain more active ingredient than specified; other concerns involved inactive ingredients and particles. The company stated that adverse medical events were not the basis for the recall.

On September 30, FDA Principal Deputy Commissioner Joshua Sharfstein described the response to Congress. He linked the Fort Washington recall to potency variability, particles, and possible microbial contamination. McNeil's reported corrective plan included stopping manufacturing, renovating the facility, improving quality systems, and obtaining outside expert review. These were reported actions and plans, not proof in the testimony that remediation was complete.

Sharfstein also reported a limit on the evidence of harm. FDA's investigation of adverse-event reports concerning the recalled products had not, overall, established a direct link to a serious adverse event, including death. That finding did not make the quality concerns acceptable or establish that no harm could have occurred. Manufacturing problems still required action.

The case connects to this chapter through the need to investigate variability, review manufacturing changes, and assess affected product. The public account does not supply enough time-ordered process data to classify every issue as common-cause or special-cause variation. It also does not establish that a single control chart would have prevented the recall. The lesson is to build evidence about the process rather than rely on isolated passing samples.

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6.7: Risks of adjusting a stable process unnecessarily

Tampering, also called overadjustment, occurs when people react to common-cause variation as though each difference needs a separate correction. The adjustments can add variation rather than reduce it. Deming used the funnel experiment to demonstrate this risk: moving a funnel in response to ordinary differences in where a marble landed could worsen the overall pattern.

For the hypothetical filler, a reading of 10.03 mL is slightly above the target. The technician lowers the setting. The next reading is 9.97 mL, so the technician raises it. If the original process was stable and these differences were expected, the technician may now be introducing additional shifts. The equipment begins responding to the operator's adjustments as well as its original sources of variation.

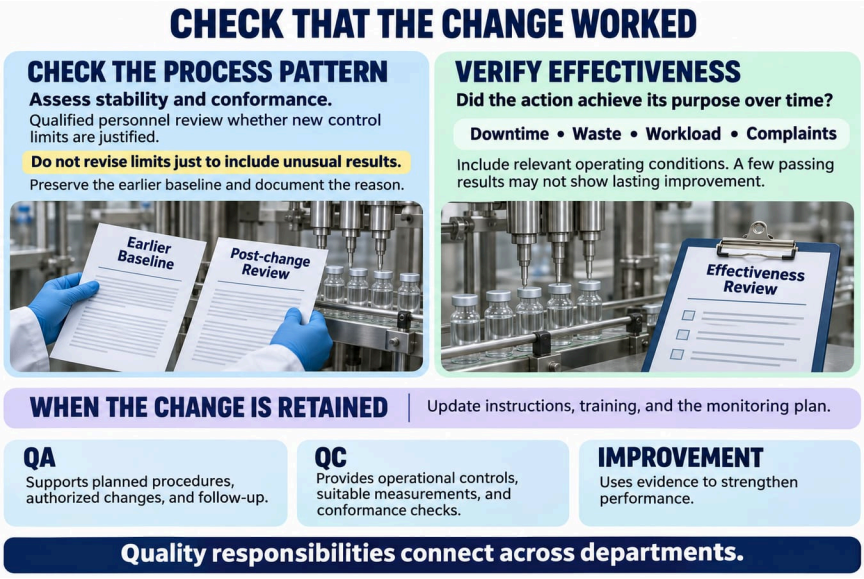
Avoiding tampering does not mean accepting bad output or ignoring a safety concern. A result outside specification still needs the required response. The distinction is between protecting affected output and making an unsupported adjustment to the process. Both the urgency and the technical response should be guided by evidence and applicable procedures.

Some processes have designed feedback controls that make justified adjustments automatically or at specified intervals. Following a validated or otherwise appropriate control strategy is different from an operator improvising a correction after every result. The goal is informed control, not a blanket ban on adjustments.

A useful pause before changing a setting is to ask: Is this a defined signal? Is the measurement reliable? What cause would the adjustment address? Is the adjustment authorized? How will its effect be checked? If the answers are unclear, escalation and investigation are often more useful than an immediate setting change.

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6.8: Using variation knowledge to guide improvement



Variation knowledge helps a team choose an improvement question. Does the process need a change in its average, a reduction in spread, removal of an unusual influence, or better measurement? These goals may require different actions. Moving the average cannot solve every problem caused by a wide spread.

An **improvement baseline** is the documented starting performance used for comparison. It should identify the process, measurement method, sampling plan, time period, and relevant conditions. Preserve time order. Grouping all results into one average can hide a change that began after maintenance or a material change.



Use a learning cycle to plan an authorized trial with a clear prediction. For example, a team might predict that a redesigned filling component will reduce individual-fill spread while keeping the average near its target. Compare results with both parts of the prediction and check unintended effects. A better average with a wider spread may not provide the intended benefit.

After a change, assess stability as well as conformance. If evidence supports a new process pattern, qualified personnel can review whether new control limits are justified. Do not recalculate limits simply to include unusual results. Preserve the earlier baseline and document the reason for revision. When the change is retained, update the relevant instructions, training, and monitoring plan.

Effectiveness verification means checking whether an implemented action achieved its intended purpose. Use an observation period that includes relevant conditions, and consider consequences such as downtime, waste, workload, and customer complaints. A few passing results immediately after a repair may not establish lasting improvement.

QA supports planned procedures, authorized changes, and follow-up that provide confidence in quality. QC contributes operational controls, suitable measurements, and conformance checks. Improvement uses the evidence to strengthen performance. These functions work together; a department's name does not assign every quality responsibility to that department.

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6.9: Chapter summary

Repeated results vary because of differences in process conditions, materials, and measurement. Common-cause variation reflects the usual process, while special-cause variation reflects an influence that changes its pattern. Chart signals support investigation but do not identify a cause by themselves. Stability supports prediction under similar conditions; it does not prove conformance or guarantee future results.

Specification limits define acceptance requirements. Control limits help assess process behavior and must match the plotted statistic. A passing result can signal an unusual change; a stable process can also be unable to meet specifications consistently. Capability considers stable process performance in relation to requirements.

Appropriate action protects affected output, preserves evidence, and addresses supported causes. Unnecessary adjustments can worsen a stable process. Planned improvement requires reliable measurements, a meaningful baseline, an authorized change, and evidence that the result lasts under relevant operating conditions.

These decisions often require knowledge from operations, QC, maintenance, purchasing, and management.

Key terms

Variation	Measurement system	Accuracy
Precision	Common-cause variation	Special-cause variation
Stable process	Statistical control	Mean
Spread	Control chart	Signals
Unstable process	Specification limits	Control limits
Target	Process capability	Containment
Corrective action	Tampering	Improvement baseline
Effectiveness verification		

Review questions

1. Identify four sources of variation in a biotechnology process and explain why measurement variation also matters.

2. Distinguish accuracy from precision using a laboratory example.

3. How does common-cause variation differ from special-cause variation?

4. Why does common-cause variation not necessarily mean acceptable performance?

5. What does process stability allow a team to predict, and what does it not guarantee?

6. What does a control chart show, and why must the chart match the data and sampling plan?

7. Distinguish specification limits, control limits, and a target.

8. How can a result meet its specification and still warrant investigation?

9. How does containment differ from corrective action?

10. Why should an investigation preserve the original result even if later testing passes?

11. Explain how tampering can increase variation. How does it differ from a designed feedback-control strategy?

12. What evidence should a team examine before concluding that an improvement is effective?

Apply your understanding

1. An individual-fill chart has established limits of 9.80–10.20 mL. The product specification is 9.50–10.50 mL. Interpret results of 10.04, 10.28, and 10.62 mL against both sets of limits. Explain the immediate response you would recommend for each and why no result alone identifies its cause.

2. Two reagent-filling lines have the same average volume. One has a narrow stable spread; the other has a much wider stable spread that extends beyond the specification. Explain why the averages do not establish equal quality. Propose an improvement goal for the second line and describe evidence needed to judge it.

3. A laboratory's results shift upward after a new reagent lot and a software update occur on the same day. An employee concludes that the reagent lot is defective. Identify the missing evidence and propose an investigation that considers both changes and the measurement system. Explain how affected results should be handled while the investigation proceeds.

4. An operator adjusts a stable filler after every result above or below target. All results are within specification, and no chart signal has occurred. Explain the risk of this behavior. Describe what the operator should check before changing settings and how the company could address a genuine need to improve performance.

5. In the McNeil story, distinguish what the inspection observations, recall statement, and congressional testimony establish. Explain why the available account does not permit a confident common-cause or special-cause classification for each issue. What additional time-ordered data and operating records would help?

6. A team changes a pump component and collects five passing results. It proposes closing the investigation and recalculating control limits immediately. Evaluate that proposal. Describe an effectiveness-verification plan that addresses process stability, conformance, relevant operating conditions, and possible effects on waste or downtime.

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7: EMPLOYEE INVOLVEMENT AND EMPOWERMENT

Learning Objectives

After completing this chapter, you should be able to:

- Define employee involvement and employee empowerment.
- Distinguish contributing to a decision from having authority to make it.
- Explain potential benefits for employees, customers, and organizations.
- Describe how leadership, training, resources, and information support participation.
- Apply accountability, decision boundaries, and escalation to biotechnology situations.
- Evaluate barriers that limit meaningful participation and propose improvements.

During a busy shift at a biotechnology company, a technician notices that two reagent labels are difficult to tell apart. The containers have similar shapes, and the labels sit beside one another at the packing station. No mix-up has been confirmed, but the technician sees how easily one could happen.

What happens next depends partly on the workplace. The technician might report the concern and help a team redesign the arrangement. Under an approved procedure, the technician might also have authority to pause packing and secure the material while a supervisor responds. These are related actions, but they involve different kinds of participation.

This hypothetical situation introduces **employee involvement** and empowerment. People who perform daily work often notice details that others miss. Their knowledge can help prevent problems when the organization provides a useful way to contribute and clear authority to act. Except for the documented case, examples and decision rules in this chapter are hypothetical teaching scenarios, not universal regulatory requirements.

7.1: Employee involvement- contributing knowledge and participating in improvement

7.2: Employee empowerment- authority to make decisions within defined boundaries

7.3: Differences and relationships between involvement and empowerment

7.4: Benefits for employees, customers, and organizations

7.5: Leadership support, training, and access to information

7.6: Accountability, escalation, and decision authority

7.7: Giving operators a better way to decide

7.8: Recognizing barriers to meaningful participation

7.9: Chapter summary

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7.1: Employee involvement- contributing knowledge and participating in improvement



Employee involvement means employees contribute knowledge, observations, and effort to decisions and improvement activities. It includes raising concerns, sharing ideas, reviewing a proposed procedure, gathering data, and helping investigate a recurring problem. Employees can influence the work even when another person makes the final decision.

Daily experience supplies information that a written procedure may not capture. A laboratory analyst may know that an instruction is difficult to interpret. A receiving employee may notice that deliveries arrive after the staff assigned to inspect them have left. A customer support employee may hear the same question from several customers. Each observation can reveal a process weakness.

Involvement is most useful when observations are specific. “This station is confusing” signals a concern, but “two similar labels are stored in the same tray and both are needed during one packing step” gives a team a clearer starting point. An observation should be recorded accurately without assuming that it proves a cause.

Participation can be informal or structured. A short shift discussion can surface immediate concerns. An improvement team can study a larger issue. A **quality circle** is a small group of employees who meet to examine work-related problems and suggest improvements. Its membership, training, and authority should be clear; belonging to a group does not automatically authorize changes to approved work.

Meaningful involvement includes a response. Employees should know how an idea will be reviewed and how they will learn the outcome. A suggestion that cannot be adopted still deserves an explanation. It may conflict with another requirement, need stronger evidence, or require resources that are not yet available. Clear follow-up helps employees understand that their contribution was considered.

In the label scenario, the technician could describe the arrangement, identify the step where confusion could occur, and join a review of alternatives. That is involvement. The final label design might still require approval from designated personnel before it is used.

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7.2: Employee empowerment- authority to make decisions within defined boundaries

Employee empowerment means employees have defined authority, information, skills, and resources to make decisions and act within their responsibilities. It goes beyond being invited to offer ideas. A person can be heavily involved in discussing a problem while still having limited authority to change the work.

Decision authority is permission to make a particular decision. Its **boundaries** state what the person may decide, under which conditions, and when another person must become involved. Useful boundaries name the action and its limits. “Use your judgment” alone may leave an employee unsure about what is permitted.

For example, a trained technician could be authorized to pause packing when product identity is uncertain, identify the affected material, and notify the designated reviewer. The same technician might lack authority to approve a replacement label or release the shipment. Authority to protect material while a concern is assessed differs from authority to decide that it is acceptable.

Empowerment requires a response from the wider organization. An employee authorized to pause work needs a reviewer who can assess the concern, a backup contact, and suitable records. Leaders should support appropriate use of that authority even if later review finds the material acceptable. Otherwise, employees may learn to stay silent when the next concern appears.

An employee should not invent a new test limit, bypass a required review, or alter an approved method simply because a supervisor encourages initiative. A proposed improvement can be valuable and still require evaluation and approval. Defined authority gives staff a reliable way to act while preserving the evidence and controls needed for the setting.

The correct scope depends on the task, its risks, demonstrated competence, and applicable requirements. A routine supply decision and a product release decision require different authority. Empowerment is effective when the employee understands those differences before a problem occurs.



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7.3: Differences and relationships between involvement and empowerment

Involvement asks employees to contribute to the understanding or improvement of work. Empowerment gives them authority to make specified decisions about that work. Both require communication, but their decision rights differ. A workplace should state those rights instead of assuming that an invitation to participate explains them.

The same employee may have both kinds of participation in one situation. A technician could use assigned authority to pause work, then contribute observations to the investigation. Other personnel might decide the material's disposition, meaning what will happen to it. These roles can work together without giving everyone the same authority.

A useful conversation before work begins is: What can I decide? What must I report? What needs approval? Who responds if the usual reviewer is unavailable? The answers should match the current procedures and assigned roles. When they conflict, the organization needs to resolve the conflict rather than leave the employee to guess.



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7.4: Benefits for employees, customers, and organizations

For employees, involvement can make daily work more understandable and give their experience a practical purpose. Helping solve a recurring problem can build skills and reduce frustration. Empowerment can reduce unnecessary waiting when staff are prepared and authorized to handle a defined situation. These benefits depend on real support; additional responsibility without resources may increase stress.

For customers and patients, early reporting can help prevent incorrect materials or unreliable information from reaching them. A receiving employee who identifies a damaged shipment may protect later laboratory work. A technician who questions an unclear instruction may prevent the same confusion from affecting several shifts.

For the organization, participation can reveal waste, strengthen handoffs, and improve the usefulness of procedures. It can also make improvement more sustainable. Employees who understand why a change was made are better prepared to recognize when it stops working. However, participation alone does not prove that a proposed change is effective. The team still needs suitable evidence.

An increase in reported concerns can have several meanings. After a reporting process improves, more reports may reflect greater willingness to speak up rather than worsening quality. Very few reports could reflect dependable work, fear, or a reporting method that is hard to use. Compare reporting patterns with other evidence before judging performance.

Useful evidence includes response time, follow-up completion, recurrence of problems, and employee views about whether concerns receive fair treatment. Counting suggestions alone can reward quantity over usefulness. The organization should examine whether participation improves the work and protects the people who rely on it.



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7.5: Leadership support, training, and access to information

Leaders make participation credible through daily actions. They can ask staff what makes a task difficult, listen without dismissing the concern, and provide time to examine it. 

When a problem is reported, an initial response focused on facts helps preserve useful information. Blaming someone before examining the evidence can discourage future reporting.

Psychological safety is a shared sense that people can ask questions, raise concerns, and acknowledge mistakes without humiliation or unfair punishment. It does not remove standards or **accountability**. Employees still need to follow requirements and report honestly. The purpose is to make truthful information available so the organization can act on it.

Training should prepare employees for their assigned decisions. A person authorized to hold suspect material needs to recognize the triggering conditions, identify the material correctly, complete the record, and contact the right person. Reading a policy may be one part of preparation, but practice and observation can show whether the employee can carry out the response.

Staff also need access to the current instructions, relevant results, equipment status, and contact information. Access should fit the role and protect confidential information. Employees do not need every record in the organization, but they do need enough reliable information to carry out their duties.

Resources include time to attend reviews, a usable reporting method, and coverage while staff participate. If meetings occur only during one shift, other employees may rarely contribute. Leaders should consider shift schedules, language needs, accessibility, and employment arrangements when creating opportunities to participate.

A complete response to a concern identifies who will review it, when feedback is expected, and what happens in the meantime. **Closing the feedback loop** means returning information about the decision or action to the people who raised the issue. It helps connect reporting with a visible outcome and allows staff to correct misunderstandings.

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7.6: Accountability, escalation, and decision authority

Accountability means being answerable for assigned responsibilities and the decisions made within them. An empowered employee should be able to explain the information used, the action taken, and whether the action followed the assigned limits. Managers remain accountable for making those limits workable and providing support.

Escalation means bringing an issue to someone with the authority or expertise to address it. Escalation is an appropriate use of judgment when an issue falls outside the employee's role. It should not be treated as failure to act independently. Recognizing the limit of one's authority is part of responsible work.

A clear response identifies the facts, protects the affected work where authorized, preserves records, and contacts the designated person. Staff should distinguish what they observed from what they suspect. "The label does not match the packing record" is an observation. "The previous shift used the wrong reagent" is a conclusion that needs evidence.These are illustrative boundaries, not instructions for every facility. Actual procedures should define who may stop work, place material on hold, evaluate it, authorize a change, and permit work to resume. A supervisor's availability does not change who has authority to release a product.

Investigations should examine individual conduct and the conditions surrounding it. Check whether instructions were clear, training was adequate, equipment worked, and records were accurate. An honest mistake and deliberate falsification call for different responses. Fair accountability depends on evidence and consistent expectations.



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7.7: Giving operators a better way to decide

At Par Sterile Products in Rochester, Michigan, filled units were being discarded during sterile filling.



The company wanted to understand the losses and reduce waste. A NIST Manufacturing Extension Partnership case published July 30, 2022 describes how it sought help from the Michigan Manufacturing Technology Center.

The response began with training in data-based improvement. With guidance from the Center, the project defined its scope, mapped the process, and developed a measurement method. The team then examined possible contributing factors through planned experiments. The work led to a fill-check calculator that supplied settings based on the product and allowed operators to adjust fill levels independently.

This is the point where the story connects directly to empowerment. An operator was given a practical tool for making a defined process decision. Independence had support: the calculator connected the decision to the product being made. The lesson is that authority becomes more useful when staff have reliable information and a method suited to the task.

The project also updated procedures and trained operators. After implementation, fill-check data were monitored for about three months. The published case reports $1.2 million in cost savings, a 19.9% reduction in variation, and a setup-time decrease from 0.86 to 0.30 hours. These are reported project outcomes, not a controlled comparison proving that empowerment alone caused them.

The sequence matters. The team first worked to understand and measure the process. It then developed a tool, prepared staff to use it, and followed performance over time. Simply telling operators to take more initiative would not have supplied the same information or structure.

The account does not describe every approval, adjustment limit, or release decision. It therefore cannot establish that operators had unrestricted authority. In a similar setting, the organization would need to define the permitted adjustments and the conditions requiring escalation. Those details would allow staff to act independently within a dependable system.

The Par Sterile case connects employee participation with a supported decision. Operators received a tool, revised procedures, training, and follow-up. A similar biotechnology workplace would need to define its own decision limits and approval responsibilities.

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7.8: Recognizing barriers to meaningful participation



Some barriers are easy to see. Employees may lack time, current information, or a clear reporting route. Others are harder to recognize. An employee may stay silent because an earlier concern was ignored or because a supervisor reacted angrily. Repeated experiences shape whether people believe an invitation to participate.

Token participation occurs when employees are asked for input but have little meaningful opportunity to influence the discussion or receive a response. A meeting held after a decision is already fixed can create that impression. Leaders should explain which matters are open for input and which constraints have already been established.

Differences in status can also limit participation. New staff, temporary employees, or people on less visible shifts may notice important problems but hesitate to challenge experienced colleagues. A useful process invites their observations, provides accessible ways to contribute, and evaluates evidence rather than the speaker's rank.

Unclear incentives can work against quality. If supervisors praise fast output but criticize every pause, employees may hesitate to use their authorized hold authority. If a team receives a reward for having no reported errors, honest reporting may appear costly. Leaders should examine whether performance goals support the behavior they say they want.

Improving participation begins by asking where the process breaks down. Staff can help examine how a concern moves from observation to review and action. The organization can then test a practical change, such as a simpler reporting form or a clearer response schedule, and review whether employees receive useful follow-up.

Employees should not be expected to fix a weak system through personal effort alone. Their contributions matter most when leadership makes room for them, authority matches competence, and the organization follows through. Involvement and empowerment are continuing practices supported by everyday decisions.

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7.9: Chapter summary

Employee involvement brings employees' knowledge, observations, and ideas into decisions and improvement activities. People who perform daily work often notice unclear instructions, difficult handoffs, or conditions that could lead to errors. They can help identify and study these concerns even when someone else makes the final decision. Specific observations give an investigation a stronger starting point than assumptions about the cause.

Employee empowerment gives employees defined authority to make decisions and act within their responsibilities. It requires suitable skills, reliable information, resources, and clear limits. For example, a trained technician may be authorized to pause packing when product identity is uncertain but may not be authorized to approve a replacement label or release the shipment. Contributing an idea and having authority to approve it are different responsibilities.

Involvement and empowerment can work together. An employee might use assigned authority to protect affected material, then contribute observations to the investigation. Both practices can help employees build skills, reduce unnecessary delays, and improve work. Customers and patients may benefit when concerns are identified before incorrect materials or unreliable information reach them. These benefits depend on support and evidence; participation alone does not establish that a change worked.

Leaders support participation by listening, responding fairly, and providing time and resources. Psychological safety helps people ask questions, report concerns, and acknowledge mistakes without humiliation or unfair punishment. It does not remove standards or accountability. Employees still need to follow requirements and report honestly. Training should prepare them for their assigned decisions, and practice or observation can help establish readiness to act independently.

Accountability means being answerable for assigned responsibilities and decisions. Employees need to understand what they may decide, what requires approval, and whom to contact when a concern falls outside their authority. Escalation is responsible judgment when another person's expertise or approval is needed. Staff should preserve evidence and distinguish what they observed from what they suspect. Managers remain responsible for providing workable boundaries, support, and a reliable response.

Meaningful participation also requires follow-through. Closing the feedback loop means telling employees how their concern or suggestion was evaluated and what will happen next. Barriers include fear of blame, lack of time, unclear authority, unequal access, and incentives that discourage reporting. Token participation occurs when employees are invited to contribute but have little meaningful opportunity to influence the discussion or receive a response. Organizations should address these conditions rather than expect employees to overcome them alone.

The documented Par Sterile Products example connects independent operator decisions with a practical tool, revised procedures, training, and follow-up monitoring. Its reported results do not establish that empowerment alone caused the improvement or that operators had unlimited authority. To evaluate participation, organizations should examine response times, follow-up, recurring problems, and employee experiences. More reports can reflect greater willingness to speak up, so reporting counts need to be interpreted alongside other evidence.

Key terms

Employee involvement	Employee empowerment
Quality circle	Decision authority
Decision boundaries	Psychological safety

Accountability	Escalation
Closing the feedback loop	Token participation

Review questions

1. What is employee involvement? Give one biotechnology workplace example.

2. What is employee empowerment? Give one biotechnology workplace example.

3. How can an employee contribute to a decision without having authority to make it?

4. What is a quality circle?

5. What should employees know about the boundaries of their decision authority?

6. Name one potential benefit of participation for employees and one for customers or patients.

7. What is psychological safety, and why does it support honest reporting?

8. What information, training, and resources can help an employee use assigned authority responsibly?

9. Why can escalation be an appropriate use of judgment?

10. What does closing the feedback loop mean?

11. Name three barriers to meaningful employee participation.

12. Why does an increase in reported concerns not necessarily mean that quality has worsened?

Apply your knowledge

1. Recognizing involvement and empowerment

A technician reports that two reagent labels are difficult to tell apart and joins a team reviewing possible improvements. Later, the technician finds a label mismatch and pauses packing under an approved procedure. Identify which actions show involvement and which show empowerment. Explain what information and authorization would be needed before labels are changed or the shipment is released.

2. Making decision authority workable

A new employee is told to solve problems independently but receives no clear decision limits, training on when to hold material, or backup contact. Propose three changes that would make this responsibility workable. Describe one decision the employee could make after appropriate preparation and one decision that should still be escalated. Explain how readiness for independent work could be assessed.

3. Interpreting a rise in concern reports

After a reporting form is simplified, monthly concern reports increase from 8 to 22. A manager concludes that employees are making more mistakes. Explain why the report counts alone do not support that conclusion. Identify three additional sources of evidence that would help distinguish changes in reporting from changes in process performance.

4. Removing barriers to speaking up

Night-shift and temporary employees perform the same packing work as day-shift staff but are rarely invited to improvement meetings. Several say their suggestions receive no response. Supervisors also praise uninterrupted output even though staff are authorized to pause work for identity concerns. Propose changes that improve access to participation, provide feedback, and support appropriate use of authority. Explain how you would evaluate whether the changes are working.

5. Supporting independent decisions with evidence

In the documented Par Sterile Products example, operators received a fill-check calculator, revised procedures, training, and follow-up monitoring. Explain how these supports could help employees make defined decisions independently. For a similar hypothetical process, propose two decision boundaries, evidence of training readiness, and one escalation trigger. Distinguish these proposals from details actually established by the case, and explain why the reported results do not prove that empowerment alone caused the improvement.

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8: TEAM PURPOSE, TYPES, AND RESPONSIBILITIES

Learning Objectives

After completing this chapter, you should be able to:

- Explain why teams can improve the identification and resolution of biotechnology quality problems.
- Distinguish a team from individual work and a loosely organized group.
- Compare process teams, continuous improvement teams, workgroups, workcells, self-managed teams, temporary teams, and cross-functional teams.
- Select a team structure based on the purpose, scope, duration, expertise, and authority needed.
- Distinguish the responsibilities of a sponsor, champion, facilitator, leader, and member.
- Explain how documentation supports team coordination and accountability.
- Connect a team's work and performance measures to organizational strategy and customer needs.

Understanding how processes connect and investigating changes in performance often require knowledge from several people. **Team** design brings that knowledge together by defining a shared purpose, selecting suitable members, and making responsibilities clear.

A biotechnology company manufactures research-use enzyme kits. Some completed batches wait several days before they can be shipped. Production says the kits are ready. **Quality control** (QC) says the test results are complete. **Quality assurance** (QA) reports that the batch documents still contain missing entries or unclear corrections.

A supervisor asks one employee to collect the incomplete records. The employee follows up with coworkers, but the same problems return with later batches. No single person controls every step. A preliminary review identifies missing information in manufacturing records and delays when laboratory results and packaging records are brought together. These observations locate problems that need investigation; they do not yet establish their causes.

This hypothetical recurring problem calls for people who understand the connected steps to investigate together. Collecting incomplete records may help with the current backlog, but it does not explain why omissions recur. A suitable team can study the handoffs and develop an improvement that the organization can maintain.

Teams are useful when work is connected, but they are not automatically the best answer to every task. This chapter explains how to choose a suitable structure and make responsibilities clear. The examples here use a hypothetical research-use kit company; its assigned responsibilities illustrate a quality system and are not a claim that every biotechnology organization has the same structure or requirements.

8.1: Why teams can improve problem identification and resolution

8.2: Teams compared with individual work and loosely organized groups

8.3: Process teams and continuous improvement team

8.4: Workgroups and workcells

8.5: Self-managed teams

8.6: Temporary and ad hoc project teams

8.7: Cross-functional teams

8.8: Selecting a team structure for the situation

8.9: Example - choosing a team for batch-document delays

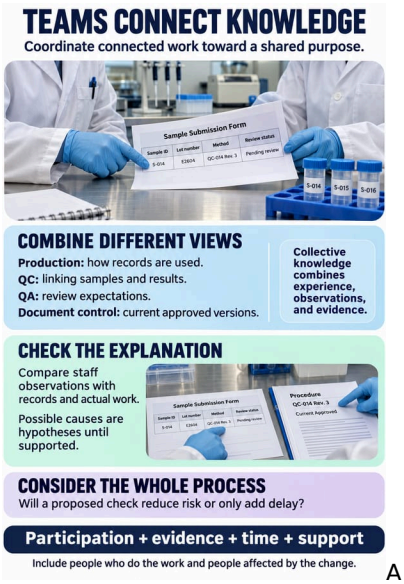
8.10: Sponsor, champion, facilitator, leader, and member responsibilities

8.11: Connecting team efforts to organizational strategy

8.12: Chapter Summary

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8.1: Why teams can improve problem identification and resolution



A team is a group whose members coordinate interdependent work toward a shared purpose or result. ASQ emphasizes those connected tasks and the common objective. A team can be temporary or ongoing; its members may also complete individual assignments.

Quality problems often cross the boundaries of departments. A missing lot number on a laboratory form may begin with a poorly designed production label. A shipping delay may reflect incomplete review information rather than slow packing. People who see only their own step may reasonably reach different explanations.

The examples above are possible explanations, not findings. A team can combine those partial views and check them against records and direct observation. Production staff understand how records are used during a run. QC analysts know what information they need to link results to samples. QA staff understand review expectations. Document-control staff know how approved versions are issued. Together, they can examine both the work and the information moving with it.

Collective knowledge is the understanding a team builds by combining members' experience, observations, and evidence. It is valuable when members explain what they know and test their assumptions. Simply placing several experts in a meeting does not guarantee a better decision.

Suppose the enzyme-kit team finds that a record field requests information before it is available. Staff observations and records would need to support that finding. The team could then examine when the information becomes available, who supplies it, and how the record should capture it. This is a possible investigation outcome, not a known cause of the company's delays.

Teams also help evaluate effects beyond one department. A proposed extra signature might make a reviewer feel more confident while adding a delay that does not improve the quality of the record. Operators and reviewers can examine whether the check addresses a real risk and whether another design would work better.

The benefit depends on participation, evidence, time, and support. A team that excludes the people doing the work can repeat management's assumptions. A team without access to records may debate opinions instead of investigating. The Institute for Healthcare Improvement emphasizes including knowledge of the process, technical expertise, leadership, and the experience of people affected by the change.

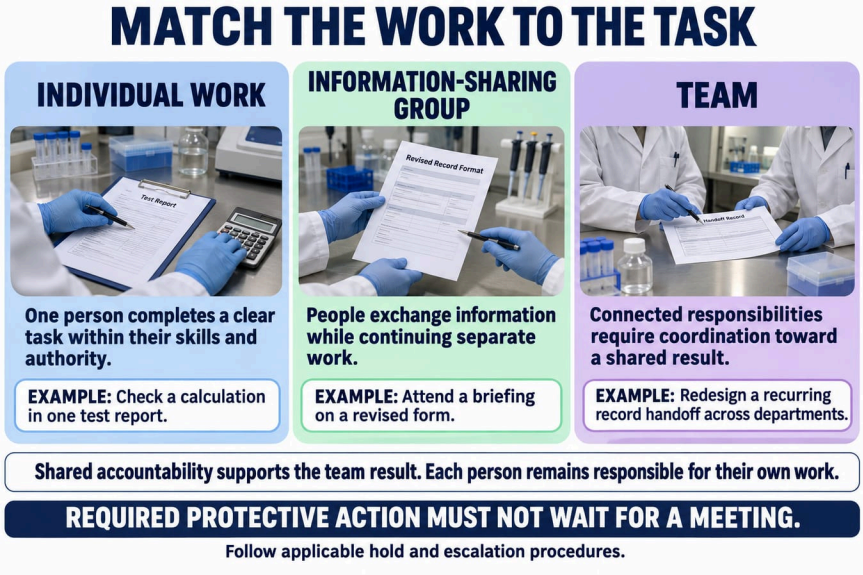
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8.2: Teams compared with individual work and loosely organized groups

Individual work places a defined task with one person who has the skills and authority to complete it. An analyst may perform an assigned calculation or review a specific dataset independently. This can be efficient when the task is clear and the needed information is available.

A **loosely organized group** brings people together with limited coordination of their work and without a shared performance result. Employees may attend an update meeting yet continue working separately. Such a meeting can still have a clear purpose and useful agenda. Information sharing alone does not establish the interdependence that defines a team.

A team has a shared result, connected responsibilities, and a way to coordinate contributions. **Shared accountability** means that members take responsibility for the team's agreed work and result. It does not erase each person's responsibility for the accuracy of their own work, records, and decisions.



Teamwork has costs. Meetings take time, coordination can be difficult, and a poorly defined team may delay a straightforward decision. The goal is to match the work arrangement to the problem. A team can assign individual tasks between meetings without turning every calculation or inspection into group work.

Immediate protective action should not wait for a committee. If a sample is unidentified or material may be unsuitable, employees should follow the applicable hold and escalation procedures. Investigation can begin alongside the response when appropriate, but meetings must not delay required protective action.

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8.3: Process teams and continuous improvement team

A **process team** has continuing responsibility for coordinating and monitoring a defined process. Here, the term emphasizes ongoing operations. A sample-receiving team might coordinate intake, resolve routine issues within its authority, and monitor submission quality. Organizations may use this label differently, so confirm the actual assignment.

A **continuous improvement team** studies performance and develops better ways of working. It may address one project or continue through several opportunities. ASQ's process-improvement teams have defined goals and project plans. The word continuous describes ongoing attention to improvement; it does not require every individual team to exist permanently.

The difference is the main purpose. An ongoing batch-document review team may coordinate the work each week. An improvement team may study why documents repeatedly arrive incomplete, test an approved change, and evaluate whether completeness improves. Both may work on the same process, but their assignments differ.

For the enzyme company, a process team might monitor which batch packages are awaiting review. A temporary improvement team could investigate missing information in those packages. After the



improvement project ends, the process team or assigned **process owner** needs to maintain the new practice.

A process owner is the person responsible for overseeing a process's ongoing performance and coordinating needed changes. Identify this role early so that the owner can help shape the improvement and accept its ongoing responsibilities. The owner may lead the team or serve as a member, but these roles are not automatically the same. Clear ownership supports continuity after the project ends.

Use records to connect the two activities. The process team's routine data can help identify recurring delays. The improvement team can document what it changed, why it changed it, and what follow-up is needed. Those records let others distinguish a tested improvement from an informal workaround.

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8.4: Workgroups and workcells

A **workgroup** carries out related routine work, often within one department. ASQ also uses the term natural team; collaboration and autonomy vary. A QC microbiology workgroup might coordinate scheduled tests and shared equipment. It functions as a team when members' work is interdependent and they share a performance result.

A **workcell** is an arrangement of people, equipment, and workstations organized around a connected sequence of tasks. Cellular manufacturing aims to support smoother flow with less movement and waiting. In this context, cell refers to the organization of work, not a biological cell.

Imagine a research-use kit assembly area where approved components are checked, assembled, labeled, and packed through nearby workstations. Staff can see the flow and identify a problem before many kits move forward. This is a hypothetical workcell; its suitability would depend on the product and operating requirements.



Hypothetical kit-assembly example. Workcell means an organization of work—not a biological cell.

A is partly a physical or operational arrangement. It does not automatically determine how the team is managed. A workcell could be supervisor-led or have defined self-management responsibilities. Likewise, a workgroup can function as an effective team when members share a result and coordinate their tasks.

Layout improvements must respect relevant constraints. Bringing workstations closer together may reduce walking while increasing the risk of mixing components or confusing labels. The team should consider identification, separation, ergonomics, safety, cleaning, and required checks before changing the area.

Documents remain important within the cell. Current instructions should be available where needed, and each person should know which activities and checks they are authorized to perform. A convenient layout cannot compensate for unclear responsibilities or unreliable records.

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8.5: Self-managed teams

A **self-managed team** manages a substantial, delegated range of daily operations. ASQ associates self-management with broad operational authority, including responsibilities often held by managers. In a particular laboratory, these might include assigning qualified staff, coordinating maintenance, and reviewing workload. Scheduling flexibility alone does not establish self-management.

Self-management requires **decision boundaries**, which state what the team can decide and what must be referred elsewhere. Those boundaries need to be explicit. A group may be allowed to arrange its work schedule without being allowed to change a test method or approve a product for release.

For example, an experienced sample-processing team might decide which trained employee covers each station. It might also adjust task order when the approved procedure allows that flexibility and the team has the necessary authority. It should escalate a proposal to remove a required identity check, because that proposal changes the process rather than simply organizing the day's work.

Readiness depends on skills, access to information, and management support. **Team members** need to understand requirements, recognize when conditions are unusual, document decisions, and ask for help. Managers remain responsible for providing resources and oversight appropriate to the work.



Self-managed does not mean that every member has every qualification. An employee may coordinate a shift yet be unqualified to perform a specialized assay. The team should use training and authorization records when assigning work, rather than assuming that membership permits every task.

A realistic self-management arrangement makes responsibility visible. Staff should know who responds to a shortage, who can pause work, and who receives an unresolved concern. Unclear authority can leave employees carrying responsibility for decisions they were never authorized to make.

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8.6: Temporary and ad hoc project teams



Duration is a separate feature from purpose or authority. A **temporary project team** is formed to achieve a defined result within a limited period. Its work ends when the agreed completion conditions are met and the result is accepted, or when the organization formally closes or ends the assignment. Extending or changing the assignment should be explicit. Examples include preparing an authorized laboratory relocation or improving a specific sample-transfer process.

An **ad hoc team** is assembled for a particular need, often in response to an unusual issue. An unexpected pattern of mislabeled samples may require a short-term group with sample collection, laboratory, quality, and information-system expertise. Ad hoc describes why the group was formed; it does not remove the need for structure.

The assignment should state the problem, expected deliverable, authority, and completion conditions. For the enzyme company, a temporary team could deliver a tested record-handoff process and a plan for maintaining it. Recommendations alone would meet the assignment only if they were the agreed deliverable.

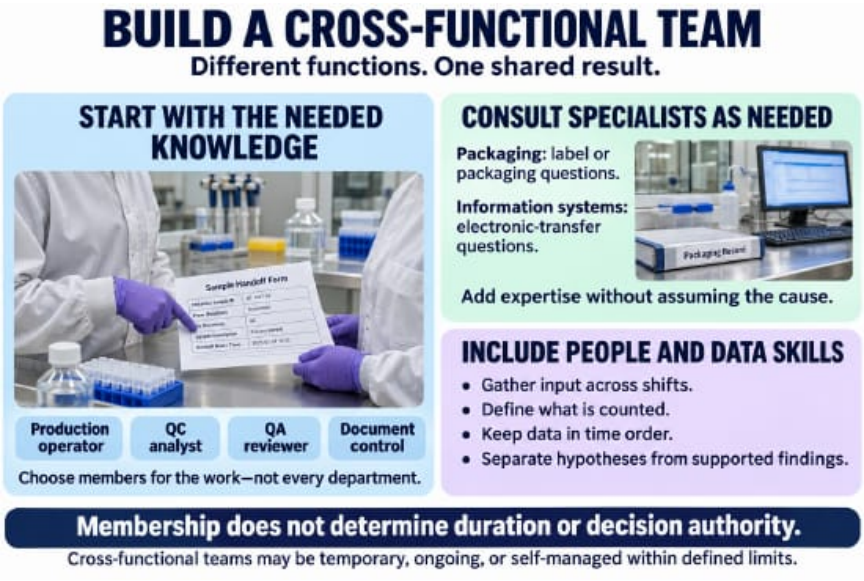
Urgency does not justify undocumented decisions. A short-term team should preserve facts, record actions, assign responsibility, and communicate unresolved risks. Temporary teams can create lasting consequences, especially when their proposals affect instructions, software, or product handling.

An **action log** records agreed tasks, assigned people, due dates, and status. A **decision log** collects records of important decisions, their reasons, supporting evidence, the decision method, responsible authority, and unresolved concerns. One person may maintain the records, but members remain responsible for checking that their own commitments are accurate.

Before disbanding, the team should transfer ongoing responsibilities to a named owner. For example, the batch-review supervisor might monitor the new completeness measure, while document control maintains the approved form. Without this transfer, a successful trial can be followed by a return to the earlier process.

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8.7: Cross-functional teams

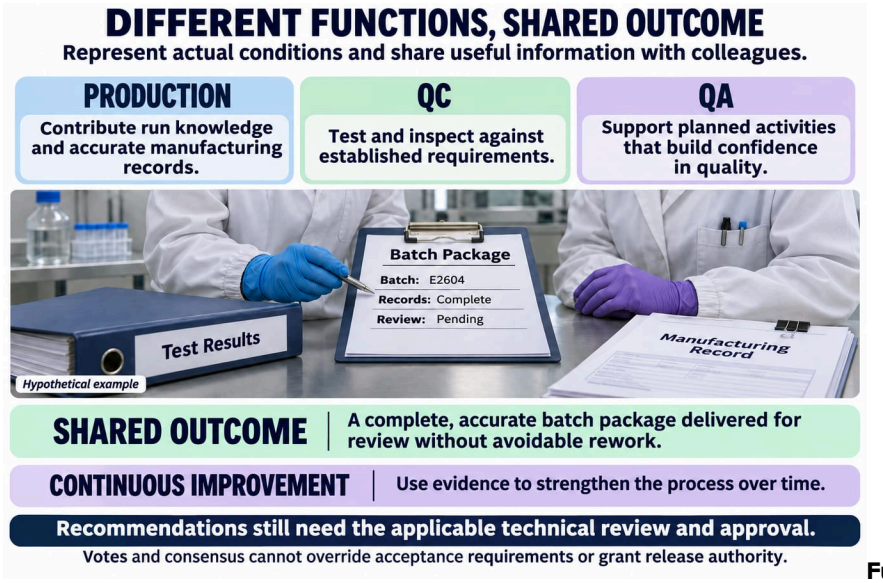


Membership provides another way to describe a team. A **cross-functional team** includes people from different organizational functions who work toward a shared result. It is useful when a problem spans departmental boundaries. The label describes membership, so a cross-functional team may also be temporary, ongoing, or self-managed within defined limits.

For the enzyme company, suitable members could include a production operator, QC analyst, QA reviewer, and document-control specialist. Include packaging knowledge if missing packaging information or label reconciliation is part of the problem. Consult an information-system specialist when electronic transfers need investigation. Add expertise because the work requires it, rather than assuming a cause before reviewing evidence.

Choose members for the knowledge needed, rather than trying to include every department. A smaller working team can consult specialists when particular questions arise. People directly affected by a proposed change should have a practical way to contribute, including staff working other shifts.

Include the ability to collect and interpret data. A team should preserve time order, define what it counts, and distinguish a suspected cause from a supported finding. A knowledgeable analyst or improvement adviser can help when those skills are not already represented.



Functional representation means bringing relevant knowledge and perspectives from a work area into the team. It does not require a member to defend that department's current practice. An effective representative helps the team understand actual conditions and carries useful information back to colleagues.

Different functions may define success differently. Production may focus on completed runs, QC on dependable results, and QA on a complete record for an authorized disposition decision. The team needs a shared outcome that connects those contributions. In this example, that outcome could be a complete, accurate batch package delivered for review without avoidable rework.

Quality assurance, or QA, focuses on planned activities that provide confidence quality requirements will be met. Quality control, or QC, focuses on fulfilling quality requirements through operational activities that include testing and inspection. Continuous improvement uses evidence to strengthen the process over time. Team members can connect these functions while preserving their distinct responsibilities.

A team recommendation does not replace required technical review or product-disposition authority. Neither a vote nor consensus can override acceptance requirements or grant release authority the team does not have. Participation helps develop an informed recommendation; the applicable approval process determines who may act on it.

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8.8: Selecting a team structure for the situation

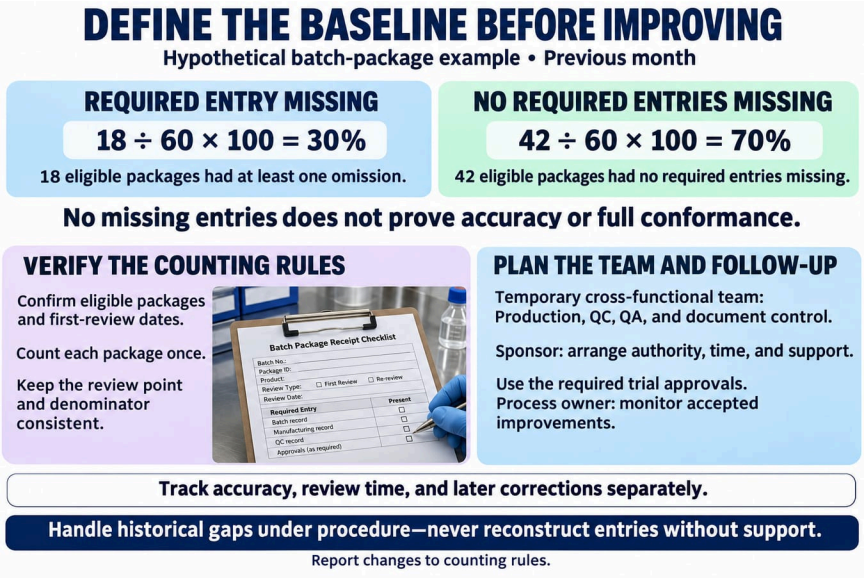
The RADx account illustrates why one label rarely captures an entire collaboration. For a local project, start with the work that needs to be done. Identify the result, the affected process, and the expertise needed. Then consider how long the work will continue, which decisions the team must make, and what resources it needs. A familiar team label is less important than a suitable design.

Team types describe different dimensions. Purpose may be routine operation or improvement. Duration may be ongoing or temporary. Membership may come from one function or several. Authority may remain with a supervisor or be partly delegated. Work may also be organized in a cell. These features can be combined.



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8.9: Example - choosing a team for batch-document delays



Suppose 18 of 60 eligible batch packages had at least one required entry missing at first review during the previous month. These counts are hypothetical. Under that definition, 18 ÷ 60 × 100 = 30% had a missing entry, and 42 ÷ 60 × 100 = 70% had none. The second figure does not prove that those 42 packages were accurate or met every other review requirement.

A temporary cross-functional improvement team is a reasonable starting choice. Its purpose is to reduce avoidable missing information and review rework. Production, QC, QA, and document control each contribute necessary knowledge. A manager with suitable authority **sponsors** the work and arranges time for staff to participate.

Before adopting these figures as a baseline, verify which packages were eligible, when first review occurred, and how missing entries were counted. Count each package once, even if it has several omissions; a separate count can describe individual omissions. Then examine the handoffs and propose a trial through the required approval process. Historical record gaps still need handling under the applicable procedure; they must not be filled through unsupported reconstruction.

A useful measure is the percentage of eligible packages with no required entries missing at first review. Keep the definition, review point, and denominator consistent. Track record accuracy, review time, and later corrections separately. If counting rules change, report the change so it is not mistaken for better performance. Once an improvement is accepted, the named process owner monitors whether it lasts.

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8.10: Sponsor, champion, facilitator, leader, and member responsibilities

Clear roles connect the team's purpose with daily work and organizational support. Titles vary, and some organizations combine roles. The following distinctions provide a practical model rather than a mandatory structure. Confirm actual authority instead of assuming that a title grants it.

A sponsor provides organizational backing and accepts responsibility for the project's fit, resources, and management-level support. The sponsor reviews progress and helps remove barriers beyond the working team's authority. The sponsor acts within their own authority and routes other decisions to the appropriate approvers. IHI identifies sponsorship as a link between the improvement effort, executive authority, and **organizational strategy**.

A **champion** actively advocates for improvement and helps connect it to broader priorities. In Six Sigma settings, ASQ describes champions as translating organizational direction into projects, identifying resources, and removing obstacles. A sponsor may also act as champion, or one champion may support several teams.

A **facilitator** helps members participate, stay focused, and use the agreed discussion and decision process. A **team leader** coordinates assignments and progress. One person may perform both roles, but the functions remain different. Facilitation does not grant technical approval authority, and a leader's expertise should not prevent other members from presenting contrary evidence.

TEAM ROLES AND FOLLOW-THROUGH

Hypothetical document-improvement project

ROLE	MAIN RESPONSIBILITY	EVIDENCE OF FOLLOW-THROUGH
Sponsor	Provide staff time; resolve resource conflicts.	Resource decisions and periodic progress review.
Champion	Connect the project with dependable service and organizational priorities.	Project support and help removing broader barriers.
Facilitator	Support fair examination of the handoff and member participation.	Focused discussion and recorded unresolved questions.
Team leader	Coordinate assignments, dates, and the deliverable.	Current action log and progress report.
Member	Contribute observations and complete agreed evidence-gathering tasks.	Accurate records and completed assigned work.



A team member contributes knowledge, performs agreed tasks, checks facts, and follows through. Members should report obstacles early rather than letting a missed commitment become a surprise. They should also identify when a proposal exceeds their own qualifications or the team's authority.

The team should also identify who maintains improvements after the project. The process owner may be the leader, but that is not automatic. Likewise, a sponsor's support does not transfer every technical approval to the sponsor. Product, method, and document decisions remain with the applicable authorized roles.

Documentation makes responsibility reviewable. A **standard operating procedure**, or SOP, gives approved instructions for recurring work. A **batch record** documents activities and results for a particular batch. An SOP revision may be a team deliverable; completed batch records provide evidence of actual practice. Writing a new instruction does not establish that it was introduced or that it improved performance.

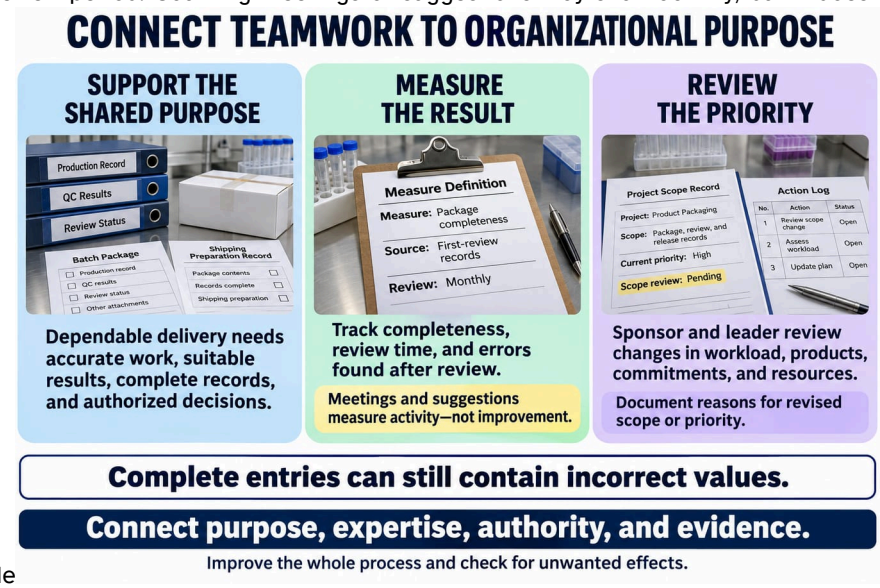
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8.11: Connecting team efforts to organizational strategy

Organizational strategy describes the priorities and choices an organization uses to pursue its purpose. A quality team should be able to explain how its assignment supports those priorities. A project that improves a local number while creating problems elsewhere may not serve the organization or its customers.

For the enzyme company, dependable delivery depends on accurate production, suitable test results, complete records, and authorized decisions. Reducing document rework can support delivery reliability and reduce employee frustration. Simply shortening review by removing useful checks could undermine the purpose of the project.

A **performance measure** is a defined indicator used to assess results or progress. Useful measures need an agreed definition, source, and review period. Counting meetings or suggestions may show activity, but it does not demonstrate that the process improved. Measure the intended result and check for unwanted effects.



For example, the team could track packages with no missing entries alongside review time and errors found after review. A package can have all required entries and still contain an incorrect value. An apparent improvement caused by reviewers no longer recording omissions would also be misleading. Honest measures help the organization decide what to do next.

The sponsor and team leader should periodically review whether the assignment still matters. A change in products, workload, customer commitments, or resources may require a revised scope or priority. Record the reason for the change so that team members understand the decision.

Good team design connects purpose, expertise, authority, and evidence. Those connections help employees contribute effectively without carrying unclear responsibilities. They also help the organization turn a successful project into a dependable way of working.

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8.12: Chapter Summary

Teams bring connected knowledge and responsibilities together around a shared result. They can reveal problems that are difficult to understand from one department's viewpoint. Their value depends on relevant participation, evidence, authority, resources, and follow-through. Individual work remains appropriate for tasks that one qualified person can complete effectively.

Team labels describe different features. Process teams coordinate ongoing work; improvement teams develop changes. Workgroups perform related routine activities, while workcells arrange a connected sequence of tasks. Self-managed teams manage a defined range of operations under delegated authority. Temporary teams have limited assignments; ad hoc teams form for a particular need. Cross-functional teams combine expertise from different functions. One team can fit several descriptions.

Sponsors and champions provide support and connection to organizational priorities. Facilitators support the team's working process, leaders coordinate delivery, and members contribute reliable work. Clear records and a named process owner help preserve improvements after a project ends. The final test is whether the team's work improves an outcome that matters while meeting applicable requirements.

Key Terms

Team	Collective knowledge	Individual work
Loosely organized group	Shared accountability	Process team
Continuous improvement team	Process owner	Workgroup
Workcell	Self-managed team	Decision boundaries
Temporary project team	Ad hoc team	Action log
Decision log	Cross-functional team	Functional representation
Quality assurance	Quality control	Continuous improvement
Sponsor	Champion	Facilitator
Team leader	Team member	Standard operating procedure
Batch record	Organizational strategy	Performance measure

Review Questions

1. Why can a team recognize a recurring biotechnology quality problem that an individual department may miss?

2. What distinguishes a team from a loosely organized group?

3. When is individual work preferable to forming a team?

4. How do process teams and continuous improvement teams differ in their main purposes?

5. Distinguish a workgroup from a workcell. Why does a workcell not automatically determine management authority?

6. What does self-management allow, and why are decision boundaries necessary?

7. How do temporary project teams and ad hoc teams relate?

8. Why can a team be both temporary and cross-functional?

9. What factors should guide team selection for a particular quality problem?

10. Distinguish the responsibilities of sponsors, champions, facilitators, leaders, and members.

11. How can action logs, decision logs, SOPs, and batch records support team work in different ways?

12. Why should a team assess results and possible unwanted effects rather than only its number of meetings?

Apply Your Understanding

1. A research-use kit company repeatedly receives incomplete batch packages from production, QC, and packaging. Select a team structure, identify the essential perspectives, and propose a shared deliverable. Explain which routine tasks can remain individual assignments and which decisions require separate authorization.

2. A laboratory calls its sample-processing group self-managed but gives no written limits on scheduling, method changes, or handling unidentified samples. Propose practical decision boundaries. Identify training and records the team needs, and explain how members should respond to an urgent concern.

3. A company proposes moving kit assembly, labeling, and packing into one workcell. Identify potential benefits and risks to investigate. Explain why a workcell layout does not establish whether the group is self-managed or whether staff are qualified for every task.

4. In the RADx story, different specialties supplied different evidence. Identify three kinds of expertise that a diagnostic-development team might need and explain how their contributions connect. Distinguish documented features of the account from your proposed team design. What cannot be concluded about teamwork's effect from the account alone?

5. A team leader asks for a software change that exceeds the project budget. Members also disagree about whether the proposal solves the problem. Explain what the sponsor, champion, facilitator, leader, and members should each contribute. Identify which decisions still need the organization's normal technical approval.

6. A project reports that review time decreased by 30%, but incomplete records were no longer counted and errors found after review increased. Evaluate whether the result supports the organization's quality priorities. Propose a better set of measures and explain who should own follow-up after the temporary team disbands.

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9: LAUNCHING AND SUSTAINING A TEAM

Learning Objectives

After completing this chapter, you should be able to:

- Explain how a team charter guides a quality improvement project.
- Define a team's purpose, scope, goals, and expected results.
- Select members whose knowledge, skills, and experience match the work.
- Establish ground rules and clear decision authority.
- Plan meeting schedules, resources, and management support.
- Describe common stages of team development.
- Track actions and results, sustain participation, and transfer completed work.

A team's **purpose**, structure, and roles should fit the work. The team turns those choices into a charter and **work plan**. Follow-up shows whether an approved change was completed, whether it improved performance, and who will maintain it.

A team can have skilled members and still struggle to get started. People may agree that a problem matters while holding different ideas about what the team should do. One person expects a new procedure. Another expects new equipment. A third assumes that attending meetings is the only commitment required. These differences often remain hidden until work slows down.

Launching a team means agreeing on the assignment, authority, and support before work begins. Sustaining a team means maintaining the conditions that let people contribute. Both matter when laboratory, production, quality, maintenance, and support staff depend on one another. A change tested only during the day may leave night-shift staff without the information or **resources** they need.

This chapter follows a hypothetical team improving freezer-alarm **handoffs** at a research-reagent facility. The situation, measurements, and charter are teaching examples, not a documented company case. A separate historical story describes the launch and early work of the National Institutes of Health's ACTIV partnership. Together, the examples show how a clear purpose becomes organized work.

9.1: Developing a team charter

9.2: Example- Freezer-alarm handoff team charter

9.3: Establishing purpose, scope, goals, and expected results

9.4: Selecting members for knowledge, skills, representation, and diversity

9.5: Establishing ground rules and decision authority

9.6: Planning schedules, meeting logistics, and resources

9.7: Securing management support

9.8: Example - Building a shared response through ACTIV

9.9: Stages of team development

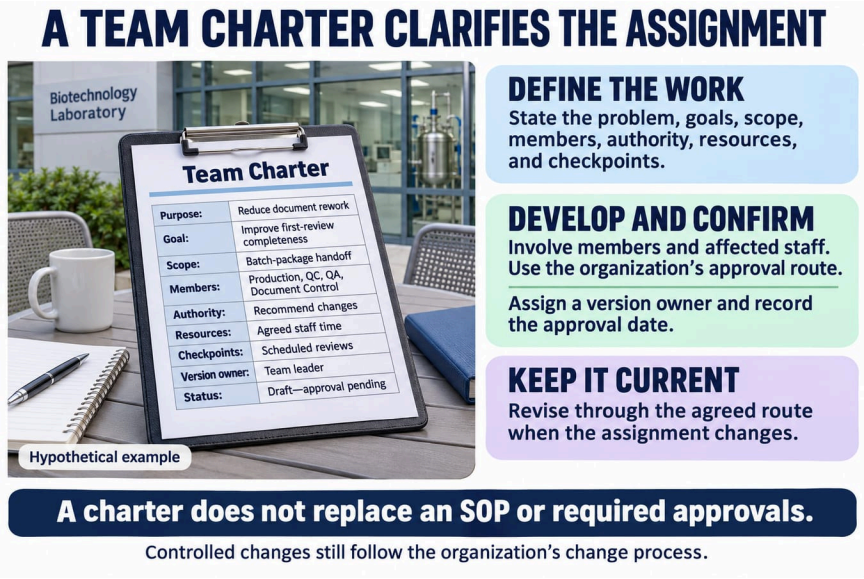
9.10: Tracking actions, progress, and accountability

9.11: Sustaining participation and recognizing contributions

9.12: Chapter Summary

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9.1: Developing a team charter



A **team charter** is a short agreement that explains why a team exists, what it will accomplish, and how it will work. It gives members and management a common reference. A charter cannot solve every disagreement, but it helps people recognize when they are discussing different assignments. AHRQ describes a charter as a high-level guide that connects a problem, **goals**, **scope**, resources, and a work plan.

Develop the charter with members and affected staff, then seek confirmation through the organization's approving authority. Start with the problem and expected result. Identify boundaries, membership, authority, resources, and checkpoints. Assign responsibility for maintaining the current version and record its approval date. The charter should be brief enough to consult during work and clear enough to reveal different expectations.

A charter is not a replacement for an approved operating procedure. It also does not give a team permission to bypass quality review or other required approvals. If the team proposes a controlled change, the organization's change process still applies. When circumstances change, revise the charter through the agreed approval route instead of silently expanding the assignment.

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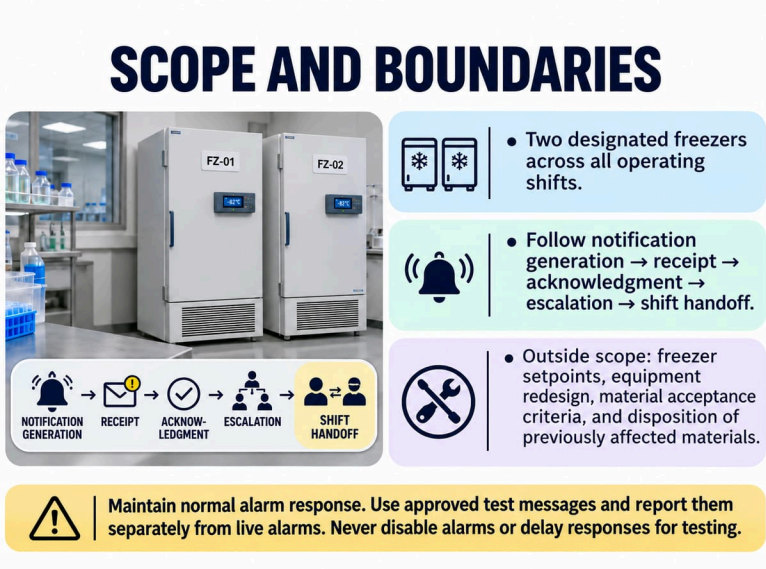
9.2: Example- Freezer-alarm handoff team charter

An eight-week quality improvement project began after a review of freezer alarm records found that 12 of 40 eligible live alarm events, or 30%, lacked documented acknowledgment within the approved response time. The review counted late, missing, and unverifiable acknowledgments and reported each category separately. These findings established the baseline, but they did not explain why acknowledgments were late or undocumented.



The team developed a charter to guide its investigation and any proposed changes. Its purpose was to improve timely, documented acknowledgment and escalation as part of the approved response used to protect research materials. The project covered two designated freezers across all operating shifts. Team members traced notifications from generation through receipt, acknowledgment, escalation, and shift handoff. Changes to freezer setpoints, equipment design, material acceptance criteria, and the disposition of previously affected materials remained outside the project's scope.

The charter set a goal of reducing live alarm events without documented timely acknowledgment from



30% to no more than 10% over four full weeks after implementation. The team agreed to report event counts and denominators alongside percentages. It planned to complete the evaluation by week 8, while allowing an extension if implementation was delayed or the evidence was insufficient.

The agreed **deliverables** included a verified map of the current workflow, an approved handoff and contact process, required

training records, an evaluation of implementation and results, and an accepted monitoring plan with a named owner. Defining these deliverables helped the team establish what it needed to complete before requesting project closure.

The team included a leader, trained users from day and night shifts, and representatives from quality, facilities, and the information technology group responsible for alerts. Other specialists were available for consultation. Team members had authority to review records and recommend improvements, but procedure revisions, system changes, and trials required the designated organizational approvals.

The charter identified the resources needed to carry out the work: scheduled staff time, coverage for



participating shifts, access to relevant records, and approved technical support. The **sponsor** took responsibility for helping resolve resource barriers within their authority and escalating those that required action from others.

The schedule reserved weeks 1–2 for confirming the baseline and verifying the current workflow. Proposal development, approvals, implementation, and required training were scheduled for completion by the end of week 4. Weeks 5–8 were reserved for evaluation. The team agreed to revise the schedule if the necessary preparations were incomplete.

Normal alarm response remained a requirement throughout the project. The charter specified that planned checks would use approved test messages and that their results would be reported separately from live alarms. It also prohibited disabling live alarms or delaying responses to create test conditions.



The team established closure requirements before testing changes. Deliverables, results, and limitations had to be reviewed with the sponsor and **process owner**. Ongoing monitoring and

unresolved actions had to be assigned to owners who accepted responsibility, with follow-up dates documented. The final review would determine whether to retain the changes, revise the approach, extend the evaluation, or end the project. Reaching the numerical target alone was not sufficient for closure.

The charter also clarified the limits of the selected measure. Acknowledgment documented receipt of an alert; it did not establish that someone had assessed the freezer, protected the materials, or corrected the condition. Existing response, escalation, and material-assessment requirements therefore continued to apply.

Developing the charter gave the team a shared understanding of the assignment before it tested a change. What began as a concern about freezer alarms became a defined quality improvement project with clear boundaries, approval requirements, measures, and responsibilities.

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9.3: Establishing purpose, scope, goals, and expected results

A team's purpose explains why its work matters. In the freezer example, the purpose is a more reliable



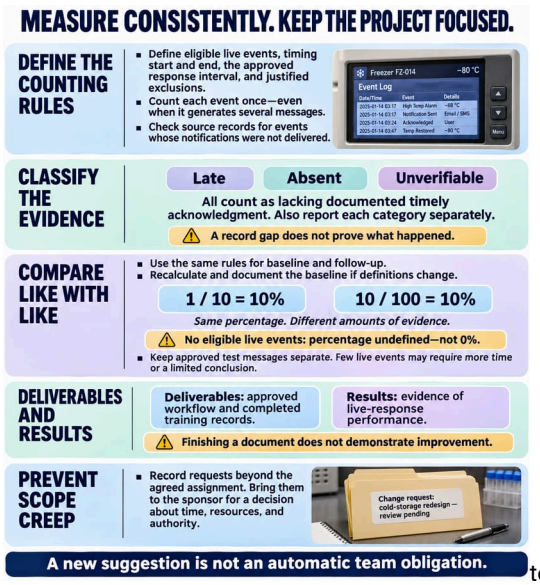
part of the alarm-response process used to protect research materials. "Hold weekly meetings" is an activity, not a purpose. People are more likely to make useful choices when they understand the result the activity is meant to support.

Scope identifies the boundaries of the assignment. It includes what the team will study and what it will leave to other people or projects. A narrow scope can still address an important problem. Improving handoffs for two freezers may provide a manageable starting point before the organization considers a wider change.

A goal states the improvement intended, its measure, and its evaluation period. In this example, 12 of 40 eligible alarm events lacked documented acknowledgment within the approved time: 12 ÷ 40 × 100 = 30%. The proposed goal is no more than 10% over four full weeks after implementation. These are hypothetical project choices, not industry standards or new acceptance limits.

Define an eligible alarm event, the timing start and end, the approved response interval, and any justified exclusions before comparing results. Count an event once even if it produces several messages or reaches several staff members. Use records that can reveal events whose notifications were not delivered. For this project, late, absent, or unverifiable acknowledgments all count as lacking documented timely acknowledgment. Report those categories separately as well, so a record gap is not mistaken for proof of what happened.

Apply the same rules to the baseline and comparison period. Show the numerator and denominator: one event out of



ten and ten out of one hundred both equal 10%, but provide different amounts of evidence. If a new definition changes the baseline count, recalculate and document the baseline before judging improvement.

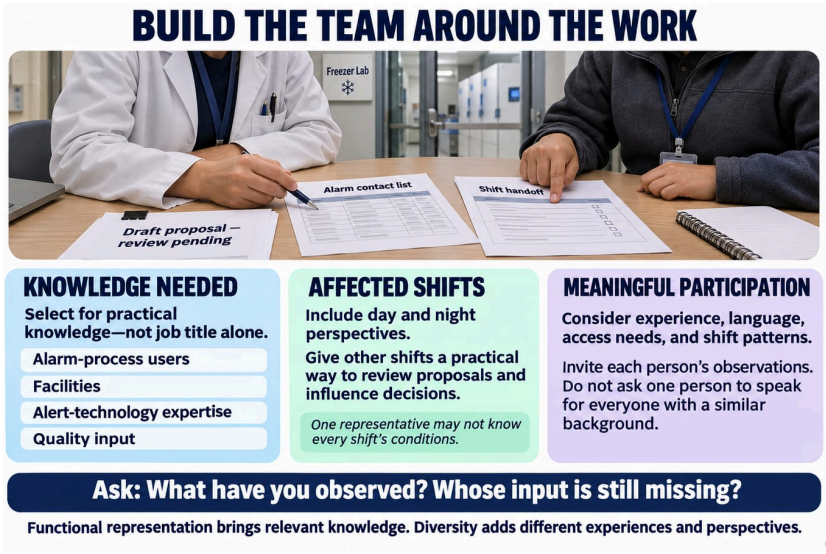
If no eligible live alarm events occur, the percentage is undefined, not zero. Approved test messages can check routing and workflow, but they do not establish live-response performance. Keep them separate from live events. Few observations may require a longer evaluation or a limited conclusion even when the numerical target is met.

Deliverables are the specific outputs the team must provide, such as an approved workflow or completed training records. They help show that assigned work was finished. However, a completed document alone does not show that performance improved. The team needs both deliverables and evidence about results.

Watch for **scope creep**, the gradual addition of work beyond the agreed assignment. A request to redesign the entire cold-storage system may be reasonable, but it requires a separate decision about time, resources, and authority. Record the request and bring it to the sponsor. Do not allow an informal suggestion to become an unplanned obligation.

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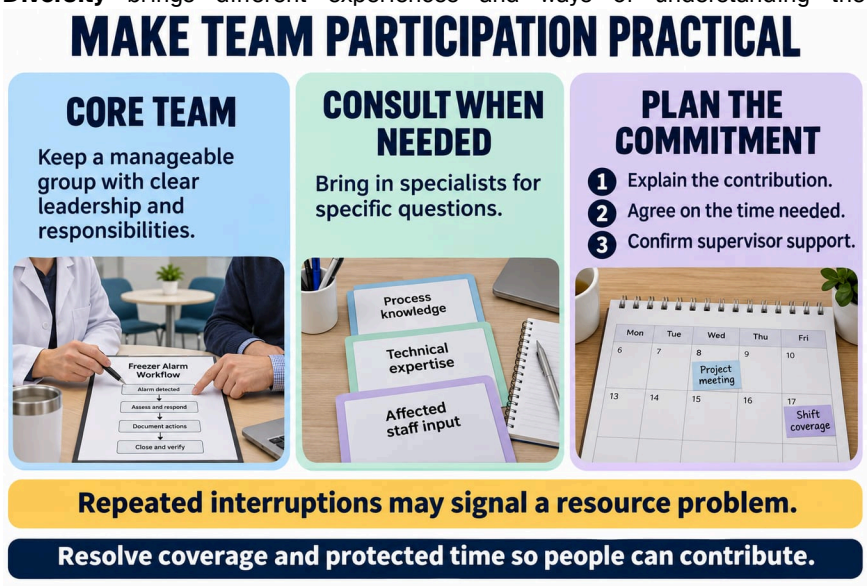
9.4: Selecting members for knowledge, skills, representation, and diversity



Once the assignment is clear, identify the people needed to carry it out. Select members by asking what knowledge the work requires. Job titles offer only part of the answer. A supervisor may understand staffing, while a technician knows that a contact list becomes hard to find during a busy handoff. Both perspectives can matter.

Functional representation brings relevant knowledge from affected functions into the project. The freezer team needs users of the alarm process, facilities staff, alert-technology expertise, and quality input. Include affected shifts or give them a practical way to review proposals and influence decisions. One representative should not be assumed to know every shift's conditions.

Diversity brings different experiences and ways of understanding the work. Consider experience level, language needs, shift patterns, access needs, and other relevant perspectives. Invite meaningful participation rather than asking one person to speak for everyone with a similar background. Ask members what they have directly observed and where additional input is needed.



A practical team does not need every possible specialist at every meeting. Maintain a manageable core group and arrange consultation when needed. AHRQ's guidance on **forming** improvement teams emphasizes a mix of roles, clear leadership, and continued attention to responsibilities. IHI likewise connects team membership to knowledge of the process and the people

affected by it.

Before inviting someone, explain the expected contribution and time commitment. Confirm that their supervisor can support participation. A person who is repeatedly called away may have valuable knowledge but insufficient protected time to share it. This is a resource problem to resolve, not evidence that the person does not care.

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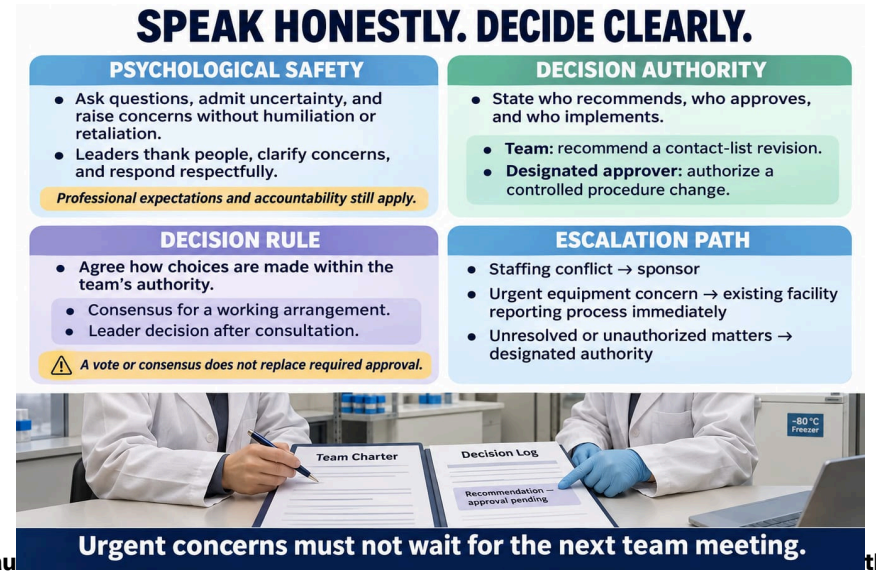
9.5: Establishing ground rules and decision authority



Ground rules are agreed expectations for working together. They make ordinary participation more predictable. Useful rules are specific enough to guide behavior and fair enough to apply to everyone, including the team leader.

- Arrive prepared or notify the leader when preparation is not possible.
- Give each affected shift an opportunity to contribute.
- Discuss evidence and process conditions without personal blame.
- Identify assumptions and check them before treating them as facts.
- Record decisions, owners, and due dates before ending the meeting.
- Use the organization's approved channels for confidential information.

Ground rules should help people speak honestly. **Psychological safety** is a shared belief that people can take interpersonal risks, such as asking questions, admitting uncertainty, or raising concerns, without humiliation or retaliation. It does not remove professional expectations or **accountability**. A leader supports it by thanking people for useful concerns, asking clarifying questions, and responding respectfully when information challenges an early idea.



Decision au **thority** identifies who may make which decisions. The team might agree on meeting times and recommend a revised contact list while lacking authority to approve

a controlled procedure. Write these boundaries into the charter. For important decisions, identify who recommends, who approves, and who carries out the result.

A **decision rule** states how the team reaches a choice within its authority. The team might use consensus for a working arrangement or assign a decision to the leader after consultation. Record the rule and who participates. Neither consensus nor a vote replaces required technical or quality approval.

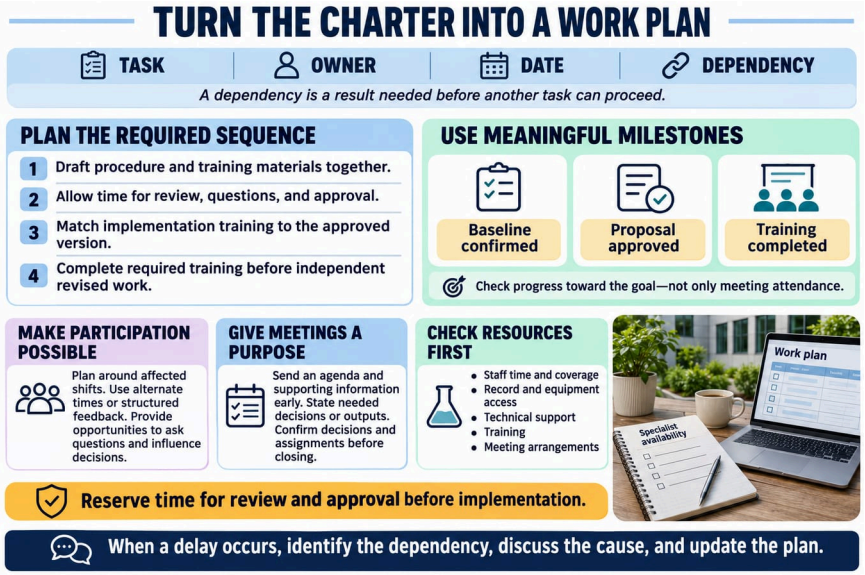
Set an **escalation path** for urgent concerns, matters outside the team's authority, and issues it cannot resolve. For example, competing staffing needs may go to the sponsor. An urgent equipment concern should follow the facility's existing reporting process immediately; it should not wait for the team's next meeting. Clear escalation keeps a project meeting from becoming a barrier to necessary action.

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9.6: Planning schedules, meeting logistics, and resources

A work plan turns the charter into tasks, owners, dates, and dependencies. A dependency means that one task needs a specified result from another before it can proceed. Training materials can be drafted alongside a proposed procedure, but implementation training must match the approved version. Complete required training before staff perform the revised work independently.

A **milestone** is a meaningful checkpoint, such as confirmation of the baseline or approval of a proposal. Milestones help the team recognize whether the project is moving toward its goal. They are more useful than a calendar filled only with meeting dates.



Plan meeting times around the people whose knowledge is needed. Alternating times, providing paid participation within workplace arrangements, or collecting structured shift feedback may improve access. Written notes help people who cannot attend, but notes alone do not replace opportunities to ask questions and influence decisions.

A brief **agenda** identifies the purpose of a meeting, the topics to address, and the decisions or outputs needed. Send supporting information early enough for members to review it. End by confirming decisions and assignments. An information-sharing meeting may not require a new assignment, but members should still understand its purpose and any implications for their work.

Resources include more than money. They include staff time, shift coverage, record access, equipment access, technical support, training, and suitable meeting arrangements. Check these needs before promising a completion date. If the team can review alarm records only when a particular specialist is available, that availability belongs in the schedule.

Allow time for review and approval. A plan that schedules implementation immediately after drafting leaves no room for questions or corrections. When a delay occurs, identify the dependency and update the plan. Quietly moving deadlines without discussing the cause hides a problem the sponsor may be able to solve.

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9.7: Securing management support



A sponsor is a manager who supports the team's purpose and helps secure the authority and resources needed for its work. Sponsorship is an active role. It includes addressing barriers, reviewing progress, and making decisions within the sponsor's own authority. Decisions requiring other approvals must go to the designated people. AHRQ and IHI both emphasize leadership support for improvement work.

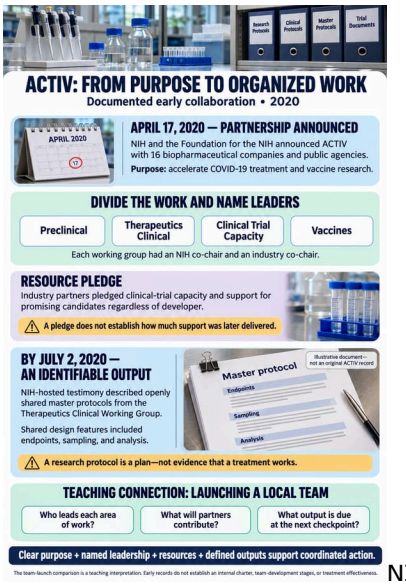
Ask for specific commitments. "Management supports quality" is encouraging but incomplete. The freezer team needs an agreement about staff time, shift coverage, technical review, and access to records. It also needs to know who will decide when two departments have conflicting priorities.

A **resource commitment** is an explicit agreement to provide needed support. Record who is providing what and when it will be available. If a promised resource changes, revise the plan and discuss the effect on the goal. A team should not be expected to meet an unchanged deadline after losing essential support without an honest review of what remains possible.

Provide concise progress reports. Explain the goal, current evidence, completed milestones, remaining risks, and decisions needed. Report a barrier early enough for management to respond. Avoid presenting a long list of activities without explaining what those activities show about progress.

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9.8: Example - Building a shared response through ACTIV



NIH records from 2020 describe a collaboration moving from an announced purpose to organized work. This historical account follows those events without invented dialogue or private thoughts. The comparison with a local quality team is a teaching interpretation.

On April 17, 2020, NIH and the Foundation for the NIH announced a partnership to speed COVID-19 treatment and vaccine research. It included 16 biopharmaceutical companies and public agencies, including CDC, FDA, and the European Medicines Agency. Its name was Accelerating COVID-19 Therapeutic Interventions and Vaccines, or ACTIV. The announcement set out a framework for prioritizing candidates, streamlining trials, and sharing research assets.

The broad assignment needed a division of work. A later NIH account described four working groups: Preclinical, Therapeutics Clinical, Clinical Trial Capacity, and Vaccines. Each had an NIH co-chair and an industry co-chair. The groups gave separate areas of work named leadership while connecting them to the larger partnership.

The same account reported a resource pledge: industry partners would contribute clinical-trial capacity and support promising candidates regardless of their developer. The pledge described support the collaboration intended to provide. It did not measure how much each partner later contributed or prove that every resource need had been met.

By July 2, 2020, official testimony hosted by NIH described an output beyond the partnership announcement. ACTIV's Therapeutics Clinical Working Group had developed and openly shared master protocols with agreed endpoints, sampling, and analysis. A master protocol is an overarching research plan for evaluating multiple interventions using shared design features. These documents provided a basis for coordinated research; they were not results showing a treatment worked.

For a student studying team launch, the sequence is useful: a stated purpose, named work areas, shared leadership, resource commitments, and an identifiable output. That sequence is a teaching interpretation of the documented events. The sources document early organization and outputs, rather than an internal charter, team-development stages, or the effectiveness of a particular treatment.

A small laboratory team operates on a different scale, but it faces related questions. Who is responsible for each area of work? What will partners contribute? What output should exist by the next checkpoint? Clear answers help a team move from agreement in principle to coordinated action.

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9.9: Stages of team development

A charter provides a starting structure, but members still need to learn how to work together. In 1965, Bruce Tuckman proposed forming, **storming**, **norming**, and **performing**. In 1977, Tuckman and Mary Ann Jensen added **adjourning**. The model is a guide to possible patterns, not a fixed timetable or proof that every team follows the same sequence. The brief descriptions below connect it to this chapter's workplace example.

- Forming involves orientation. Members learn the purpose, boundaries, and expectations. The leader can help by explaining the charter and inviting questions.
- Storming involves disagreement about roles, priorities, or ways of working. The team needs respectful discussion and clear decisions. Conflict does not excuse harassment or unsafe behavior.
- Norming involves developing shared expectations and more dependable coordination. Members become clearer about how to communicate and complete work.
- Performing involves using established relationships and routines to carry out the work effectively. Oversight and required approvals still apply.
- Adjourning involves closing the assignment and transferring responsibilities. Members review results, record lessons, and recognize contributions.

Membership changes or a revised assignment may bring earlier questions back into discussion. If a night-shift representative is replaced or an additional shift perspective is needed, the freezer team may need to revisit an earlier decision. Treat the new information as a reason to improve the plan. Do not label a person "storming" simply because they raise an inconvenient concern.

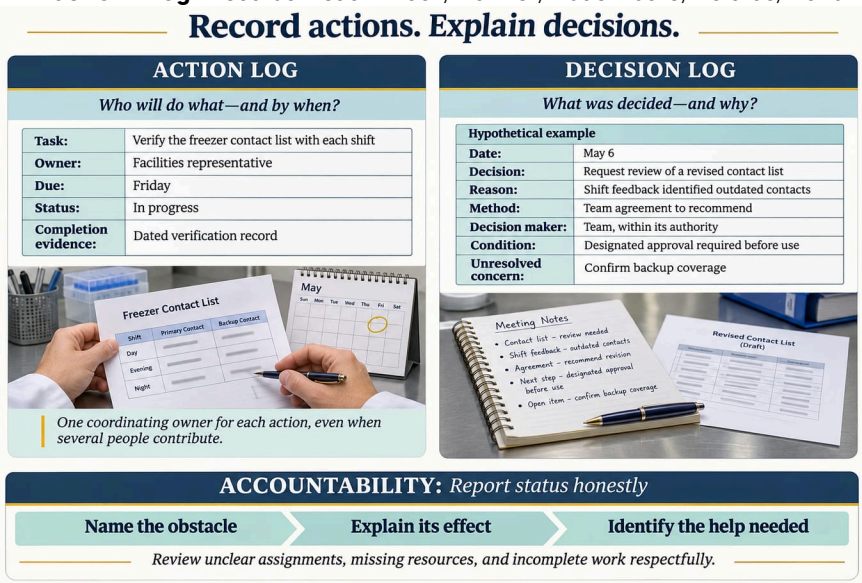
Use the model to select helpful leadership actions. A newly formed team may need more explanation. A team facing role conflict may need clarified authority. A team ready to close needs an orderly handoff. Ask what support the team needs now rather than assuming that time alone will improve its work.



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9.10: Tracking actions, progress, and accountability

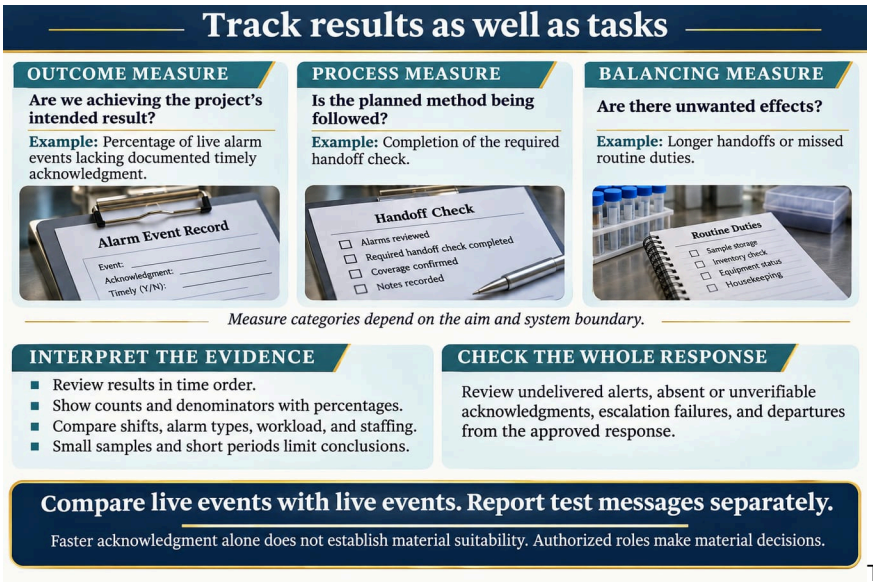
An **action log** records each task, owner, due date, status, and relevant completion evidence. Assign one



person to coordinate each action even when several contribute. “Everyone will check the contact list” is difficult to follow up. “The facilities representative will verify the list with each shift by Friday” identifies an accountable owner and a clear task.

A **decision log** records important choices and their reasons. Include the date, decision method, decision maker or approving role, and any conditions or unresolved concerns. This helps the team avoid reopening settled questions because nobody remembers why a choice was made. It also helps new members understand the project.

Accountability means being answerable for agreed responsibilities and reporting honestly on their status. It requires more than checking whether a deadline passed. If work is blocked, identify the obstacle, its effect, and the help needed. A respectful review can distinguish an unclear assignment from a missing resource or a task that was not completed.



Track results as well as tasks. An **outcome measure** addresses the intended result. Here, the percentage of live alarm events lacking documented timely acknowledgment is an outcome measure for the limited project and a process-performance measure within the wider system protecting materials. A **process measure** checks whether the planned method is followed, such as completion of a handoff check. A **balancing measure** examines possible unwanted effects, such as longer handoff time or missed routine duties. The categories depend on the aim

and system boundary.

Review data in time order. Report counts and denominators alongside percentages. Examine alarm types, shifts, workload, and staffing that may affect interpretation. A lower overall percentage can conceal worse performance on one shift. A short period or small sample limits claims about lasting improvement.

For this project, review undelivered alerts, absent or unverifiable acknowledgments, escalation failures, and departures from the approved response. Compare live events with live events; report test messages separately. Faster acknowledgment is not sufficient if messages are lost or required steps are bypassed. Acknowledgment performance alone also cannot establish material suitability. Route those decisions to the authorized roles.

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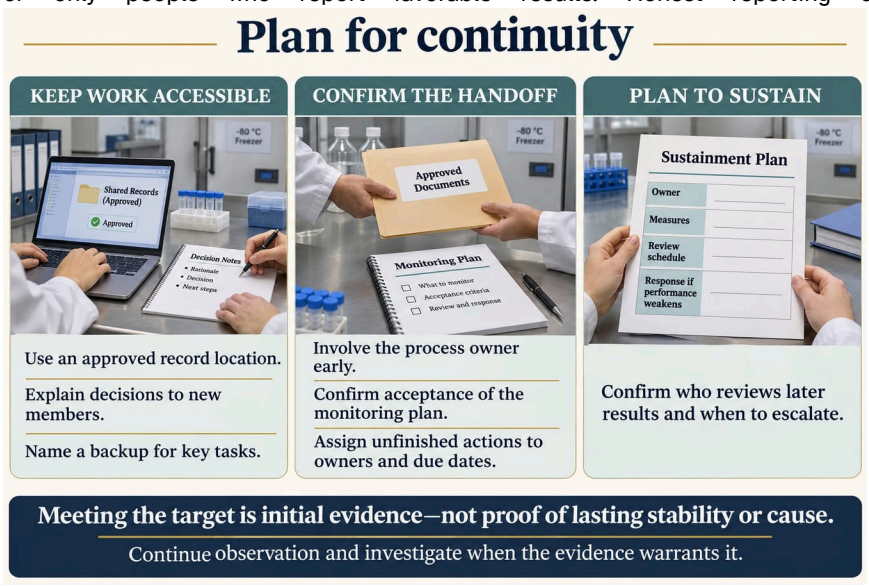
9.11: Sustaining participation and recognizing contributions



Participation is easier to sustain when people can see that their work matters. Show how a member's observation changed the plan or helped the team avoid a problem. Share progress in terms members can connect to their daily responsibilities.

When participation falls, ask about the conditions. A member may lack shift coverage, receive materials too late, or believe that decisions are already settled before discussion begins. Adjust the arrangements where possible. Repeated reminders to "be engaged" will not correct a meeting schedule that consistently excludes the same shift.

Recognition is an acknowledgment of a useful contribution. Be specific and fair. Recognize careful record review, thoughtful questions, reliable follow-through, and the effort of staff who provide coverage. Avoid recognizing only the most visible speaker or only people who report favorable results. Honest reporting of a problem is valuable quality work.



Plan for continuity. Keep current records in an approved location, explain decisions to new members, and identify a backup for key coordination tasks. A team that depends on one person's memory becomes vulnerable when that person is absent.

A handoff transfers ongoing work and responsibilities to identified people. The process owner oversees the process's continuing performance and coordinates needed changes. Involve that person early. Before closure, confirm that the owner has accepted

the monitoring plan, received the approved documents, and knows how to escalate unresolved issues. Transfer each unfinished action to a named owner with a due date.

A **sustainment plan** identifies the owner, measures, review schedule, and response when performance weakens. Meeting the project target provides initial evidence; it does not establish long-term statistical stability or prove that a change caused the result. An eight-week project may need further observation. Confirm who will conduct the later review and what evidence would trigger another investigation or change.

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9.12: Chapter Summary

A team charter connects the problem, purpose, scope, goals, authority, resources, and expected results. It helps members begin with a shared understanding and provides a reference when priorities change.

Effective teams include people who know the work and represent affected functions and shifts. Ground rules support respectful participation, while clear decision authority prevents confusion about approvals. Realistic schedules and specific management commitments make the assignment possible.

Teams may experience changing patterns of orientation, disagreement, coordination, performance, and closure. Leaders can respond by clarifying expectations and providing the support needed at each point. Action and decision logs make responsibilities visible. Measures show whether completed tasks produced a useful result.

Sustained improvement requires continued participation, fair recognition, and a planned transfer to an accountable process owner. Closing a project should leave the organization able to maintain and review the work.

Checking that an agreed action was completed is separate from checking that it achieved its purpose.

Key Terms

Team charter	Purpose	Scope
Goal	Deliverables	Scope creep
Functional representation	Diversity	Ground rules
Psychological safety	Decision authority	Decision rule
Escalation path	Work plan	Milestone
Agenda	Resources	Sponsor
Resource commitment	Forming	Storming
Norming	Performing	Adjourning
Action log	Decision log	Accountability
Outcome measure	Process measure	Balancing measure

Team charter	Purpose	Scope
Recognition	Handoff	Process owner
Sustainment plan		

Review Questions

1. What information belongs in a team charter, and how can the team use it after the first meeting?

2. Explain the difference between a purpose, a goal, and a deliverable.

3. Why should a charter state what is outside the project's scope?

4. How can a team include knowledge from people who cannot attend every meeting?

5. What is the difference between ground rules and decision authority?

6. How do dependencies affect a project schedule?

7. What specific commitments should a team request from its sponsor?

8. Describe the five stages in the model developed by Tuckman and extended with Jensen. Why should it be used flexibly?

9. How do action logs and decision logs support accountability in different ways?

10. Distinguish outcome, process, and balancing measures using the freezer-alarm example. Why does a zero denominator prevent calculation of a performance percentage?

11. What should be included in a handoff and sustainment plan, and why should the process owner be involved early?

Apply Your Understanding

1. A label-review team receives the assignment "reduce errors" but has no defined product group, baseline, deadline, or approving authority. Draft a brief charter outline that identifies the missing decisions. State what information you would collect before choosing a numerical goal.

2. A sample-receiving team has six day-shift members and no evening-shift members. Evening staff report that revised paperwork is difficult to use when deliveries arrive together. Propose a membership and meeting plan that gives evening staff meaningful input while maintaining routine work coverage.

3. A maintenance improvement team has an approved six-week schedule. Its technical specialist becomes unavailable for two weeks, and equipment testing depends on that specialist's review. Explain how the team should revise its plan and what decision it should request from the sponsor.

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10: COMMUNICATION, CONFLICT, AND TEAM DECISIONS

Learning Objectives

After completing this chapter, you should be able to:

- Use active listening and clear messages during a team discussion.
- Distinguish productive disagreement from harmful conflict.
- Address a disagreement respectfully and recognize when escalation is needed.
- Recognize groupthink and protect independent judgment.
- Identify meeting logistics, unclear agendas, and training gaps that limit participation.
- Compare voting and consensus and select a suitable decision method.
- Confirm agreement and record the reasons, limits, and responsibilities attached to a decision.
- Verify that assigned actions were completed and achieved their intended result.

A team's purpose, membership, authority, and work plan give its members a structure they can use to exchange evidence, handle disagreements, and reach decisions. It also follows an agreed action through completion and evaluation, keeping the distinction between implementation and effectiveness clear.

At a hypothetical biotechnology laboratory, a team meets to review a delayed protein assay. An analyst says a control result did not meet the method's acceptance criterion. A production representative asks when the material will be available. The supervisor begins discussing tomorrow's schedule. Each person has raised a relevant issue, but the group has not yet agreed on the question it must answer first.

The analyst may interpret the scheduling discussion as pressure to overlook the control. The production representative may not understand why results are delayed. The supervisor may assume that everyone knows the results remain under review. These possible interpretations show how a conversation can become strained even before anyone clearly states a disagreement.

Communication helps a team build a shared understanding of the evidence, the problem, and the next step. It also allows members to question an idea without attacking a colleague. In quality work, a concern may need attention even when only one person raises it. The number of supporters does not determine whether evidence is correct.

This chapter explains how teams listen, manage disagreements, select decision methods, and follow through. Laboratory situations are hypothetical teaching examples. A separate documented story examines communication during the decision to launch the space shuttle Challenger in 1986. Although the industry differs, the story raises questions that matter whenever technical evidence must reach people with decision authority.

10.1: Active listening and constructive communication

10.2: Recognizing productive disagreement and harmful conflict

10.3: Addressing conflict respectfully

10.4: A missed review handoff

10.5: Groupthink and barriers to independent judgment

10.6: A recommendation changes before Challenger launches

10.7: Poor logistics, unclear agendas, and training gaps

10.8: Voting and consensus

10.9: Selecting an appropriate decision method

10.10: Confirming agreement and recording decisions

10.11: Follow-up techniques and action verification

10.12: Chapter Summary

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10.1: Active listening and constructive communication

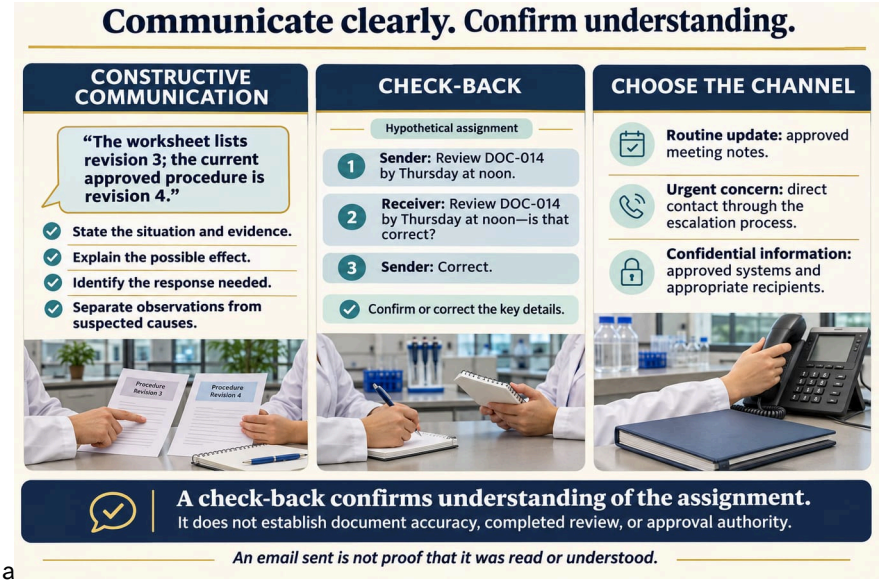


Active listening means giving a speaker focused attention and checking that you understand the message before responding. It involves more than waiting for your turn. Listen for the observation, the concern, and the action the person is requesting. Ask a question when any part is unclear.

In the assay meeting, the leader should first clarify which control failed its criterion, what the approved method requires, and which results may be affected. Summarize the analyst's explanation and invite correction. A failed assay control may affect whether results can be used; it does not by itself establish that the tested material failed its product specification. Follow the method and authorized review before relying on affected results or estimating a completion time.

Paraphrasing means restating another person's message in your own words to check its meaning. A useful paraphrase identifies the issue without adding blame. "You are saying that the run needs review before these results can be used" is more accurate than "You do not want production to move forward." Listening carefully does not require agreeing with every conclusion.

Constructive communication shares information in a clear, respectful way that helps the team act. Separate what was observed from what is suspected. "The worksheet lists revision 3, but the current approved procedure is revision 4" identifies a checkable difference. "Nobody follows instructions" turns one observation into a broad accusation.



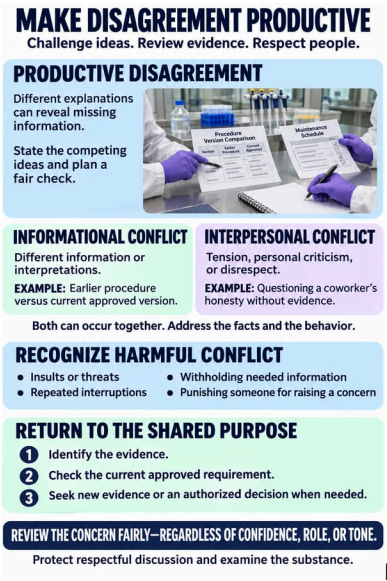
A useful message states the situation, relevant evidence, possible effect, and response needed. Define unfamiliar abbreviations and include units. Distinguish a result from an estimate and an observation from a suspected cause. State what remains unknown and identify where the supporting record can be found.

Closed-loop communication checks that a message was received and understood. In a **check-back**, the sender gives the message, the receiver repeats its key details, and the sender confirms or corrects the response. AHRQ teaches this approach in TeamSTEPPS. For example, a reviewer repeats the document identifier, assigned task, and Thursday-noon deadline; the coordinator confirms them. This confirms the assignment, not the accuracy of the document, completion of the review, or permission to approve it.

Choose a communication channel suited to the need. A routine meeting note can wait for a normal review period. An urgent concern may require direct contact through the organization's **escalation** process. Sending an email does not establish that someone has read or understood it. Keep confidential information within approved systems and share it only with appropriate recipients.

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10.2: Recognizing productive disagreement and harmful conflict



Productive disagreement occurs when people challenge ideas, evidence, or proposed actions in ways that improve understanding. Two analysts may interpret a pattern differently. A maintenance specialist may question whether a proposed schedule allows enough time for equipment checks. These differences can reveal information the team would otherwise miss.

Disagreement can concern the task, the working relationship, or both. **Informational conflict** involves different information or interpretations of the work. One member may be using an earlier procedure, while another is using the current approved version. **Interpersonal conflict** involves tension between people, such as repeated personal criticism or disrespect. AHRQ distinguishes these forms of conflict because they may need different responses.

Both types can occur in the same discussion. A disagreement about a training record may become personal if someone questions a coworker's honesty without evidence. The team must address the factual question and the behavior. Correcting the record alone may not repair the working relationship.

Harmful conflict interferes with safe, respectful, and effective work. Warning signs include insults, threats, repeated interruptions, withholding needed information, or punishing someone for raising a concern. AHRQ identifies behaviors such as condescending language and refusal to answer questions as barriers to teamwork.

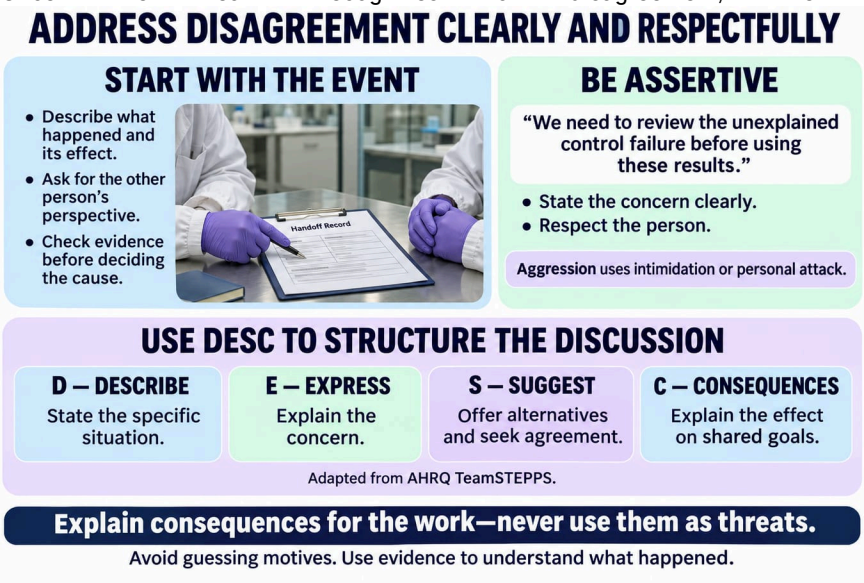
Do not judge a concern only by the speaker's confidence or tone. A quiet trainee may identify a real error, and an experienced manager may be mistaken. A frustrated speaker may still have important evidence. The leader should protect respectful discussion while making sure the substance receives a fair review.

A disagreement becomes useful when the team can state the competing explanations, identify supporting evidence, and plan a fair check. Return to the shared purpose when discussion stalls. Some concerns can be resolved by finding the current approved requirement; others need new evidence or an authorized decision. Repeating positions more forcefully does not resolve those differences.

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10.3: Addressing conflict respectfully

Once the team recognizes a disagreement, the next step is to make the



issue clear enough to address. Begin by identifying it in neutral language. Describe the specific event, explain its effect, and ask for the other person's perspective. Avoid guessing motives. A missed handoff might reflect an unclear assignment, an unavailable record, a workload problem, or a failure to complete an agreed task. The team needs evidence before deciding which explanation fits.

Assertiveness means stating a concern or need clearly while respecting others. It differs from aggression, which uses intimidation or personal attack. A person can be courteous and still be direct: the team needs to review an unexplained control failure before relying on the affected results.

AHRQ's **DESC** approach offers a structure for addressing conflict: describe the situation, express the concern, suggest alternatives and seek agreement, and explain the consequences for shared goals. Adapt the wording to the workplace. Consequences should explain the effect of the problem or proposed solution; they should not become threats.

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10.4: A missed review handoff

The following statements are hypothetical practice language for a routine workplace disagreement.



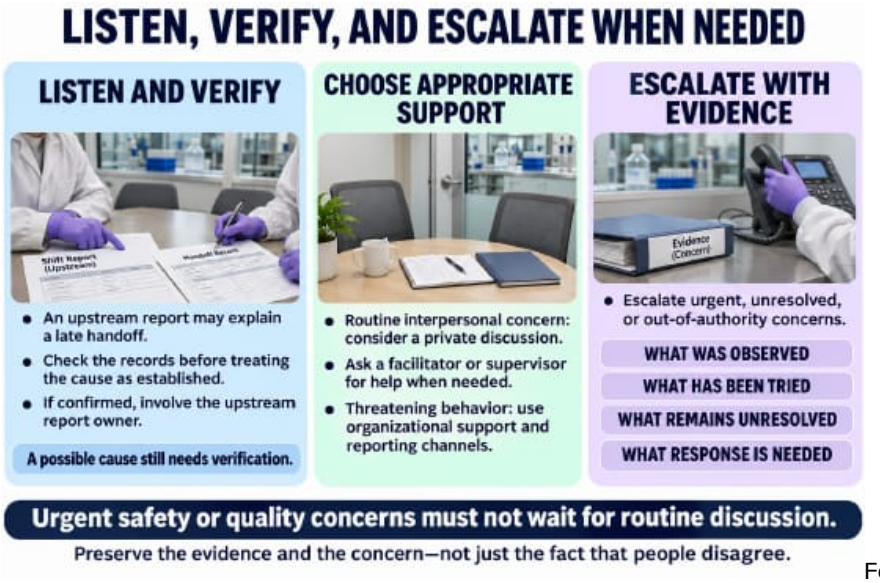
Describe: "The last two review packages arrived after the time listed in our work plan."

Express: "I am concerned that the receiving shift does not have enough time to complete the review."

Suggest: "Could we confirm an earlier transfer time and identify a backup when the owner is absent?"

Consequences: "That would give the receiving shift time to ask questions and reduce unfinished reviews at shift change."

The next step is to listen. The sending shift may explain that an upstream report arrives late. That explanation suggests a scheduling dependency that the team should check against the records. If confirmed, the team can involve the owner of the upstream report. Listening reveals a possible cause; **verification** is still needed before treating it as established.



For a routine interpersonal concern, a private discussion may allow people to focus without embarrassment. A facilitator or supervisor can help if the conversation remains difficult. However, urgent safety or quality concerns should follow the appropriate reporting route promptly. A person facing

threatening behavior should use organizational support and reporting channels rather than being expected to resolve it alone.

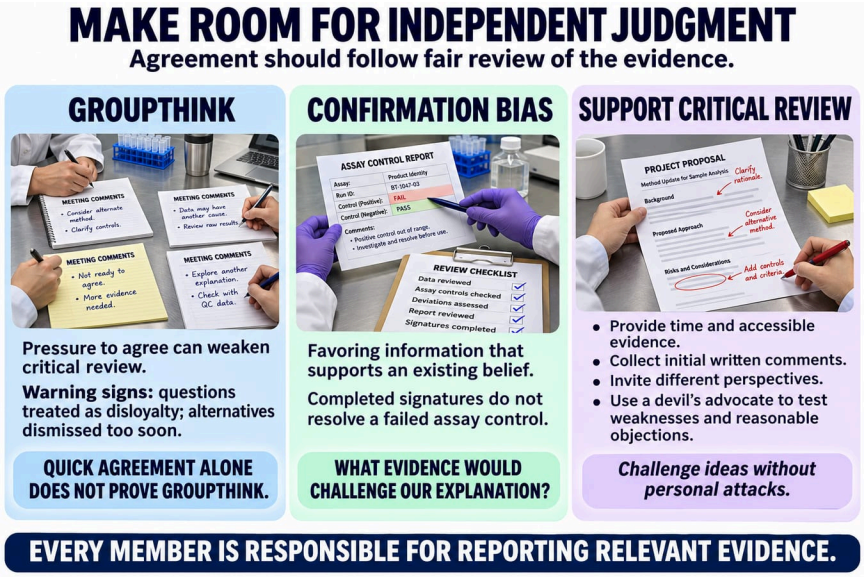
Escalation brings a concern to someone with the authority or expertise to address it. It is appropriate when a concern is urgent, exceeds the team's authority, or remains unresolved; members do not need to exhaust routine discussion before reporting an urgent issue. State what was observed, what has already been tried, what remains unresolved, and what response is needed. Escalation should preserve the evidence and the concern, not merely report that two people disagree.

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10.5: Groupthink and barriers to independent judgment

Respectful discussion also requires room for **independent judgment**. A team may avoid open conflict while still overlooking important evidence. **Groupthink** occurs when pressure to maintain agreement weakens critical review. Members may withhold concerns to avoid disrupting a friendly team or challenging an influential leader. OpenStax describes this risk in group decision-making.

Warning signs include treating questions as disloyalty and accepting a preference before reviewing alternatives. Quick agreement alone does not establish groupthink; the evidence may be clear. Ask whether members had a fair opportunity to review it and speak.



Confirmation bias is a tendency to favor information that supports an existing belief. In the assay example, a team convinced that a delay is "just paperwork" may focus on completed signatures while overlooking the failed control. Ask what evidence would challenge the preferred explanation.

Support independent judgment by giving members time to review evidence before discussion and inviting different perspectives. Initial written comments can help members state concerns before hearing a leader's preference. Check whether the information is accessible and understandable; an invitation to comment is ineffective when some members cannot review the evidence.

A **devil's advocate** tests a proposal by identifying weaknesses and reasonable objections. This role can support critical discussion. It does not make one person responsible for all concerns or permit personal attacks. Every member remains responsible for reporting relevant evidence.

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10.6: A recommendation changes before Challenger launches



The Rogers Commission's report describes how engineering concerns and a final recommendation moved through the Challenger launch process. This historical account follows the documented events without invented dialogue or private thoughts. Its location after the discussion of groupthink does not establish that groupthink explains every participant's actions.

The concern did not begin the night before launch. The shuttle's solid rocket booster joints had a design problem involving O-rings intended to seal them. Tests and earlier flights had shown damage. The Commission later reported that NASA and Morton Thiokol had failed to correct the problem and had increased the damage considered acceptable. Management briefings had also minimized the concerns.

On January 27, 1986, Thiokol and NASA personnel discussed cold conditions before the next day's launch. Thiokol initially recommended waiting until O-ring temperatures reached at least 53°F, the lowest temperature in its previous flight experience. During a private caucus, engineers Arnold Thompson and Roger Boisjoly continued to object, but Thiokol management reversed its recommendation. At about 11 p.m. Eastern Standard Time, the teleconference resumed. Thiokol recommended launch, and NASA requested the recommendation in writing.

The written recommendation carried the company's final position, not agreement from all its engineers. The Commission found that key launch decision makers lacked the initial recommendation against launch and the engineers' continuing opposition. It identified communication failures and a management structure that allowed important safety concerns to bypass key managers.

Challenger launched on January 28, 1986. Seventy-three seconds later, the vehicle broke apart. All seven crew members died.

The account shows how a final organizational recommendation can obscure unresolved technical disagreement. The Commission examined engineering and organizational failures, so communication alone does not explain the accident. For team decisions, the teaching lesson is to preserve concerns and get them to the appropriate authority, rather than infer agreement from a final signature.

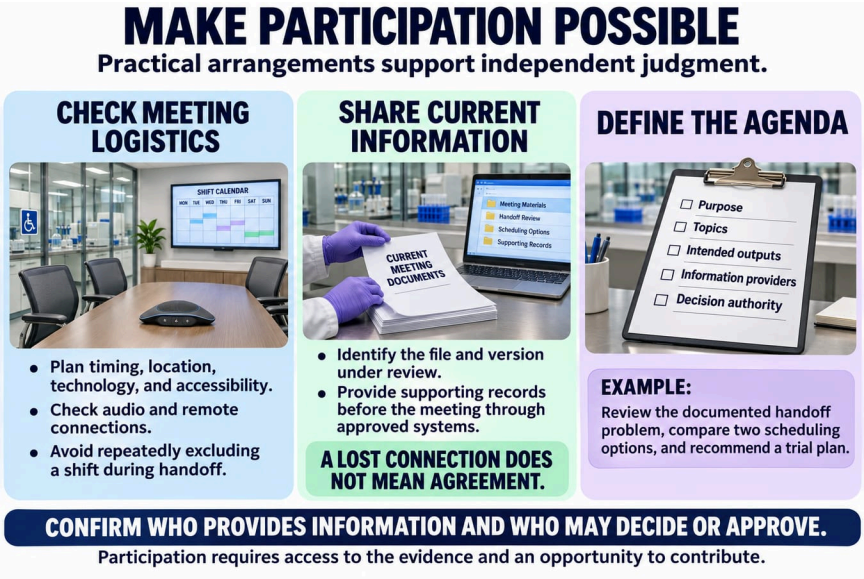
In a laboratory, an approved-looking summary should not erase a relevant concern that remains unresolved. A useful **decision record** distinguishes who decided, what evidence was considered, what objections remain, and who must review them. A formal recommendation identifies an organizational position. It should not be treated as proof that all technical contributors agreed. This distinction becomes important when teams compare **voting**, **consensus**, and approval later in the chapter.

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10.7: Poor logistics, unclear agendas, and training gaps

Protecting independent judgment requires practical support as well as a willingness to listen. Team communication can fail even when people intend to cooperate. **Meeting logistics** are the practical arrangements that allow people to participate, including timing, location, technology, accessibility, and access to materials. Poor audio can hide a qualification in a technical explanation. A meeting scheduled during a shift handoff may repeatedly exclude the people most affected by a proposal.

Check whether all members can see the same current information. Label files clearly and identify the version under review. Make supporting records available through approved systems before the meeting. If a remote member loses connection, do not assume that the person heard or accepted a decision made during the interruption.



An **agenda** states the meeting's purpose, topics, and intended outputs. "Discuss assay delays" is broad. "Review the documented handoff problem, compare two scheduling options, and recommend a trial plan" gives members a clearer preparation task. Identify who will provide information and who has authority to make or approve the decision.

Separate information sharing from decision-making. Some topics need an update; others need a recommendation or approval. If the team discovers that essential evidence is missing, identify who will obtain it and when the decision can return for review. Postponing a choice for a defined reason is different from allowing the same discussion to continue without progress.

A **training gap** exists when someone lacks knowledge or skill needed for an assigned contribution. A member who does not understand assay controls cannot evaluate a proposal confidently simply because the data are on screen. Provide an explanation, worked example, or appropriate training before asking for judgment. Invite questions without treating them as a sign that the person does not belong on the team.

Training should also address how the team works. New members may need to learn where records are stored, how decisions are made, and how to report an urgent concern. Distinguish a training need from missing information, inadequate time, or inaccessible technology. Each barrier requires a different response.

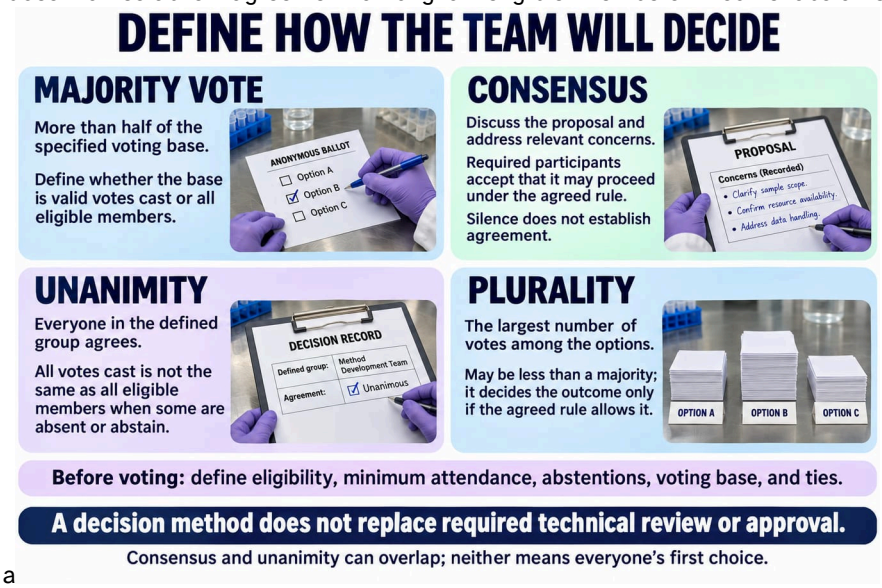
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10.8: Voting and consensus

Voting is a decision method in which eligible members express a choice under an agreed rule. A **majority vote** requires more than half of the specified voting base. That base might be valid votes cast or all eligible members. Define eligibility, the minimum attendance needed for a valid decision, abstention handling, the voting base, and tie handling before voting. The option with the most votes does not necessarily meet a majority requirement.

Consensus is a shared decision developed by discussing a proposal and addressing relevant concerns. Because organizations define it differently, agree on the standard first. Here, consensus means that the required participants accept that the decision may proceed under the stated rule. Define whose participation is needed and whether recorded reservations or standing aside are allowed. A required technical concern must still be resolved through the appropriate review; silence does not establish agreement.

Unanimity means agreement by everyone in the defined group. State which group is meant. Agreement among all votes cast does not establish agreement among all eligible members if some abstained or were absent. Consensus describes how a shared decision is developed; unanimity describes the extent of agreement. They can overlap. Neither means the selected option was everyone's first choice. Ask members directly what they accept and what concerns remain.



A **plurality** is the largest number of votes among the options, even when that number is less than a majority. It determines the outcome only if the agreed rule allows it.

Worked example: Choosing a meeting time

Seven eligible members must choose between two acceptable meeting times. They agree beforehand that an option needs at least four votes, a majority of all seven eligible members. Four vote for time A, two for time B, and one abstains. Time A meets the agreed voting rule. The outcome does not show that all members prefer it or that the team reached consensus.

Now suppose the team instead agrees to seek consensus from all seven members. They discuss coverage and revise time A so a rotating representative can attend for the affected shift. Each member confirms acceptance of the arrangement. That meets this stated consensus rule. If a member identifies an unresolved coverage problem, record and examine it before claiming consensus. Do not treat absence or silence as acceptance.

Multivoting helps a group narrow a long list of choices to a shorter set of priorities. ASQ describes it as a way to identify leading options. It can help choose which improvement ideas deserve further study. It does not establish that a technical claim is true or replace required approvals.

Voting and consensus organize participation. Neither can make unacceptable evidence acceptable. A team cannot resolve a

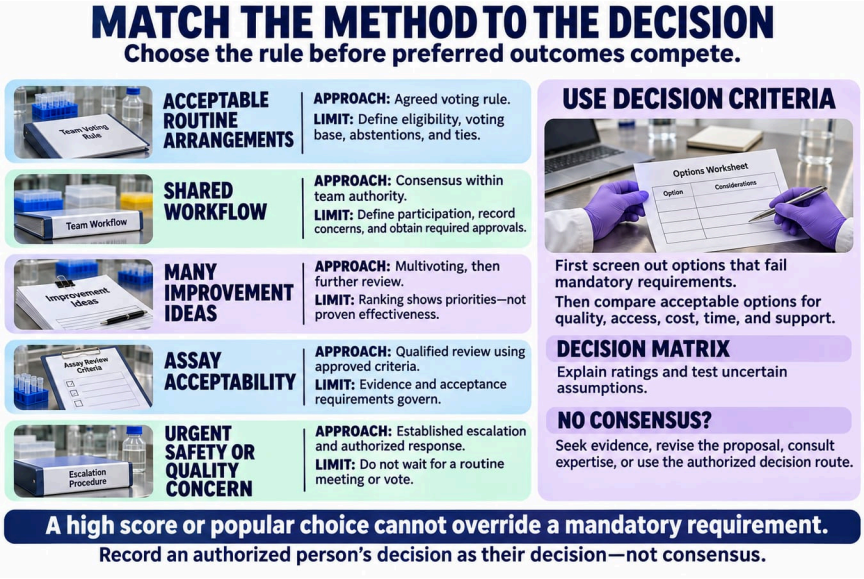
control failure by voting that the run passed. It must apply the approved method and the organization's review process. Likewise, a unanimous preference cannot authorize a change outside the team's authority.

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10.9: Selecting an appropriate decision method

Choose the method before the discussion becomes a contest between preferred outcomes. Start with the decision itself. Is the team selecting a routine arrangement, recommending an improvement, interpreting technical evidence, or responding to an urgent concern? These questions require different combinations of participation, expertise, and authority.

Decision criteria are the factors used to compare



options. They may include quality requirements, staff access, cost, time, and available support. Identify mandatory requirements first. An option that fails a required condition should not win because it is convenient or popular.

For decisions that need broad cooperation, consensus may help people understand the tradeoffs and support implementation. Voting may suit a limited choice among acceptable options when the group has agreed to the rule. A designated decision maker may need to act after consulting specialists when authority or time demands it. Urgent concerns should follow established response procedures rather than waiting for a full team discussion.

A **decision matrix** compares options against agreed criteria. It can make tradeoffs visible, but scores depend on the information and judgments used. Explain the ratings and test uncertain assumptions. A high total should not hide failure to meet a mandatory requirement. First screen out options that do not meet those requirements; then compare the remaining options using the agreed criteria.

When consensus is not reached, state the unresolved issue and choose the next route. More evidence, a revised proposal, or additional expertise may help. A designated decision maker may decide if the agreed governance allows it, but record that as the authorized person's decision, not consensus. Sponsor support does not transfer technical approval authority.

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10.10: Confirming agreement and recording decisions



After selecting a method and considering the evidence, confirm exactly what the team has decided. Before closing the discussion, state the proposed decision in plain language. Ask members to check its meaning, limits, and conditions. “We agree to improve the review process” is too broad to guide action. The record should identify what will change, where it applies, and what must happen before implementation.

A decision record preserves the choice, its reasons, the decision method, participants or voting base, and the responsible authority. Identify the supporting evidence and version. Record conditions, reservations, **dissent**, and unresolved questions fairly. Distinguish a team recommendation from required approvals, and state what must happen before implementation. A decision log collects these records.

Suppose a later investigation confirms that completed review packages also arrive late because of a scheduling problem. Keep this separate from the original control failure. The team might recommend a revised handoff for one product group, specifying the trial period, owner, evidence to collect, and approval required before use. A scheduling change does not resolve the failed control or change assay acceptance criteria. Both issues need their appropriate review paths.

Dissent is a stated disagreement with a proposal or decision. Record its substance fairly, including the evidence or unresolved question. Avoid labels such as “not a team player.” If the disagreement concerns a mandatory requirement or a possible safety issue, route it for appropriate review. A vote should not make such a concern disappear from the record.

Meeting minutes summarize important discussion, decisions, and actions. They do not need to reproduce every sentence. Keep decisions separate from suggestions, and mark items still awaiting approval. Share the draft promptly so that members can correct misunderstandings through the agreed process. A corrected record should remain traceable according to the organization’s document practices.

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10.11: Follow-up techniques and action verification

The decision record establishes what should happen; **follow-up** checks what actually happens. A decision has limited value if nobody carries it out. An **action item** states a specific task, an owner, and a due date. Include the expected evidence of completion. “Improve communication” is difficult to verify. “Prepare the revised handoff checklist for approval by Friday” identifies a reviewable output.

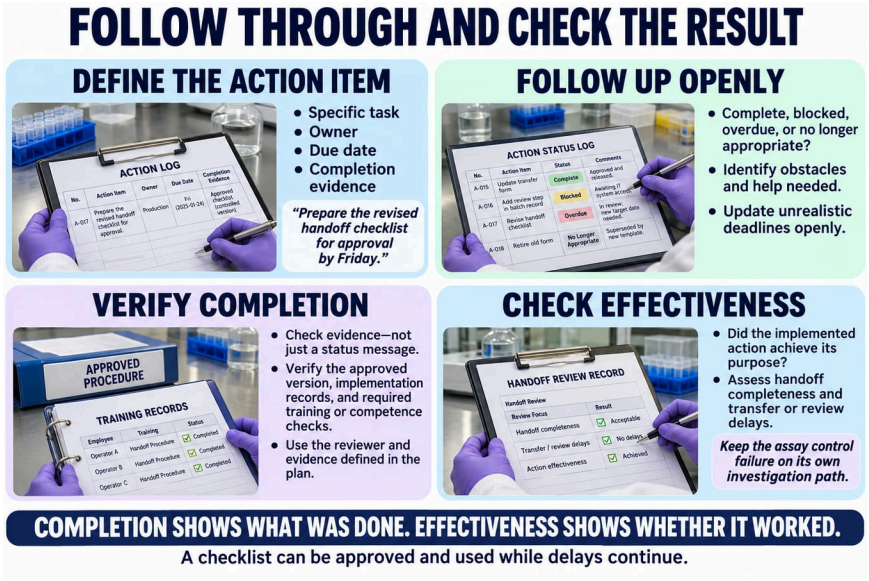
Follow-up is the planned review of progress after an assignment or decision. Ask whether the action is complete, blocked, overdue, or no longer appropriate. If it is blocked, identify the obstacle and the help needed. Update the plan openly rather than allowing the record to show an unrealistic deadline.

Verification of completion checks evidence that an assigned action was carried out as specified. It goes beyond a status message. If the action requires an approved procedure and training for both shifts, a draft presentation or emailed file is insufficient. Check the approved version, implementation records, and completion of required training, including any required demonstration of competence. Use the reviewer and evidence defined in the work plan.

An **effectiveness check** examines whether the implemented action achieved its purpose. For the assay team’s scheduling change, assess handoff completeness and transfer or review delays; keep the control failure on its own investigation path. A checklist may be approved, introduced, and used while delays continue. Completion evidence shows what was done. Effectiveness evidence addresses whether performance improved.

Set the observation period, measures, and comparison rules before judging success. Preserve time order, show counts and denominators, and consider differences in shifts, workload, or case mix. A short favorable sequence does not establish sustained performance. Use balancing measures to detect extra workload or delays elsewhere. A goal met once is a reason to review the evidence, not automatically close the concern.

Define **closure criteria**: the evidence and approvals required to close an action or project item. Name the reviewer authorized to accept it. An implementation task can be complete while its linked effectiveness review remains open. If the change fails to achieve its purpose, preserve the finding, assess the cause, and assign the next step. Project closure may transfer unresolved work to an accepted owner; it must not hide it or imply success that the evidence does not support.



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10.12: Chapter Summary

Active listening helps a team understand an issue before choosing a response. Clear messages separate observations from assumptions, and check-backs confirm important information. The team should select communication channels that match the urgency and sensitivity of the message.

Productive disagreement can improve a decision by bringing different evidence and experience into the discussion. Harmful conflict interferes with respectful work and requires an appropriate response. Assertive statements, structured conflict discussions, and escalation help concerns reach people who can address them.

Groupthink can weaken independent judgment when maintaining agreement becomes more important than reviewing evidence. Leaders can invite questions, seek other perspectives, and avoid treating silence as consent. Clear agendas, accessible meetings, and suitable training support informed participation.

Voting, consensus, and authorized individual decisions serve different purposes. A majority exceeds half of the stated voting base; a plurality is the largest share. Consensus develops a shared decision under an agreed participation and acceptance rule. Unanimity means everyone in the defined group agrees. Requirements, technical evidence, and approval responsibilities remain in effect under every method.

Decision records preserve reasons, conditions, responsibilities, and unresolved concerns. Follow-up then connects the decision to action. Verification checks completion; an effectiveness check examines whether the action produced the intended result.

Key Terms

Active listening	Paraphrasing	Constructive communication
Closed-loop communication	Check-back	Productive disagreement
Informational conflict	Interpersonal conflict	Harmful conflict
Assertiveness	DESC	Escalation
Groupthink	Confirmation bias	Independent judgment
Devil’s advocate	Meeting logistics	Agenda
Training gap	Voting	Majority vote
Consensus	Unanimity	Plurality
Multivoting	Decision criteria	Decision matrix

Active listening	Paraphrasing	Constructive communication
Decision record	Dissent	Meeting minutes
Action item	Follow-up	Verification
Effectiveness check	Closure criteria	

Review Questions

1. How does active listening differ from waiting for a turn to speak?

2. What are the steps in a check-back? What can it confirm, and what does it not establish?

3. Distinguish informational conflict, interpersonal conflict, and productive disagreement.

4. What does each part of DESC contribute to a respectful conflict discussion?

5. What is groupthink, and why does quick agreement alone not establish that it occurred?

6. How can meeting logistics, unclear agendas, and training gaps limit independent participation?

7. Compare majority voting, plurality, consensus, and unanimity. Why should the team define its rule in advance?

8. Why can neither a vote nor consensus replace approved technical acceptance criteria?

9. What information should a decision record contain, including when a member dissents?

10. Distinguish verification of completion from an effectiveness check.

11. What should happen when the evidence does not meet an action's closure criteria?

Apply Your Understanding

1. During a sample-labeling review, a technician says that two identifiers do not match. The leader responds that the group has already discussed labels and moves to the next topic. Draft a clear statement of the concern and a check-back exchange. Explain how the leader should separate the evidence from assumptions about the technician's intentions.

2. Two laboratory shifts disagree about incomplete records. One shift describes missing details; the other says that the required information arrives late from a third department. Use DESC to outline a respectful discussion. Identify the evidence needed before assigning responsibility and explain when another person should be involved.

3. A seven-member team agrees that a decision needs a majority of all eligible members. Three vote for option A, two for option B, and two abstain. The chair announces that A won and that the team reached consensus. Use the distinction between plurality and majority to evaluate both claims, identify the missing next step, and propose an appropriate record of the outcome.

4. A manager announces a preferred equipment-training plan before anyone reviews the alternatives. Remote staff cannot open the supporting file, and new members do not understand a key technical term. Propose changes that address independent judgment, meeting logistics, and training. Explain how the team should check readiness before choosing a plan.

5. A team closes an action because an updated checklist has been emailed to staff. A month later, missing handoff details remain

common. Design separate checks for completion and effectiveness. Identify who should review the evidence, what information is needed, and what should happen if the action did not achieve its purpose.

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11: THE REGULATION OF MEDICAL AND FOOD PRODUCTS

Learning Objectives

After completing this chapter, you should be able to:

- Discuss how public health events and scientific advances influence regulation.
- Describe the FDA's role and the functions of major centers and programs.
- Distinguish binding regulations from FDA guidance and Points to Consider documents.
- Locate cGMP, GLP, and clinical research requirements in Title 21 of the eCFR.
- Explain the purpose and limits of international harmonization.
- Describe the food safety responsibilities of FDA, USDA, and EPA.
- Explain how federal oversight applies to genetically engineered crops.

Protecting consumers from unsafe products is not a new idea. Historical societies used laws and penalties to address fraud and harmful products. Over time, consumer protection expanded from punishment after harm occurred to systems designed to prevent harm.

Modern regulation emphasizes prevention. Although recalls, legal action, and other remedies remain important after a problem occurs, regulations also require controls that reduce risks before products reach consumers. This workbook examines how these controls apply to medical products, food, and agricultural biotechnology. Understanding these requirements will help you prepare for work in the biotechnology industry.

11.1: History of Regulations in the Pharmaceutical Industry

11.2: The Food and Drug Administration (FDA)

11.3: FDA Centers and Programs

11.4: Rulemaking Adjudication and Guidance

11.5: The Code of Federal Regulations (CFR)

11.6: Selected Regulations Relevant to Biotechnology

11.7: Current Good Manufacturing Practice

11.8: Good Clinical Practice

11.9: International Harmonization Efforts

11.10: Regulation of Food and Agriculture in the United States

11.11: Food Safety

11.12: Laws Governing Food and Agricultural Biotechnology

11.13: Regulation of Agricultural Biotechnology and GMOs

11.14: Chapter Summary

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11.1: History of Regulations in the Pharmaceutical Industry

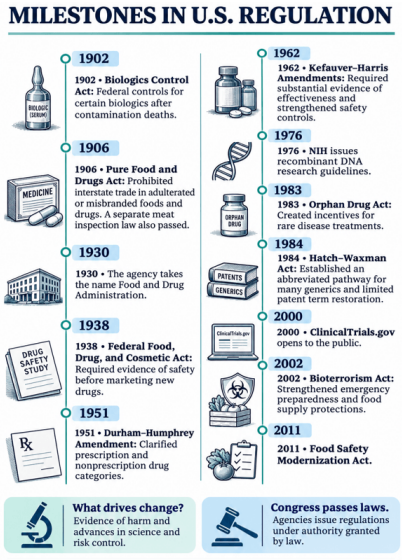
Pharmaceutical manufacturing is a major part of the biotechnology industry. Drug regulation addresses safety, effectiveness, identity, strength, quality, purity, and accurate labeling. Current good manufacturing practice requirements are legally enforceable; compliance is not voluntary. Characteristics such as color, taste, and texture can also matter when they affect product identity, stability, acceptability, or an established specification. For example, the FDA does not require all aspirin tablets to be blue, but a manufacturer must control applicable product specifications and any changes to them.

Many protections now taken for granted developed after unsafe or misleading products caused harm. Earlier medicines sometimes contained potent ingredients without adequate safety testing or labeling. The FDA history resources describe how public health events and scientific advances shaped federal oversight.

Important events and laws include the following:

1902 — The Biologics Control Act, also called the Virus Toxin Law, followed deaths in 1901 linked to contaminated diphtheria antitoxin and smallpox vaccine. It established federal controls over certain biological products. Diphtheria antitoxin is a treatment and should not be confused with a diphtheria vaccine.

1906 and 1938 — The Pure Food and Drugs Act of 1906 prohibited interstate commerce in adulterated and misbranded foods



and drugs. The separate Federal Meat Inspection Act also became law in 1906. The Federal Food, Drug, and Cosmetic Act of 1938 expanded federal authority and required evidence of safety before new drugs could be marketed.

1930 — The agency received its current name, the Food and Drug Administration. Its modern regulatory functions had begun under earlier federal laws.

1951 — The Durham Humphrey Amendment clarified the distinction between prescription and nonprescription drugs, including drugs that require supervision by a licensed practitioner.

1962 — The Kefauver Harris Drug Amendments required substantial evidence of effectiveness for new drugs and strengthened drug safety controls. New drug approval requires evidence of both safety and effectiveness.

1976 — The NIH first issued its recombinant DNA research guidelines. Revised versions address research involving recombinant or synthetic nucleic acid molecules and establish biosafety and oversight expectations within their scope. These guidelines are distinct from FDA product approval requirements.

1983 — The Orphan Drug Act, signed on January 4, created incentives to develop treatments for rare diseases. In the United States, an orphan indication generally involves a disease affecting fewer than 200,000 people, although an alternative cost

recovery criterion also exists.

1984 — The Drug Price Competition and Patent Term Restoration Act, often called the Hatch Waxman Act, established an abbreviated approval pathway for many generic drugs and allowed limited patent term restoration for eligible products to account for time spent in regulatory review.

2000 — ClinicalTrials.gov became publicly available. It provides information about publicly and privately supported clinical research. A study listing does not mean that the government has approved the treatment or confirmed the study's scientific quality.

2002 — The Public Health Security and Bioterrorism Preparedness and Response Act strengthened the nation's ability to prepare for and respond to public health emergencies. It also expanded protections for the food supply.

Additional milestones include the Food Safety Modernization Act of 2011 and later changes in medical device quality system requirements. Regulatory systems continue to change as risks, technologies, and laws change.

Regulations often change as we learn more about what can go wrong and how to prevent it. Reports of harm can reveal risks that existing rules do not fully address. Advances in science and technology can also give manufacturers better ways to detect or control those risks.

Congress passes federal laws, and agencies issue regulations within the authority those laws give them. Public health findings, input from people and organizations affected by a rule, and court decisions can all shape how an agency responds. The FDA is the main federal agency responsible for regulating human drugs. A drug manufacturer may also need to follow rules from other agencies that oversee worker safety or environmental protection.

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11.2: The Food and Drug Administration (FDA)

FDA Organization

The U.S. Food and Drug Administration (FDA) is part of the U.S. Department of Health and Human Services. It regulates a wide range of products, including human and animal drugs, many biological products, medical devices, most foods, cosmetics, tobacco products, and certain products that emit radiation.



What the FDA does

The FDA carries out laws passed by Congress. Three parts of its work are especially relevant to biotechnology.

- **Rulemaking.** The FDA issues regulations under authority granted by Congress. These regulations explain what companies must do to comply with federal law.
- **Application review.** FDA specialists evaluate the evidence companies submit about their products. The agency uses that evidence to make decisions such as whether to approve a new drug.
- **Investigation and enforcement.** FDA staff inspect facilities, review records, and collect samples for testing. The agency uses the findings to decide whether further action is needed.

How the FDA organizes its work

The **Office of the Commissioner** leads the agency and coordinates work that involves multiple centers and offices. Support teams handle functions such as information technology, budgeting, purchasing, human resources, and records management.

Three centers oversee medical products that biotechnology students are likely to encounter.

FDA center	Examples of products it oversees
Center for Drug Evaluation and Research (CDER)	Prescription and over-the-counter drugs, including many therapeutic proteins
Center for Biologics Evaluation and Research (CBER)	Vaccines, blood products, and cell and gene therapies

Center for Devices and Radiological Health (CDRH)	Medical devices, including many diagnostic tests, and certain products that emit radiation

Other parts of the FDA focus on different product areas. The **Center for Tobacco Products** oversees tobacco products within the FDA's authority. The **Human Foods Program (HFP)** oversees the agency's work on human food safety and nutrition. When the program launched on October 1, 2024, it brought together work previously handled by the Center for Food Safety and Applied Nutrition (CFSAN) and other FDA offices.

The **Office of Inspections and Investigations (OII)** leads the FDA's field work. Older documents may refer to it as the **Office of Regulatory Affairs (ORA)**, its name before the October 2024 reorganization. OII staff inspect facilities, investigate possible violations, and review products entering the United States. They work with FDA centers, programs, and laboratories to gather evidence and respond to product safety problems.

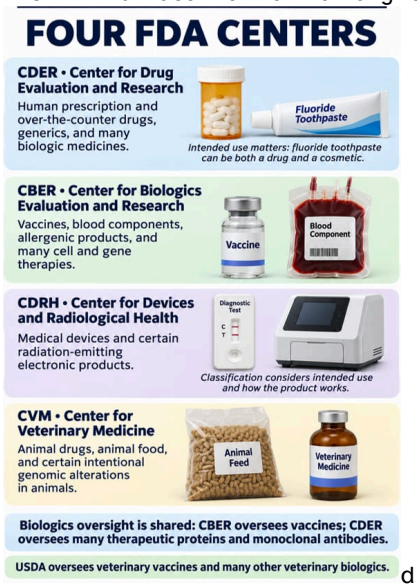
For example, during an inspection of a vaccine manufacturing site, an FDA investigator may review batch records and ask how the company handled an unexpected test result. The investigator's findings can help specialists at CBER evaluate the problem and determine what follow-up is needed. If you need to identify the office responsible for a particular product or issue, check the FDA's current organization pages.

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11.3: FDA Centers and Programs

FDA Centers and Programs

The FDA divides its work among centers and programs with different areas of expertise. Which office takes the lea



d depends on how the product is classified. For example, a test kit used to diagnose an infection and a vaccine used to prevent it are both biotechnology products, but different FDA centers typically oversee them. Some products require more than one office to work together.

Center for Drug Evaluation and Research (CDER) oversees human prescription and over-the-counter drugs, including generic drugs and many biologic medicines. A product's **intended use**, or what it is meant to do, helps determine whether the FDA regulates it as a drug. For example, fluoride toothpaste helps prevent cavities, and dandruff shampoo treats dandruff. Both can be regulated as drugs and cosmetics. Sunscreens and antiperspirants also have uses that bring them under drug regulation.

Center for Biologics Evaluation and Research (CBER) oversees vaccines, blood and blood components, allergenic products, and many cell and gene therapies. The FDA divides oversight of biologics between centers. For example, CBER oversees vaccines, while CDER oversees many therapeutic proteins and monoclonal antibodies.

Center for Devices and Radiological Health (CDRH) oversees medical devices and certain electronic products that emit radiation. Medical devices include diagnostic tests, instruments, and implants. When determining whether a product is a medical device, the FDA considers what the product is intended to do and how it achieves that purpose. For example, a kit that uses antibodies to detect an infection can be regulated as a medical device.

Center for Veterinary Medicine (CVM) oversees animal drugs and animal food, including food additives used in animal feed. It also evaluates certain changes deliberately made to an animal's DNA, known as *intentional genomic alterations*. The U.S. Department of Agriculture (USDA) oversees veterinary vaccines and many other veterinary biologics.

Human Foods Program (HFP) oversees most foods for people, including dietary supplements, and handles food ingredients and labeling within the FDA's authority. The USDA oversees most meat, poultry, and processed egg products. Shell eggs illustrate how responsibilities can differ within one product category. The FDA generally oversees shell egg production, storage, and transportation, while the USDA oversees most processed egg products. The FDA also regulates cosmetics through a separate office.



Center for Tobacco Products (CTP) carries out federal requirements for tobacco products. Its work includes reviewing products before they can be sold when the law requires it, setting product standards, and enforcing rules for labeling, advertising, and promotion. Tobacco products carry health risks even when they meet FDA requirements.

National Center for Toxicological Research (NCTR) studies how substances can affect health. Its scientists develop methods and gather evidence that other FDA centers can use when making decisions about product safety.

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11.4: Rulemaking Adjudication and Guidance

Federal agencies such as the FDA use **rulemaking** to develop regulations and **adjudication** to decide individual matters. For example, the FDA uses rulemaking to establish requirements that apply to a group of products. It uses adjudication when it makes a decision on a specific product application. The steps the agency follows depend on the product and the law that applies.

From a proposed rule to a regulation

When an agency proposes a rule, it usually publishes the proposal in the *Federal Register* and gives the public a chance to comment. The proposal describes what the agency is considering. If the agency issues a final rule, it publishes that rule in the *Federal Register* as well. The introduction to the final rule, called the **preamble**, usually explains the agency's reasons for the rule and how it responded to significant comments.

A final rule identifies its **effective date**, when the rule takes effect. It may also list a separate **compliance date**, when regulated companies must begin following certain requirements. The *Federal Register* publishes proposed rules, final rules, and notices. Regulations of general and lasting application are organized in the *Code of Federal Regulations* (CFR). The **eCFR** is a regularly updated online version of the CFR.

How to read FDA guidance

FDA guidance explains the agency's current thinking and often describes ways to meet a legal requirement. When reading guidance, ask where the obligation comes from. A guidance document may quote a law or regulation that companies must follow. The guidance itself generally offers recommendations. A company may use a different approach if it meets the applicable laws and regulations.

Check the document's status before relying on it. **Draft guidance** is issued for comment and may change before the FDA finalizes it. **Final guidance** reflects the agency's thinking when issued and can later be updated or withdrawn. Some older FDA biotechnology documents use the title *Points to Consider*. If you find one, check whether the FDA has revised, withdrawn, or replaced it.

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11.5: The Code of Federal Regulations (CFR)

How to Read the Code of Federal Regulations

The *Code of Federal Regulations* (CFR) organizes federal regulations of general and lasting application into 50 titles. **Title 21, Food and Drugs**, includes regulations on manufacturing, nonclinical laboratory studies, clinical investigations, and other activities relevant to biotechnology. The electronic CFR (eCFR) is updated frequently. When you look up a requirement, check the date shown on the page and the effective date of any amendment that applies.

How the CFR is organized

A CFR citation works like an address. Each part of the citation helps you find the exact text you need.

- **Titles** cover broad subjects, such as food and drugs.
- **Chapters** generally group regulations by the agency that issued them.
- **Parts** cover specific regulatory topics. A part may be divided into subparts.
- **Sections** are the numbered units within a part.
- **Paragraphs** break a section into smaller pieces and often contain specific requirements.

For example, **21 CFR 211.25(a)** points to Title 21, Part 211, § 211.25, paragraph (a). When you refer to a specific requirement, include the paragraph letter or number so someone else can find the same text.

FDA regulations in Title 21 Finding

Chapter I contains the FDA's regulations. Other chapters in Title 21 contain regulations issued by other agencies. The table below highlights selected parts of Chapter I to help you find your way around.

Try it. Open Title 21 in the eCFR, select Chapter I, and find Part 211. Read the scope section, § 211.1, before looking up § 211.25(a). The scope helps you determine whether the part applies to the product or activity you are reviewing. Open Title 21 in the eCFR

Parts or series	Selected subjects
100 series	Human food including Part 117 cGMP and preventive controls and Part 111 dietary supplement cGMP
200 and 300 series	Human drugs including Parts 210 and 211 cGMP and Part 314 new drug applications
500 series	Animal drugs and animal food including Part 507 animal food cGMP and preventive controls
600 series	Biological products including Part 606 blood cGMP and Part 610 general standards
700 series	Cosmetics regulations read alongside current statutory requirements

Parts or series	Selected subjects
800 series	Medical devices including Part 803 reporting and Part 820 QMSR
900 series	Mammography quality standards in Part 900
1000 series	Radiological health and electronic product radiation requirements
1200 series	Additional public health requirements including Part 1271 HCT/Ps
Other selected parts	Part 11 electronic records Part 50 human subjects Part 54 financial disclosure Part 56 IRBs and Part 58 GLP

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11.6: Selected Regulations Relevant to Biotechnology

Selected Title 21 Regulations for Biotechnology

Title 21 of the *Code of Federal Regulations* (CFR) covers many activities in biotechnology, from keeping electronic records to labeling drugs and reporting problems with medical devices. The examples below can help you find the right part of Title 21. Start by reading the regulation's **scope**. It tells you which products, records, or activities the requirements cover.

21 CFR Part 11 — Electronic Records and Electronic Signatures

Part 11 sets criteria for making covered electronic records and signatures trustworthy and reliable. To determine whether it applies, start with the underlying FDA requirement and look at how the organization uses the record. For example, an electronic batch record a company relies on to meet an FDA recordkeeping requirement may fall under Part 11. Simply saving a file on a lab computer does not bring it within the rule's scope. FDA guidance on the scope and application of Part 11

21 CFR Part 201 — Labeling

Drug labeling helps people identify a product, understand what it is for, and learn how to use it. The sections below show how Part 201 addresses specific labeling questions. The full set of requirements depends on the product.

Section	What it covers
§ 201.1	How the label identifies the manufacturer, packer, or distributor and gives its place of business.
§ 201.5	What counts as adequate directions for use. Exemptions may apply under other sections.
§ 201.15	How required information must be displayed so people can notice and read it.
§ 201.17	Where the expiration date must appear when one is required.
§ 201.117	A narrow exemption from adequate directions for use for certain substances intended for use as inactive ingredients.
§ 201.122	The conditions for an exemption from adequate directions for use when a drug is intended for processing, repacking, or use in manufacturing another drug.
§ 201.128	How the FDA determines a product's intended use. Evidence can include labeling, advertising, and the circumstances of distribution.

21 CFR Part 314 — Applications for FDA Approval to Market a New Drug

Part 314 covers how companies apply for FDA approval to market a drug. It includes new drug applications and abbreviated new drug applications, which are used for generics. It also covers responsibilities after approval, such as reporting certain changes to how a drug is made. 21 CFR Part 314

21 CFR Part 610 — General Biological Products Standards

Part 610 sets standards for biological products. It covers areas such as product testing, labeling, and other quality controls. Which requirements apply depends on the specific biological product. 21 CFR Part 610

21 CFR Part 803 — Medical Device Reporting

Part 803 explains when certain deaths, serious injuries, and malfunctions involving medical devices must be reported. The duties differ for manufacturers, importers, and device user facilities. These reports help the FDA spot possible safety problems after devices are in use. 21 CFR Part 803

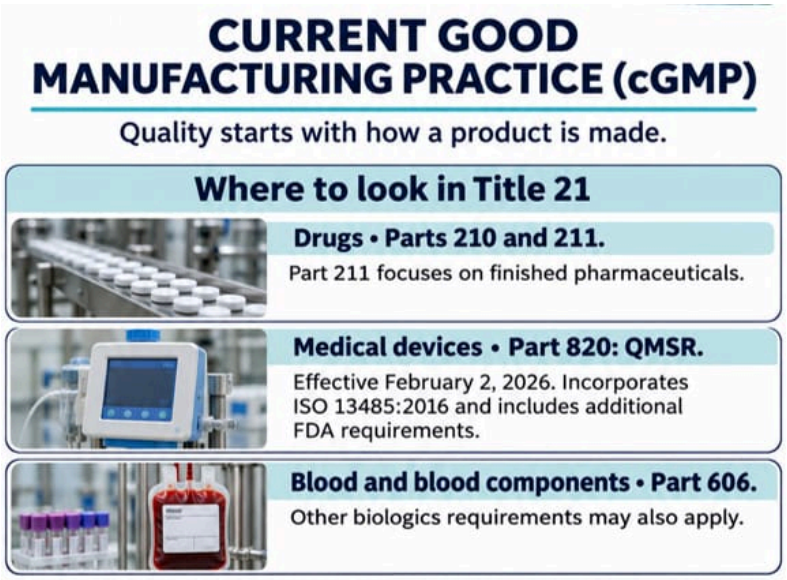
21 CFR Part 1271 — Human Cells, Tissues, and Cellular and Tissue-Based Products

Part 1271 covers certain products made from or consisting of human cells or tissues. It addresses topics such as registering

facilities, determining whether donors are eligible, and following practices that reduce the risk of spreading communicable disease. Depending on the product and its intended use, drug, biologic, or medical device requirements may also apply. 21 CFR Part 1271

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11.7: Current Good Manufacturing Practice



Current Good Manufacturing Practice (cGMP)

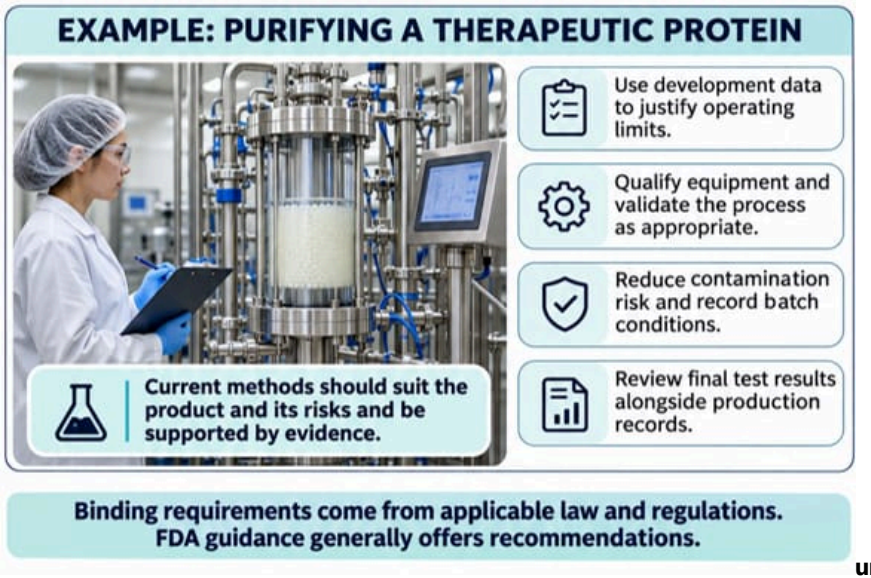
Quality starts with how a product is made. A finished-product test can show whether a sample meets a specification, but it gives only part of the picture. Manufacturers also need to control the steps that affect product quality and keep records that show what happened during production.

Where to find cGMP requirements

The requirements a manufacturer follows depend on what it makes. Title 21 of the *Code of Federal Regulations* (CFR) includes several examples.

What cGMP looks like in practice

Manufacturers use suitable facilities, equipment, procedures, and trained personnel to keep production under control. The controls should fit the product and its risks so that each batch can consistently meet applicable requirements and specifications. Production records show what was done, who did it, when it happened, and what the results were. Those records help reviewers check whether the process worked as intended and investigate problems when it did not.



The word **c** **urrent** matters because manufacturing methods and technology change. Regulations often specify what manufacturers must control while leaving room to choose a method vetted by scientific evidence. A control can help a manufacturer meet a requirement even when the CFR leaves its technical details open. Whether a practice is legally required depends on the law and regulations that apply. FDA guidance can help explain the agency's expectations, and draft guidance is issued for comment. Binding requirements come from applicable law and regulations.

Consider a biotechnology company that uses **chromatography** to purify a therapeutic protein. The team uses development data to justify operating limits, such as the acceptable flow rate. It qualifies the equipment for its intended use and validates the process as appropriate. During production, staff follow controls that reduce contamination risk and record the conditions used for each batch. When the quality team reviews the batch, it can look at both the final test results and the evidence that the purification step stayed within its limits.

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11.8: Good Clinical Practice

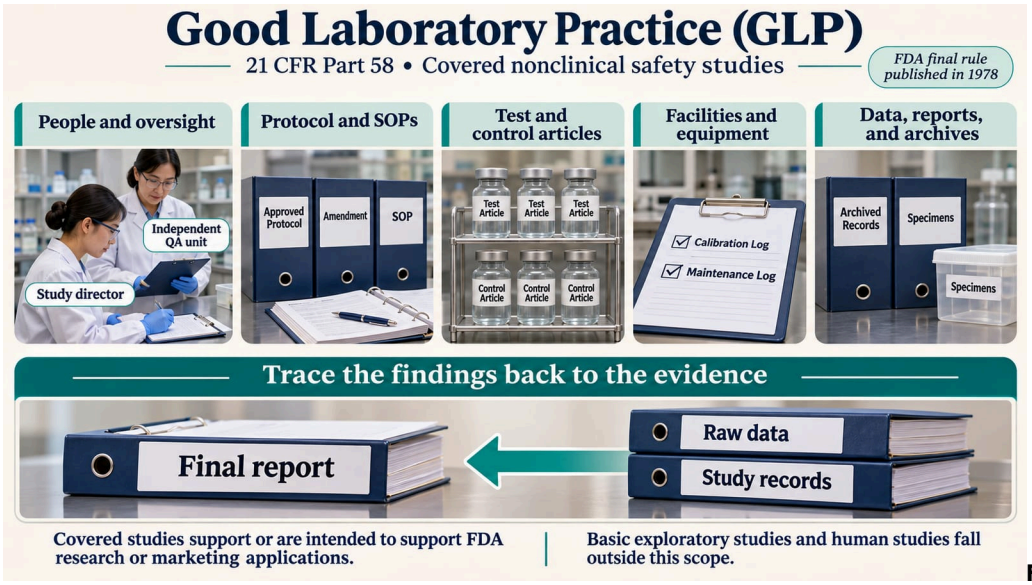
When the FDA reviews a nonclinical safety study, it needs to know how the study was run and whether the records support its findings. **Good Laboratory Practice (GLP)** sets requirements that help protect the quality and integrity of those studies. The FDA published its final GLP rule in 1978 after investigations uncovered serious problems with how some studies were conducted and documented.

When GLP applies

21 CFR Part 58 applies to covered nonclinical laboratory studies that support, or are intended to support, FDA applications for research or marketing. These studies may evaluate the safety of drugs, biologics, medical devices, food additives, or other FDA-regulated products. For example, a laboratory study designed to evaluate the safety of a new drug before human trials may fall under Part 58. Basic exploratory studies and studies involving human participants fall outside Part 58's definition of a nonclinical laboratory study.

What GLP looks like in practice

- **People and oversight.** A designated study director is responsible for how the study is conducted. A quality assurance unit, independent of the staff who direct or conduct the study, checks whether the work follows GLP.



- **Facilities and equipment.** The laboratory uses facilities and equipment suited to the study. Staff document equipment inspections, maintenance, and calibration as appropriate. Studies involving animals also require suitable housing and care. Other animal welfare laws and institutional review requirements may apply.

- **Protocols and procedures.** An approved protocol describes the study's objectives and methods. Changes to the protocol are documented. Written **standard operating procedures (SOPs)** explain how staff carry out routine tasks.

- **Test and control articles.** Staff document what is being tested and what is used for comparison. They control how those materials are handled and stored so the study team knows what was used.

- **Data, reports, and archives.** Staff record observations and measurements as raw data. The final report describes the methods and findings. The laboratory retains required records and specimens so reviewers can trace the findings back to the original evidence.

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11.9: International Harmonization Efforts

Good clinical practice (GCP) provides ethical and scientific standards for clinical trials involving people. FDA requirements are distributed across several regulations; international guidance also helps explain good practices. Protecting participants and producing reliable data are central goals.

Informed consent is a process that helps a potential participant understand a study before deciding whether to take part. It includes information about the study's purpose, procedures, foreseeable risks, potential benefits, and voluntary participation. FDA informed consent requirements are primarily in 21 CFR Part 50, Protection of Human Subjects, subject to defined exceptions and additional protections.

An institutional review board (IRB) reviews covered clinical research to protect participants' rights and welfare. FDA IRB requirements are in 21 CFR Part 56, not Part 50. An IRB must meet membership and conflict of interest requirements; it is not necessarily a separate institution from the sponsor or research site.

For investigational drugs and biologics, 21 CFR Part 312, Subpart D describes sponsor and investigator responsibilities. Device investigations are generally addressed in Part 812. Part 54 addresses financial disclosure by clinical investigators. Applicable FDA and ICH GCP guidance provides additional recommendations.

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11.10: Regulation of Food and Agriculture in the United States

A company seeking to market a product internationally may face different national requirements. International harmonization aims to align scientific and technical expectations where appropriate while maintaining public health protections. It does not create a single worldwide approval or remove each regulator's authority.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) develops guidelines on quality, safety, efficacy, and related topics. FDA participates alongside other regulatory authorities and industry organizations. ICH guidelines take effect through each participating region's regulatory processes.

FDA international activities include regulatory cooperation, information sharing, foreign inspections, and participation in standards development. Consult current FDA international program resources rather than relying on an outdated list of offices and staff.

The Common Technical Document (CTD), developed through ICH, organizes information for pharmaceutical regulatory submissions. Its electronic form is the eCTD. Mutual recognition agreements may allow regulators to rely on certain inspection findings under defined conditions; they do not automatically approve a product in another country.



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11.11: Food Safety

Food safety starts with knowing what could make a food unsafe and where that problem could arise. A food safety team looks for three main types of hazards.

The CDC estimates that foodborne illness causes about **48 million illnesses, 128,000 hospitalizations, and 3,000 deaths** in the United States each year. The often-cited figure of **1 in 6 Americans** describes the estimated burden in a single year. These figures estimate the overall burden, including illnesses that are never diagnosed or reported. Safe practices during production, processing, storage, handling, and preparation all help prevent illness.

How HACCP helps prevent food safety problems

Hazard Analysis and Critical Control Point (HACCP) is a system for identifying significant food safety hazards and controlling them during production. The USDA requires HACCP in covered meat and poultry establishments. The FDA requires HACCP for covered seafood and juice operations. Many other facilities regulated by the FDA follow the preventive controls requirements in **21 CFR Part 117**, where applicable. USDA meat and poultry HACCP requirements · FDA seafood HACCP · FDA juice HACCP · FDA preventive controls.

- **Analyze the hazards.** Review each step and identify which biological, chemical, or physical hazards require control under the rules that apply.
- **Identify critical control points and set limits.** A **critical control point (CCP)** is a step where control is essential to prevent or eliminate a food safety hazard or reduce it to an acceptable level. A **critical limit** is a measurable boundary for that control, such as a minimum temperature and holding time for a heat treatment.
- **Monitor the control and respond to problems.** Check whether the process stays within its critical limits. If it falls outside a limit, take corrective action and determine how to handle the affected product.
- **Verify the system and keep records.** Review records and perform other checks to confirm that the plan is being followed and is effective. Keep the records required by the applicable rules.



Hazards can arise anywhere from raw material production to distribution. The hazard analysis helps the team decide which steps need to be designated as critical control points. During an inspection, HACCP records can help show whether the facility monitored those steps and responded when something went wrong.

How biotechnology helps make cheese

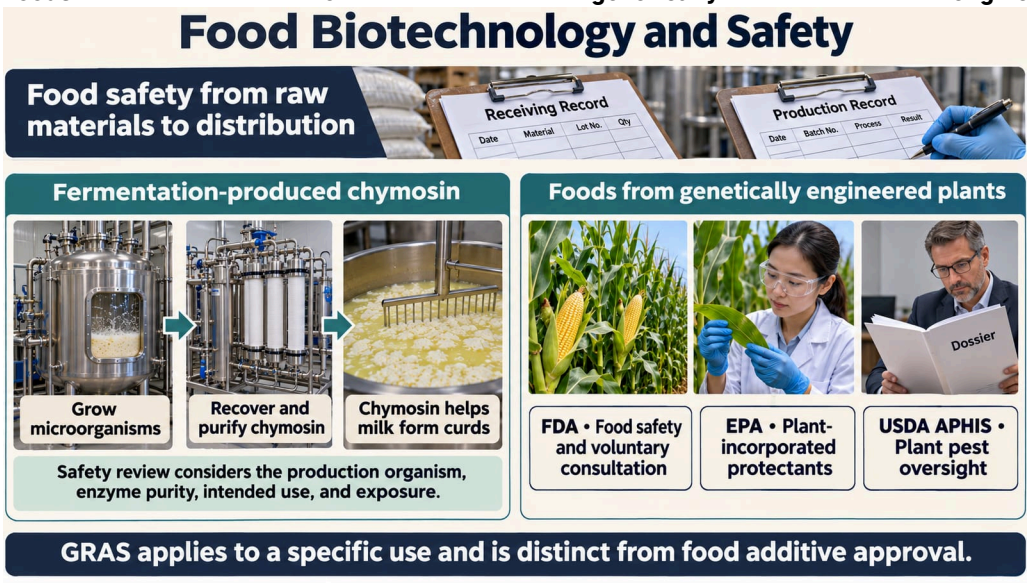
During cheesemaking, an enzyme called **chymosin** helps milk form curds. Traditionally, cheesemakers obtained chymosin from calf stomachs. Today, manufacturers can also use genetically engineered microorganisms to produce it. They grow the microorganisms under controlled conditions in a fermentation tank, then recover and purify the enzyme. The production method changes, but the enzyme serves the same purpose in the cheese.

Evaluating the safety of an enzyme made by fermentation involves looking at both the production process and the final enzyme preparation. A review may consider:

- Which microorganism produced the enzyme and what genetic material was introduced.
- What the enzyme preparation contains, how pure it is, how it will be used, and how much people are likely to consume.
- Whether it could cause harmful effects or allergic reactions, and whether it contains relevant residues or contaminants from manufacturing.

Comparing the enzyme with one made by a conventional method can help reviewers spot differences that need further study. The safety evaluation also considers the proposed use and expected exposure. Substances that meet the legal definition of a **food additive** generally require FDA approval before use. A use that is **generally recognized as safe (GRAS)** is excluded from that definition. A GRAS conclusion applies to a specific use and is a separate regulatory outcome from FDA food additive approval. FDA overview of GRAS.

Foods from genetically engineered plants



Foods from genetically engineered plants must meet the same applicable safety requirements as other foods. Developers can use the FDA's voluntary consultation process to discuss safety and regulatory questions about a particular new plant variety. If a new substance in the food meets the definition of a food additive, the applicable approval requirements still apply. FDA consultation programs for foods from new plant varieties.

Other agencies have specific roles. The Environmental Protection Agency (EPA) regulates certain pesticidal substances that plants produce, such as proteins that protect a crop from insect pests. The USDA's Animal and Plant Health Inspection Service (APHIS) oversees organisms that fall within its plant pest authority. EPA overview of plant-incorporated protectants.

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11.12: Laws Governing Food and Agricultural Biotechnology

Federal laws give agencies the authority to oversee food safety and agricultural biotechnology. Regulations explain how those laws apply to specific products and activities. An agency's role often depends on how a product will be used.



- **Federal Meat Inspection Act, Poultry Products Inspection Act, and Egg Products Inspection Act.** These laws give the U.S. Department of Agriculture (USDA) authority to oversee covered meat, poultry, and processed egg products. USDA oversight includes inspection and labeling requirements. USDA Food Safety and Inspection Service laws and regulations

- **Toxic Substances Control Act (TSCA).** This law gives the Environmental Protection Agency (EPA) authority over certain chemical substances, including some microorganisms used for industrial purposes. For example, a microorganism created by combining genetic material from organisms in different genera may require EPA review. Whether TSCA applies depends on the organism and its intended use. Substances used as pesticides, foods, or drugs are generally excluded from TSCA for those uses. EPA biotechnology regulation under TSCA

- **Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).** The EPA uses this law to regulate the sale, distribution, and use of pesticides. It covers products such as microbial pesticides and certain pest-control substances that plants are engineered to produce. The *Federal Food, Drug, and Cosmetic Act* gives the EPA separate authority to set limits for pesticide residues in food or grant exemptions from those limits. EPA overview of pesticide laws

- **Plant Protection Act of 2000.** This law gives the USDA authority to protect plant health. The USDA's Animal and Plant Health Inspection Service (APHIS) regulates certain genetically engineered organisms under **7 CFR Part 340**. Whether an organism is covered depends on the criteria in the regulation. The Plant Protection Act replaced earlier laws, including the Federal Plant Pest Act.

- **FDA Food Safety Modernization Act (FSMA).** Signed into law on January 4, 2011, FSMA strengthened the FDA's ability to prevent and respond to food safety problems. It requires many covered facilities to identify hazards and put preventive controls in place. It also gives the FDA authority to order recalls of certain foods when specific legal conditions are met. FDA overview of FSMA

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11.13: Regulation of Agricultural Biotechnology and GMOs

What Are Genetically Modified Organisms

A genetically modified organism (GMO) is commonly understood to be an organism whose genetic material has been altered using genetic engineering. Depending on context, genetic engineering includes recombinant DNA methods and some genome editing methods. Agricultural biotechnology is broader: it includes tools used to improve or modify crops, animals, or microorganisms, including traditional breeding and modern molecular methods. Genetic changes are not necessarily improvements in every setting.

Genetically engineered foods entered the U.S. market in the 1990s; the Flavr Savr tomato became commercially available in 1994. Engineered traits include insect resistance, herbicide tolerance, virus resistance, and changes in composition. Adoption varies by crop, country, and year. Use current USDA data when reporting percentages rather than repeating undated estimates.

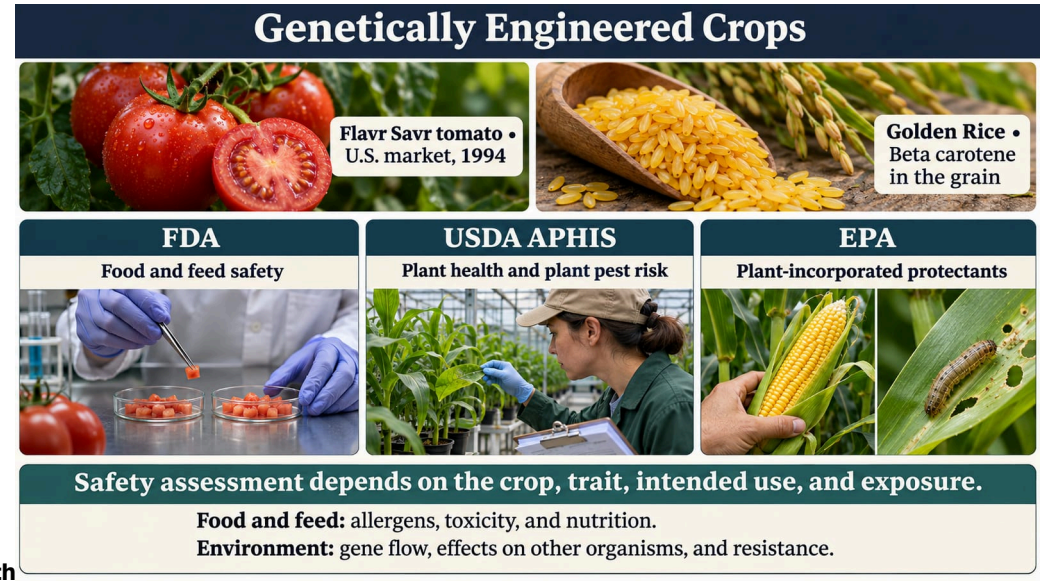
Agricultural biotechnology raises questions about food safety, resistance management, gene flow, biodiversity, access, and farming practices. Benefits and risks depend on the specific trait and how it is used. For example, Golden Rice was engineered to produce beta carotene, a precursor of vitamin A, in the edible grain. It was developed to help address vitamin A deficiency, which can cause preventable blindness. Nutritional benefit depends on factors such as access, intake, and the broader diet; genetic engineering alone does not solve malnutrition.

Regulatory Agencies for Genetically Engineered Crops

Three federal agencies have complementary responsibilities for agricultural biotechnology. The scope of each agency's review depends on the product and applicable law.

FDA Food and Feed Safety

FDA evaluates food and feed safety within its jurisdiction. The Human Foods Program and CVM consider issues such as potential allergens, toxins, nutritional changes, and composition. Comparisons with conventional foods can guide an evaluation. A completed voluntary consultation does not transfer the producer's legal responsibility for safety to FDA or serve as general marketing approval.



USDA Plant Health

USDA APHIS Biotechnology Regulatory Services (BRS) regulates certain genetically engineered organisms that may pose a plant pest risk under the Plant Protection Act and 7 CFR Part 340. Requirements may cover importation, interstate movement, and environmental release. A court vacated the 2020 biotechnology rule in December 2024, and APHIS returned to the earlier regulatory framework. Check the current APHIS guidance before determining a product's status; it is inaccurate to say that APHIS

regulates every genetically engineered crop.

EPA Pesticides and Environmental Protection

EPA regulates pesticidal substances produced by plants and the genetic material necessary for their production, called plant incorporated protectants (PIPs). For example, certain Bt corn varieties produce proteins that target particular insect pests. EPA evaluates relevant human health and environmental risks and establishes pesticide residue tolerances or exemptions when appropriate. Not every genetically engineered crop contains a PIP.

Assessing Genetically Engineered Crops for Safety

Safety assessment focuses on the specific organism, trait, intended use, and relevant exposure. Comparisons with conventional counterparts help identify changes that need further evaluation, including potential allergenicity, toxicity, and nutritional effects. Environmental assessment may address gene flow, effects on other organisms, and resistance development. Avoid blanket claims that every engineered product is safe or unsafe. FDA states that GMO foods on the market meet the same safety standards as other foods.

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11.14: Chapter Summary

Regulation helps protect people who use medicines, medical devices, foods, and other biotechnology products. Many protections developed after unsafe products caused harm. Scientific advances also shape regulation by providing better ways to identify risks and prevent problems. Quality practices support these protections through controlled processes, trained employees, reliable testing, and accurate records.

Congress passes federal laws, and agencies develop regulations under the authority those laws provide. The Food and Drug Administration (FDA) oversees many medical products and most foods in the United States. The United States Department of Agriculture (USDA) oversees certain food products and plant health activities. The Environmental Protection Agency (EPA) regulates pesticides and addresses related environmental and human health risks. Oversight depends on the product, its intended use, and the applicable law.

Regulations and guidance serve different purposes. Regulations establish legally enforceable requirements within their scope. Guidance generally explains an agency's current thinking and recommends ways to meet requirements. Employees must recognize this difference and check whether a document applies to their work. The Code of Federal Regulations (CFR) organizes federal regulations. The electronic version, the eCFR, helps users locate updated regulatory text.

Different activities require different controls. Current good manufacturing practice (cGMP) addresses the consistent manufacture of products that meet applicable quality requirements. Good laboratory practice (GLP) addresses the quality and integrity of covered nonclinical safety studies. Good clinical practice (GCP) supports ethical research involving people and reliable clinical trial results. These practices serve related purposes, but they do not apply to every activity in the same way.

Food safety systems also emphasize prevention. Hazard analysis and critical control point (HACCP) systems identify significant hazards and establish controls at essential process steps. Agricultural biotechnology requires careful evaluation of the specific organism, trait, and intended use. A genetically engineered crop may involve more than one agency because food safety, plant health, and pesticide risks are different areas of responsibility.

Across these settings, regulation and quality systems work together to reduce preventable harm. Employees contribute by following applicable procedures, maintaining accurate records, reporting concerns, and checking requirements before making decisions. These actions protect patients, research participants, consumers, and communities.

Key Terms

Food and Drug Administration (FDA)	United States Department of Agriculture (USDA)	Environmental Protection Agency (EPA)
Regulation	Guidance document	Rulemaking
Federal Register	Code of Federal Regulations (CFR)	Electronic Code of Federal Regulations (eCFR)
Current good manufacturing practice (cGMP)	Good laboratory practice (GLP)	Good clinical practice (GCP)
Standard operating procedure (SOP)	Informed consent	Institutional review board (IRB)

International harmonization	Hazard analysis and critical control point (HACCP)	Critical control point
Genetically modified organism (GMO)	Plant-incorporated protectant (PIP)	Food Safety Modernization Act (FSMA)

Review Questions

1. What are two reasons that regulations develop or change over time?

2. What is the FDA's general role in protecting public health?

3. How does a federal law differ from a regulation issued by an agency?

4. How does an FDA guidance document differ from a binding regulation?

5. What is the purpose of the CFR, and how can the eCFR help employees locate requirements?

6. What is the main purpose of cGMP?

7. How do GLP and GCP differ in the activities they address?

8. What are the purposes of informed consent and IRB review?

9. What is the purpose of a HACCP system?

10. Why might FDA, USDA, and EPA have different responsibilities for the same genetically engineered crop?

Apply Your Knowledge

The following situations are hypothetical teaching scenarios.

1. A manufacturer discovers that employees used different mixing times while preparing a medicine. A supervisor suggests releasing the batch if the finished product passes its laboratory tests. Explain why passing those tests may not provide enough assurance of quality. What process information and records should the quality team review before making a decision?

2. A biotechnology company conducts an early exploratory experiment, a nonclinical safety study intended to support an FDA application, and a clinical trial involving volunteers. A new employee says that GLP applies to all three because each involves scientific research. Explain the problem with that statement and identify the quality or ethical considerations the team should investigate for each activity.

3. An employee reads an FDA guidance document and concludes that every recommendation is a legal requirement. Another employee decides that guidance can be ignored because it is generally nonbinding. Explain why both conclusions are incomplete. Describe how the employees should determine which requirements and recommendations apply.

4. A juice processor finds that a pasteurization step did not meet its established critical limit. The affected juice has not been shipped. Explain what the team should do with the product, which records it should review, and why correcting the equipment alone may not be enough.

5. A company develops corn that produces a protein intended to control an insect pest. Its marketing team assumes that completing an FDA food safety consultation addresses every federal oversight question. Explain why this assumption is incomplete. Identify the food safety, plant health, and pesticide questions the company should investigate.

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12: DRUG DEVELOPMENT, APPROVAL, AND POSTMARKET OVERSIGHT

Learning Objectives

After completing this chapter, you should be able to:

- Describe how discovery, nonclinical studies, clinical trials, and FDA review contribute to drug development.
- Distinguish the purposes of an IND, NDA, BLA, and ANDA.
- Compare the purposes of the three main clinical trial phases and explain how researchers protect participants.
- Explain how manufacturing controls, quality assurance, and quality control support reliable study material and commercial batches.
- Distinguish selected FDA review programs and designations from marketing approval.
- Use complaint and lot records to explain how a manufacturer investigates a problem and defines recall scope.
- Distinguish recall classes, inspection observations, warning letters, and consent decrees.

A team has found an enzyme that may help people with a rare disease. Cells in the lab respond as researchers hoped. Before the first patient receives it, the team must answer two questions. Does the evidence support testing the enzyme in people? Can the team make a supply that consistently meets its quality requirements? Years later, a pharmacist who reports particles in an approved vial depends on the same kind of careful records the team began keeping in the lab.

12.1: From Discovery to the Market

12.2: Discovery and Nonclinical Development

12.3: Clinical Development and Participant Protection

12.4: FDA Marketing Review and Other Pathways

12.5: Manufacturing Quality and Contamination Prevention

12.6: Postmarket Monitoring and Recall Decisions

12.7: Inspections and Enforcement

12.8: Case Study McNeil Recalls and FDA Oversight

12.9: Chapter Summary

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12.1: From Discovery to the Market

This work can take years. The time, cost, and chance of success depend on the product, the disease, and the development plan. A team may stop development when the risks are too high, the benefits are too small, or the product cannot be made reliably.

The drug substance is the active material. It is often called the **active pharmaceutical ingredient** (API). The **drug product** is the finished form a patient receives, such as a tablet or an injectable solution. A **therapeutic biological product** can be a medicine such as a therapeutic protein or antibody. The term **biopharmaceutical** often refers to a medicine made using biological systems or biotechnology.

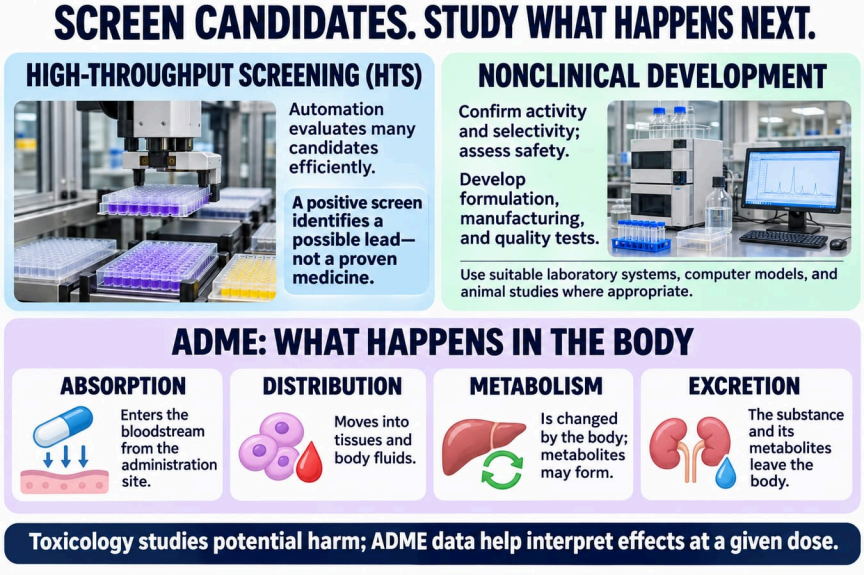


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12.2: Discovery and Nonclinical Development

Discovery can start with a clue about how a disease works. If a disease involves an overactive receptor, for example, researchers might look for a compound that blocks it. They may search collections of compounds, study substances from natural sources, or design candidates around a specific target.

High-throughput screening (HTS) uses automated methods to evaluate many



compounds or biological candidates efficiently. A positive screening result identifies a possible lead, not a proven medicine. Researchers must confirm the result and examine selectivity, activity, safety, and other properties.

During nonclinical development, researchers study the candidate's activity and safety using suitable laboratory systems, computer models, and animal studies where appropriate. They also develop the formulation, the manufacturing process, and tests for properties such as identity, purity, potency, and stability.

Nonclinical studies help characterize biological activity, toxicity, and how a candidate moves through the body. Appropriate studies can examine:

Absorption — How the substance enters the bloodstream from the administration site.

Distribution — How it moves into tissues and body fluids.

Metabolism — How the body changes the substance and what metabolites are formed.

Excretion — How the substance and its metabolites leave the body.

Together, these processes are called ADME. They help explain what happens to a drug in the body over time. **Toxicology** looks at the harm a candidate might cause. A toxicologist may use ADME data to help interpret why an effect occurs at a particular dose.

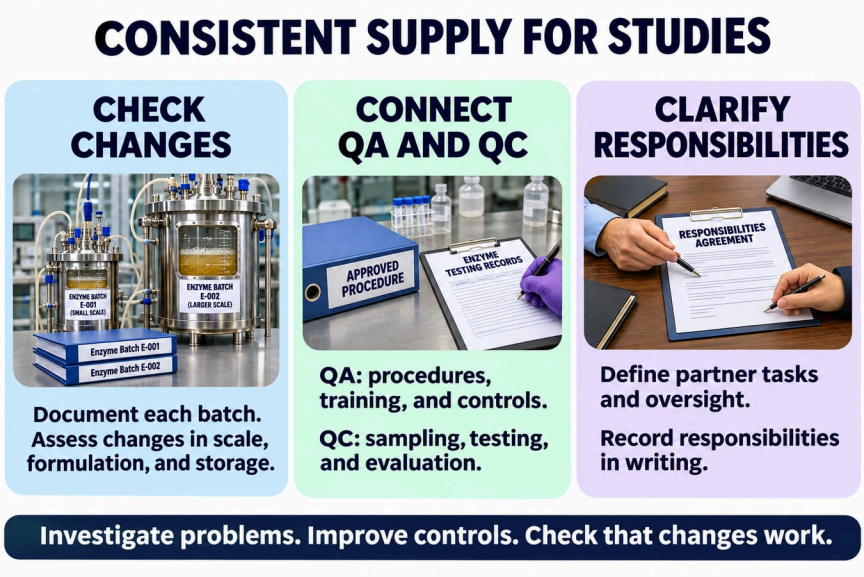
For covered U.S. studies, the sponsor generally submits an **investigational new drug application** (IND). The submission describes the relevant nonclinical findings, how the study material will be made and controlled, and how the study will be run, including plans to protect participants.

Making a Consistent Supply for Studies

As the studies progress, the manufacturing team needs to know how each supply of study material was made. A change in formulation, production scale, or storage can affect the material. Comparing supplies helps the team judge whether results from

earlier studies still apply.

Imagine a team developing a therapeutic enzyme made by cultured cells. Early experiments may need only a small amount. A clinical trial needs enough material for participants, with records showing its identity, quality, and handling. Commercial production may require many batches. In a larger vessel, the cells may experience different mixing or temperature conditions, so the team checks whether the enzyme still meets its specifications.



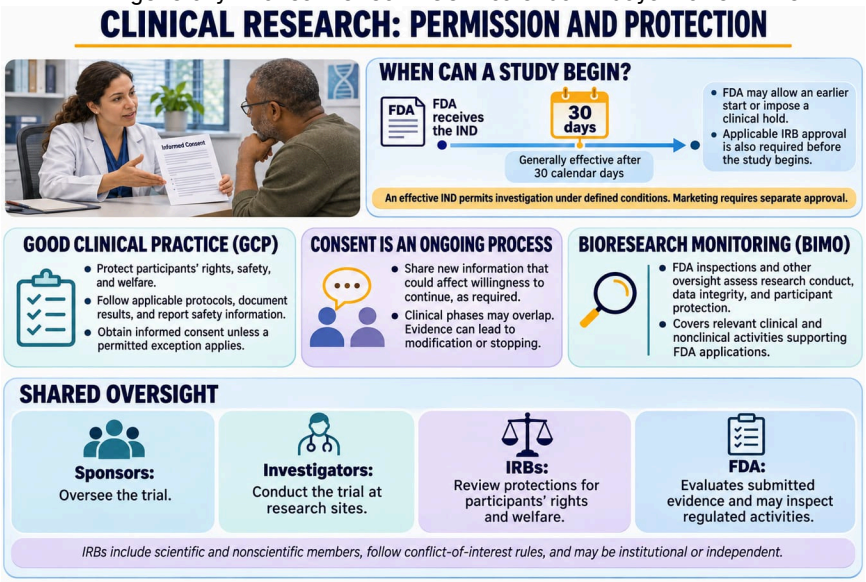
Quality assurance (QA) focuses on the systems used to plan and control work. Examples include approved procedures, training, supplier oversight, change control, and investigation processes. **Quality control** (QC) includes activities such as sampling, testing, and evaluating results against established criteria. QA and QC support one another throughout development and production.

In the enzyme example, the quality assurance team helps ensure that staff have the approved procedure and the training to follow it. Quality control staff test the enzyme against established criteria. If a result falls outside a specification, the team investigates the result and the process. **Continuous improvement** uses those findings to strengthen controls and checks whether the changes work.

A sponsor may hire a contract research organization (CRO) to carry out research activities or a contract development and manufacturing organization (CDMO) to develop a process or make the product. The parties need to define who will do each task and how the work will be overseen. Any transfer of sponsor obligations to a CRO under the IND regulations must be described in writing.

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12.3: Clinical Development and Participant Protection



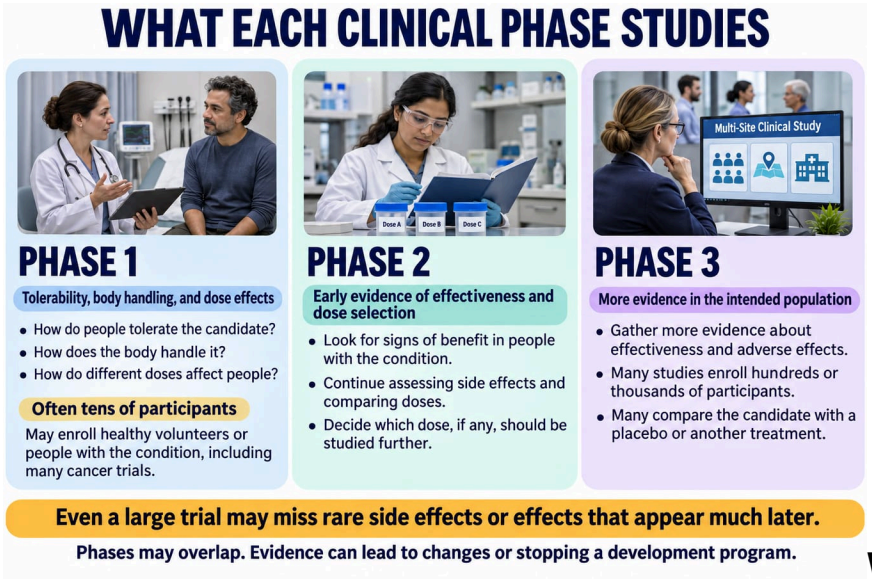
An IND generally takes effect 30 calendar days after the FDA receives it. The FDA can allow the study to begin sooner or place the investigation on clinical hold. The study also needs applicable IRB approval before it begins. An effective IND allows the drug to be studied under defined conditions. Marketing requires separate approval.

Good clinical practice (GCP) protects participants' rights, safety, and welfare and supports reliable study results. Investigators must follow applicable protocols, obtain **informed consent** unless a permitted exception applies, document results, and report safety information. Clinical phases can overlap, and a development program may be stopped or modified when evidence raises concerns.

An **institutional review board** (IRB) reviews covered research to protect participants' rights and welfare. It includes members with scientific and nonscientific backgrounds and follows conflict-of-interest rules. An IRB may be based at a research institution or operate independently.

Consent continues after a participant signs the form. If researchers learn something that could affect a person's willingness to stay in the study, they must share it as required. Investigators, sponsors, and IRBs each have a role in overseeing safety.

Sponsors oversee the trial. Investigators conduct it at research sites, and IRBs review protections for participants. The FDA evaluates submitted evidence and can inspect regulated activities.FDA's **bioresearch monitoring** (BIMO) program uses inspections and other oversight to assess research conduct, data integrity, and participant protection in studies submitted to support FDA applications. It covers relevant clinical and nonclinical activities.

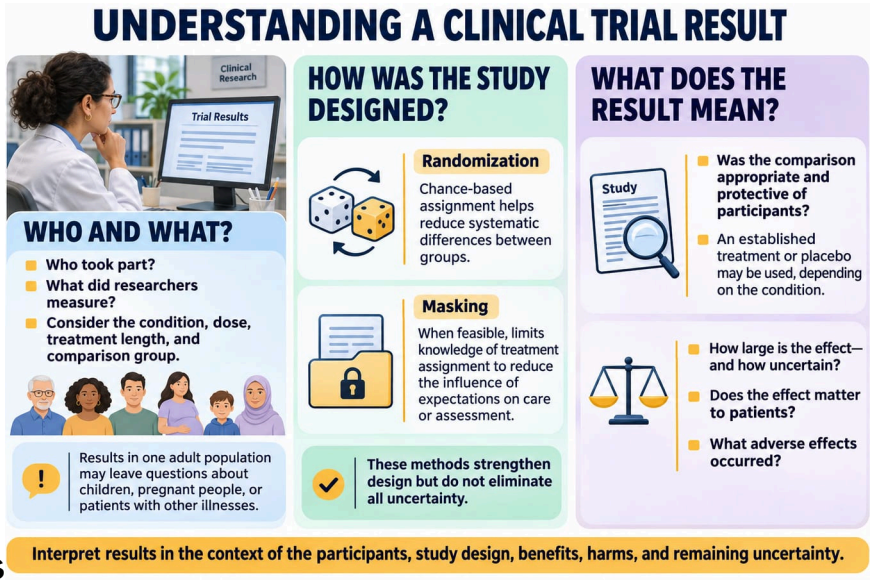


What Each Phase Studies

Phase 1 studies usually ask how people tolerate the candidate, how the body handles it, and how different doses affect them. These studies often enroll tens of participants. Some enroll healthy volunteers, while others, including many cancer trials, enroll people with the condition.

Phase 2 studies look for signs that the candidate works in people with the condition. Researchers also continue to study side effects and compare doses. The results help them decide which dose, if any, to study further.

Phase 3 studies gather more evidence about effectiveness and adverse effects in the intended population. Many enroll hundreds or thousands of participants and use a placebo or another treatment for comparison. Even a large trial may miss a rare side effect or one that appears much later.



Reading Clinical Results

To understand a trial result, first ask who took part and what the researchers measured. A study in adults with one condition may leave open questions about children, pregnant people, or patients with other illnesses. The dose, length of treatment, and comparison group also shape what the results can tell us.

Randomization assigns participants to study groups through a chance-based process, helping reduce systematic differences between groups. **Masking** limits knowledge of treatment assignment when feasible, reducing the chance that expectations influence care or assessment. These approaches strengthen study design, but they do not remove every source of uncertainty.

The comparison should fit the study question and protect participants. Depending on the condition, researchers may compare the candidate with an established treatment or a placebo. When reading the results, consider how large and uncertain the effect is, whether it matters to patients, and what adverse effects occurred.

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12.4: FDA Marketing Review and Other Pathways



A sponsor seeking approval for a proposed use generally submits a new drug application (NDA) or a **biologics license application** (BLA). FDA weighs the benefits and risks, reviews the proposed labeling, and evaluates whether the manufacturing process and facilities can consistently supply a product that meets applicable requirements.

A BLA requests FDA licensure of a biological product under the Public Health Service Act. It includes evidence supporting safety, purity, and potency, along with manufacturing and facility information. FDA's CBER or CDER reviews the application, depending on the product. Biosimilars use a separate abbreviated BLA pathway and are not approved through ANDAs.

Within the FDA, the Center for Drug Evaluation and Research (CDER) reviews most human drugs and many therapeutic biologics. The Center for Biologics Evaluation and Research (CBER) oversees products such as vaccines and many cell and gene therapies. The USDA has separate responsibilities, including oversight of many veterinary biologics.

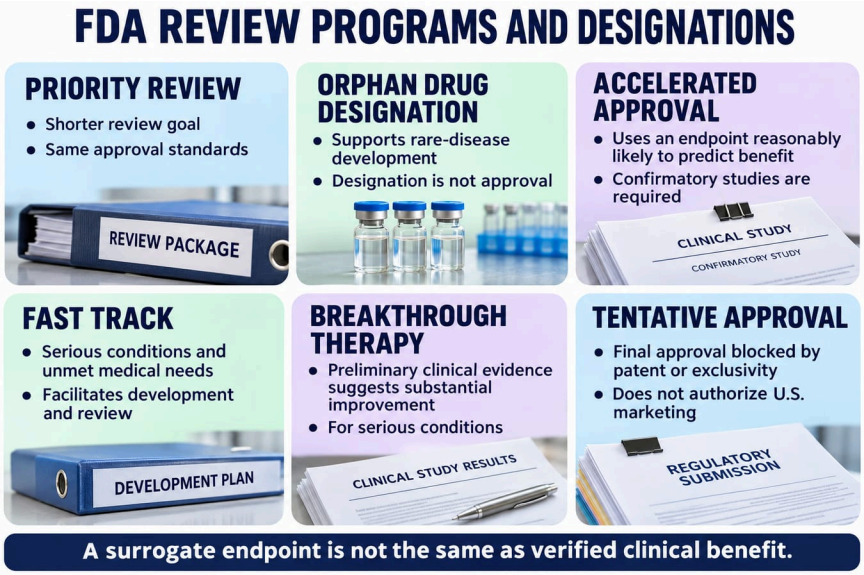
Generic and Over-the-Counter Drugs

A manufacturer typically applies to market a generic drug through an **abbreviated new drug application** (ANDA). FDA can rely on its previous finding of safety and effectiveness for the reference drug. The generic applicant still provides evidence on the product's composition, manufacturing controls, labeling, and **bioequivalence** or an applicable waiver.

Bioavailability describes how quickly and how much of an active ingredient or active moiety becomes available at its site of action. Bioequivalence compares that rate and extent for products given at the same molar dose under similar conditions. The right test depends on where and how the drug works. Blood levels may be less informative for a drug that acts locally.

Nonprescription, or over-the-counter (OTC), drugs may be marketed through an approved application or under the OTC monograph framework when all applicable conditions are met. The CARES Act of 2020 modernized the monograph system through an administrative order process. Applicable orders describe conditions such as ingredients, doses, uses, warnings, and labeling. A conforming monograph drug generally does not need an individually approved application, but manufacturing, labeling, registration, listing, and other requirements still apply.

Review Programs and Designations



Priority review — FDA gives additional attention to applications for drugs that, if approved, would offer significant improvements in the treatment, diagnosis, or prevention of serious conditions. The review goal is shorter than for standard review. Priority review does not lower approval standards.

Orphan drug designation — Supports development of drugs and biologics for rare diseases. A rare disease generally affects fewer than 200,000 people in the United States, although an alternative cost-recovery criterion exists. Designation is separate from marketing approval.

Potential orphan drug incentives include tax credits for qualifying clinical testing, certain fee exemptions, access to grants, and seven years of orphan drug exclusivity after qualifying approval. Eligibility and limitations apply. Designation does not guarantee approval, a grant, or exclusivity for every use of the product.

Accelerated approval — Allows approval for certain serious conditions based on a **surrogate endpoint**, or an intermediate clinical endpoint, reasonably likely to predict clinical benefit. Required confirmatory studies assess the anticipated benefit. FDA can withdraw approval if benefit is not verified or other requirements are not met.

Fast track — Facilitates development and review of drugs intended for serious conditions that address unmet medical needs. **Breakthrough therapy designation** is another expedited program; it requires preliminary clinical evidence suggesting substantial improvement over available therapy on a clinically significant endpoint.

Tentative approval — Indicates that an application meets applicable approval requirements but cannot yet receive final approval because of a patent or exclusivity barrier. It does not authorize U.S. marketing. Final approval is required before marketing under that application.



Accelerated approval also requires careful interpretation. An effect on a surrogate endpoint may support an expectation of clinical benefit, but the two are not identical. For example, a laboratory measurement may change before researchers know whether people feel better, function better, or live longer. The relationship must be scientifically supported for the particular setting, and the required follow-up evidence remains important.

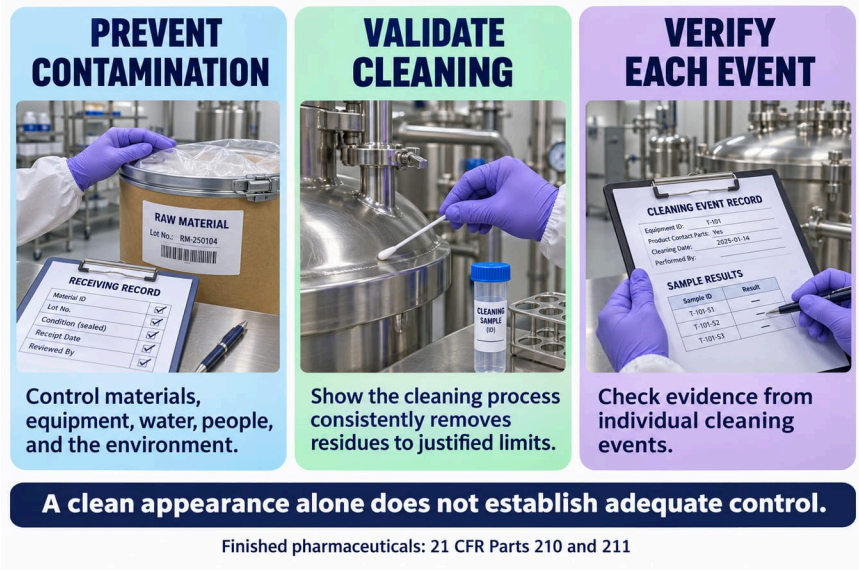
The Animal Rule

The Animal Rule allows FDA to rely on adequate and well-controlled animal studies for evidence of effectiveness in certain serious conditions when human efficacy studies are unethical and field trials are not feasible. Human safety must still be established. The requirements appear in 21 CFR Parts 314, Subpart I, and 601, Subpart H. This is not a general exemption for drugs or vaccines, and orphan designation does not waive safety or effectiveness standards.

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12.5: Manufacturing Quality and Contamination Prevention

For an approved medicine, every new batch must meet the applicable quality requirements. U.S. **current good manufacturing practice** (cGMP) requirements for finished pharmaceuticals are found in 21 CFR Parts 210 and 211. Other rules can apply depending on the product and the activity. FDA guidance explains the agency's current thinking and can help manufacturers decide how to meet applicable requirements.



Finished pharmaceuticals: 21 CFR Parts 210 and 211

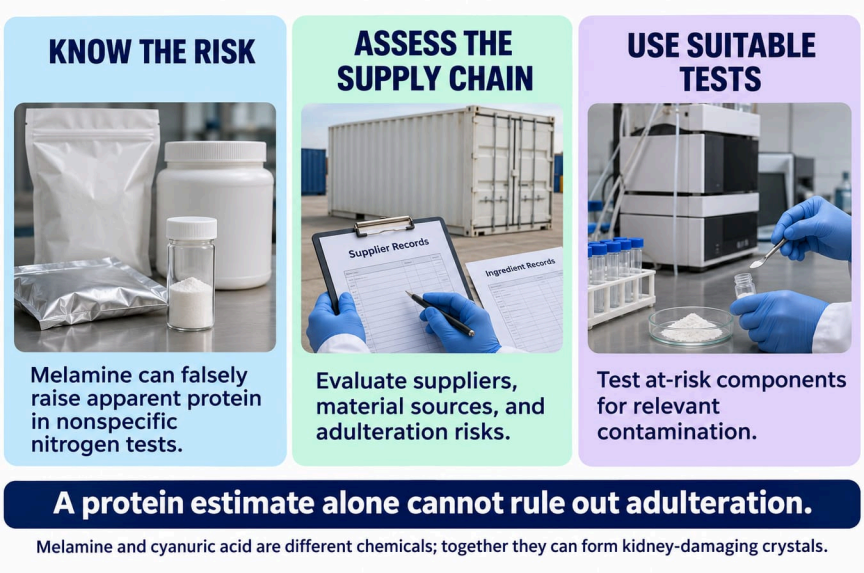
Drug contamination can arise from raw materials, equipment, water, people, packaging, or the manufacturing environment. Examples include unwanted particles, microorganisms, residues from other products, and endotoxins. Endotoxins are components of Gram-negative bacterial outer membranes; not all production organisms make them. A product may also be legally adulterated because of inadequate manufacturing controls even when a specific contaminant has not been detected.

Contamination prevention works best as a set of connected controls. Purchasing staff communicate material requirements and use approved suppliers. Receiving staff check shipment identity, condition, and handling information. Production staff follow cleaning and operating procedures. Laboratory staff use suitable methods, and quality personnel review evidence before material or product is released.

Imagine that a supplier changes the manufacturing site for an ingredient. A familiar product name does not establish that the new source has the same risks. The manufacturer should evaluate the change through its approved system, including relevant supplier information, material characteristics, and any additional testing or qualification needed. This is a hypothetical example of prevention through communication and oversight.

Cross-contamination can occur when residue from one product reaches another. A cleaning program therefore needs justified limits, suitable sampling, and methods capable of finding relevant residues. A clean appearance can be useful information, but it cannot establish that invisible chemical or microbial residues are adequately controlled.

Cleaning validation demonstrates that a defined cleaning process can consistently remove residues to justified limits. A sound program considers product carryover, cleaning-agent residues, microbial risks, equipment design, sampling, and analytical method suitability. Cleaning verification checks individual cleaning events; it is not identical to validating the process.



Documented Example

Melamine and Supplier Risk

Melamine is a nitrogen-rich industrial chemical used in products such as resins and plastics. It is different from cyanuric acid. When added fraudulently to certain food ingredients, it can make nonspecific nitrogen tests suggest a higher protein content. Exposure to contaminated products has caused serious kidney injury. Melamine and cyanuric acid together can form crystals that damage the kidneys.

FDA guidance on pharmaceutical components at risk for melamine contamination recommends evaluating the supply chain and appropriately testing at-risk components. The lesson for quality assurance is broader than a single chemical: manufacturers must understand raw-material risks and use tests that can detect relevant adulteration.

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12.6: Postmarket Monitoring and Recall Decisions

Postmarket surveillance looks for safety problems that may not have appeared in trials. Sources include reports from



patients and health professionals, required manufacturer reports, research studies, and other surveillance systems. A report does not by itself prove causation. Findings may lead to labeling changes, further studies, risk controls, recalls, or withdrawal of approval when warranted.

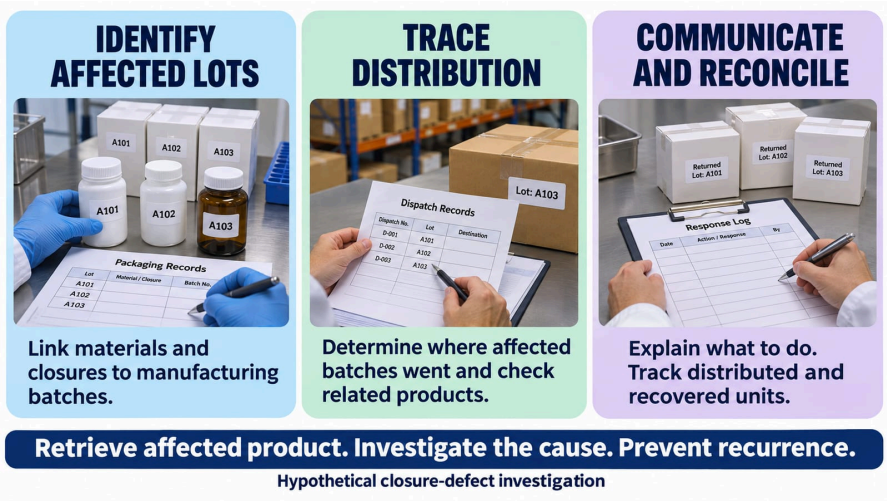
A new indication usually requires additional supporting evidence and an appropriate supplemental application before the company may market the drug for that use. Existing evidence may help, but its relevance depends on factors such as dose, route, population, and treatment duration.

After approval, a report of a problem is a signal to evaluate, not automatic proof that the product caused the event. The company may need information about the product, lot, dose, storage, other medicines, timing, and the person's condition. Missing details can make interpretation difficult, so accurate intake and follow-up processes matter.

Safety monitoring and quality investigations can overlap. For example, several complaints about unusual particles may prompt a review of retained samples, manufacturing records, packaging components, and distribution information. A reported symptom may also require safety evaluation. Different specialists contribute, and communication helps prevent a concern from being lost between departments.

Quality trends can reveal a developing problem before one result clearly fails. Increasing complaints about leaking containers, for example, may justify closer examination even if individual laboratory results remain acceptable. The response should be based on the pattern, product risks, and available evidence rather than waiting for confirmed harm. This example is hypothetical.

Tracing an Affected Batch



Hypothetical closure-defect investigation

Traceability is the ability to follow materials and products through manufacturing and distribution records. A recall investigation uses these records to identify affected lots and determine where they went. Useful identifiers include strength, dosage form, lot number, package size, and expiration date.

Consider a hypothetical investigation that links a closure defect to containers used in three batches. The team must determine where those batches went and whether other products used the same closures. Manufacturing, purchasing, laboratory, warehouse, distribution, and quality personnel may all hold part of the evidence.

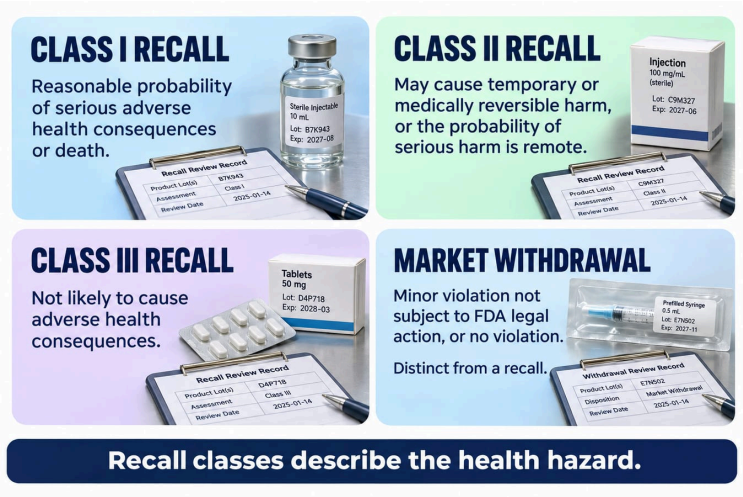
Communication must tell the intended audience how to recognize the affected product and what action to take. Staff also need to track the response and reconcile available information about distributed and recovered units. Retrieving product addresses the immediate concern, while investigation and corrective action address the conditions that allowed it to occur.

A recall can protect people while creating difficult practical consequences. Patients and caregivers may need clear information, and health professionals may need to help identify alternatives. These human effects show why prevention, timely investigation, and accurate records matter long before a recall is considered.

Most drug recalls are voluntary, initiated by a company or requested by FDA. FDA lacks broad mandatory recall authority for most drugs, but it has specific authority for certain controlled substances when statutory serious-risk criteria are met. Other product categories have their own authorities. Therefore, the statement that FDA can never order a drug recall is too broad.

The existence and scope of mandatory recall authority depend on the product and legal provision. Do not assume that a food or device authority applies to all medicines.

Recall Classes



Class I recall — There is a reasonable probability that use of, or exposure to, the product will cause serious adverse health consequences or death.

Class II recall — Use of, or exposure to, the product may cause temporary or medically reversible adverse health consequences, or the probability of serious adverse health consequences is remote.

Class III recall — Use of, or exposure to, the product is not likely to cause adverse health consequences.

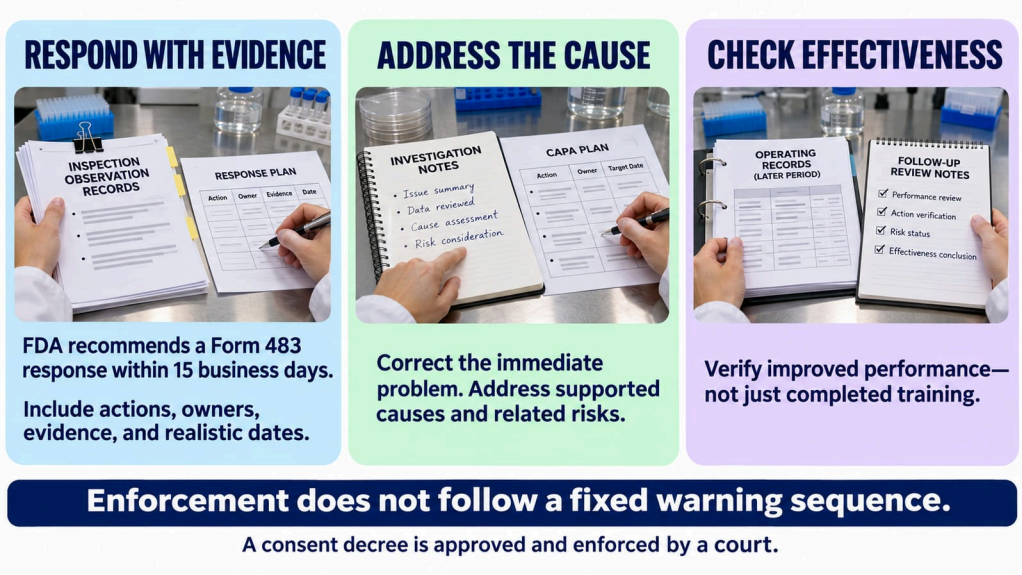
Market withdrawal — A company removes or corrects a marketed product for a minor violation that would not be subject to FDA legal action, or for a reason involving no violation. A withdrawal is distinct from a recall. A tampering incident must be assessed on its facts; the term does not automatically apply to every tampering event.

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12.7: Inspections and Enforcement

FDA has legal authority to inspect covered pharmaceutical establishments and examine relevant records. Inspections may evaluate whether a facility follows cGMP and whether its systems consistently produce products that meet requirements. Manufacturers should maintain readiness through routine quality practices rather than preparing only when an inspection is expected.

Inspection coverage depends on the product, facility, and risks. For example, an inspector may examine a pharmaceutical water system, equipment cleaning, laboratory controls, deviation investigations, supplier qualification, and batch release decisions. Guidance and inspection manuals help explain FDA approaches but do not replace applicable law.



A drug can be legally adulterated because its manufacturing methods, facilities, or controls fail to meet cGMP requirements even without a demonstrated defect in a tested batch. Depending on the circumstances, enforcement can include court-ordered corrective actions, restrictions on manufacturing or distribution, and criminal proceedings pursued through the Department of Justice.

At the end of an inspection, investigators may issue **Form FDA 483**, Inspectional Observations, when they observe conditions that may violate the laws FDA administers. The form communicates significant observations to facility management; it is not a final agency determination of compliance.

A **warning letter** is a separate advisory action describing violations FDA has identified and requesting corrective action. It may follow an inspection or other evidence. A Form 483 does not automatically lead to a warning letter, and a warning letter is not required before every enforcement action.

FDA may also issue public communications or recommend legal action. Court proceedings, including injunctions, seizures, and criminal prosecutions, involve the Department of Justice and the courts. Serious or persistent problems may justify action without a fixed sequence of warnings.

FDA recommends a written response to Form 483 observations within 15 business days. A useful response addresses the investigation, root cause, immediate corrections, **corrective and preventive actions** (CAPA), supporting evidence, and realistic completion dates. This response period is not a grace period that prevents enforcement or a requirement to finish every complex correction in 15 days. Follow the specific instructions in any FDA correspondence.

A strong investigation response connects a finding to evidence, actions, responsibilities, and follow-up. Immediate correction addresses the problem at hand. Corrective action addresses a supported cause so the problem is less likely to recur. Broader preventive work may address similar vulnerabilities in other processes or sites.

Effectiveness checks ask whether the action achieved its purpose. Counting how many employees attended retraining may show completion of training but not improved performance. Reviewing later records, observing practice, and monitoring repeat events can provide more direct evidence. Measures and follow-up timing should fit the problem and risks.

A **consent decree** is a court-entered agreement resolving a legal action. In an FDA enforcement case, the United States and the defendants agree to terms that a federal court approves and enforces. The decree may require corrective work, independent expert review, reporting, or restrictions on operations. It is not simply a notice issued by FDA after a fixed number of inspection findings.

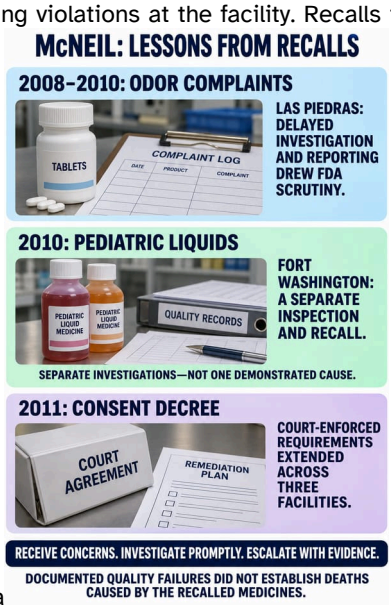
Terms vary by case and may include reimbursement of inspection costs, deadlines, and penalties for noncompliance. Operations may be restricted until specified conditions are met. Changes to, or termination of, a decree depend on its terms and the court; compliance does not automatically end the order.

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12.8: Case Study McNeil Recalls and FDA Oversight

In 2008, complaints about a musty odor in certain Tylenol Arthritis products reached McNeil. An odor complaint might initially appear to be a narrow product issue. It was also information that needed a timely, documented investigation: which products were involved, what they had in common, and whether the concern pointed to a wider quality problem. FDA later documented concerns about the timeliness of McNeil's investigation and reporting.

By January 2010, the response had become a regulatory concern. A Form FDA 483 issued for McNeil's Las Piedras facility on January 8 described observations connected with the odor complaints and reporting. A warning letter that month addressed manufacturing violations at the facility. Recalls involving odor and quality concerns affected several OTC brands. To understand



the scope, a customer or investigator needed more than a brand name; lot numbers, dosage forms, and dates identified which products were involved.

A separate problem then drew attention to McNeil's Fort Washington facility. An April 2010 inspection documented manufacturing and quality-system concerns involving pediatric liquid products. McNeil recalled affected infant and children's medicines sold under the Tylenol, Motrin, Zyrtec, and Benadryl brands. These concerns involved a different facility and investigation and should not be merged with the earlier odor issue as if they had one demonstrated cause.

For families using familiar medicines, the recalls created a practical need to identify affected products and understand the recall instructions. For a manufacturer, answering those questions depends on records connecting ingredients, production, packaging, and distribution. This is the quality lesson of the events; the source documents do not establish the experiences of particular families.

On September 30, 2010, FDA Principal Deputy Commissioner Joshua Sharfstein described McNeil's quality failures and FDA oversight in testimony before a House committee. The testimony addressed delayed investigations and reporting. It also stated that the information available at that time did not establish an overall direct link between a recalled product and a serious adverse event, including death. That limitation matters: the documented quality failures should not be presented as proof of deaths caused by the recalled medicines.

In 2011, a federal consent decree imposed requirements on McNeil operations at three facilities. The story had moved from complaints and inspections to court-enforced remediation. The decree illustrates how recurring weaknesses in manufacturing controls, investigation, reporting, and oversight can require a response extending across operations.

The case does not show that every complaint predicts a major recall. It shows why a quality system needs a reliable way to receive concerns, investigate them, recognize related events, and escalate decisions. Laboratory results are part of that system, but they cannot replace timely communication or management accountability. The historical enforcement record also should not be used as a complete statement of FDA's current recall authority.

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12.9: Chapter Summary

A medicine moves from discovery through nonclinical and clinical studies, FDA review, and oversight after approval. The evidence at each stage helps teams decide whether to continue, change direction, or stop. An IND supports covered research in people. Marketing applications ask FDA to evaluate the evidence, labeling, and manufacturing controls for a proposed product and use.

Quality assurance supports consistent work through procedures, training, and oversight. Quality control checks materials and products against requirements. After approval, complaint patterns and safety reports can prompt investigations. Traceability helps the team identify affected lots and contact the people who received them. The McNeil case shows why timely investigations, management follow-through, and checks on corrective actions matter.

Key Terms

active pharmaceutical ingredient (API)	drug product	therapeutic biological product
biopharmaceutical	quality assurance (QA)	quality control (QC)
high-throughput screening (HTS)	ADME	toxicology
investigational new drug application (IND)	good clinical practice (GCP)	institutional review board (IRB)
informed consent	randomization	masking
bioresearch monitoring (BIMO)	new drug application (NDA)	biologics license application (BLA)
abbreviated new drug application (ANDA)	bioavailability	bioequivalence
priority review	orphan drug designation	accelerated approval
surrogate endpoint	fast track	breakthrough therapy designation
tentative approval	cross-contamination	cleaning validation
postmarket surveillance	traceability	Form FDA 483

warning letter	consent decree	corrective and preventive actions (CAPA)
continuous improvement	current good manufacturing practice (cGMP)	

Review Questions

1. How do a drug substance and a finished drug product differ?

2. What does ADME stand for, and what does it help researchers understand?

3. What three types of information does an IND provide?

4. What questions do Phases 1, 2, and 3 generally address?

5. How do informed consent and IRB review protect participants?

6. What does FDA evaluate in an NDA or BLA? How does an ANDA use evidence about a reference drug?

7. How do priority review, accelerated approval, and orphan designation differ?

8. How do supplier controls and cleaning validation help prevent contamination?

9. How can traceability help a manufacturer define the scope of a recall?

10. How do Class I, II, and III recalls differ?

11. What are the purposes of Form FDA 483, a warning letter, and a consent decree?

Apply Your Understanding

1. A candidate enzyme shows promising activity in cultured cells. A manager wants to begin giving it to volunteers immediately. Identify the additional evidence, manufacturing information, and participant protections that should be addressed before a covered clinical investigation begins.

2. A team plans to transfer production of a clinical study material to a larger vessel. Explain why scale-up is more than a change in volume. What information could help determine whether material made at the new scale remains suitable for the study?

3. A hypothetical candidate improves a laboratory marker but causes frequent severe side effects. Explain why the marker alone does not settle the benefit-risk question. What additional information would help interpret the findings?

4. A manufacturer detects residue from a previous product after cleaning shared equipment. The next batch passes its final tests. Explain why those tests alone do not settle the concern and identify evidence needed before a disposition decision.

5. An inspection ends with one Form FDA 483 observation about incomplete investigations. Management calls it minor because there is only one observation. Explain why this reasoning is inadequate and propose a response with evidence, actions, responsibilities, and effectiveness checks.

6. Using the documented McNeil case, identify two points where stronger investigation, communication, or management oversight could have improved the response. Propose two measures that would help evaluate whether complaint handling is improving.

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13: QUALITY DOCUMENTATION

Learning Objectives

After completing this chapter, you should be able to:

- Describe the purposes of instructions, data records, and quality commitments.
- Explain the roles of laboratory notebooks, SOPs, forms, logs, labels, training records, master batch records, and completed batch records.
- Apply **good documentation practice**s to paper and electronic records.
- Distinguish a performer's signature, **independent verification**, record review, and release authorization.
- Explain how change control, retention, and retrieval protect records throughout their life cycle.

Imagine that a laboratory result looks unusual, but the analyst who ran the test is away. Can someone else find the method, check the calculations, and understand what happened? Good documentation makes that possible. This chapter explains how instructions and records help biotechnology teams work consistently, investigate problems, and make decisions they can support with evidence.

13.1: The Importance of Documentation

13.2: Types of Documentation

13.3: Good Documentation Practices

13.4: Signatures and Independent Verification

13.5: Laboratory Notebooks

13.6: Standard Operating Procedures

13.7: Forms, Protocols & Reports

13.8: Reports

13.9: Equipment and Instrument Logbooks

13.10: Instrument and Computer Records

13.11: Analytical Laboratory Documentation

13.12: Identification Systems and Labels

13.13: Chain of Custody

13.14: Training Records

13.15: Master and Completed Batch Records

13.16: Regulatory Submissions and Product Release

13.17: Electronic Documentation

13.18: Managing Changes in Documentation

13.19: Storage Retention and Retrieval

13.20: Documentation Requirements and Oversight

13.21: Chapter Summary

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13.1: The Importance of Documentation

Documentation helps people understand what to do, what actually happened, and why a decision was made. A useful record tells the reader which work was performed, which materials and methods were used, who was involved, and when it took place. It also captures changes and unexpected events that may affect the result.

Traceability is the ability to follow an item's history, use, or location through records. For a production batch, those records can connect raw materials and components to equipment, processing, samples, test results, labels, packaging, and distribution. Together, they allow a reviewer to reconstruct the batch's history.

When a complaint arrives or a result fails, staff turn to these records to identify the affected work and decide what to do next. Before releasing a product, authorized personnel must review the evidence and determine whether the applicable specifications and manufacturing requirements have been met. Any unresolved issues need evaluation through the quality system before a disposition decision.

The requirements for documentation come from regulations, standards, contracts, and the organization's procedures. For finished



pharmaceuticals, 21 CFR Part 211 is an important source. Good laboratory practice studies, clinical research, and medical devices have additional or different requirements. For devices, the Quality Management System Regulation became effective on February 2, 2026.

You may hear the saying, "If it isn't documented, it wasn't done." The point is that other people need evidence of the work. A missing record can leave a company unable to show what happened or whether requirements were met. The response is to report and investigate the gap, never to invent an entry.

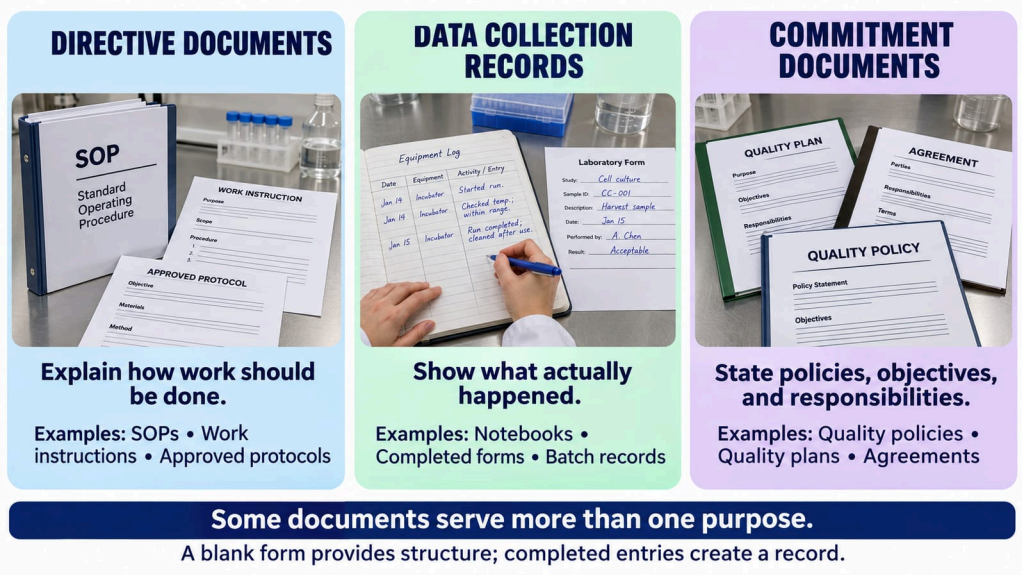
A small company may use a simpler system than a large manufacturer, but it still needs to meet its applicable obligations. Clear forms, practical procedures, and suitable electronic tools can make accurate recording easier. Poor records create extra work and may delay decisions, weaken conclusions, or lead to regulatory action.

Documentation also supports research accountability, agreements, and intellectual property matters. Its value depends on the record and the circumstances; a notebook entry alone does not settle ownership or create a contract.

People rely on records long after a task is finished. A colleague may need to repeat an experiment, a quality reviewer may need to assess a batch, or an investigator may need to trace a complaint. Writing with those future readers in mind makes documentation more useful.

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13.2: Types of Documentation



The following three categories help organize the documents used in this chapter. They describe common purposes, and some documents serve more than one purpose.

Directive documents explain how work should be done. SOPs, work instructions, approved protocols, and master production instructions belong in this group.

Data collection records show what actually happened. Examples include laboratory notebooks, completed forms, equipment logs, batch records, instrument files, and chain-of-custody records. A blank form provides the structure; completed entries turn it into a record of the activity.

Commitment documents describe the organization's policies, objectives, responsibilities, and quality arrangements. Quality policies, quality plans, and relevant agreements help employees understand what the organization has committed to doing.

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13.3: Good Documentation Practices

Good documentation practice supports complete, trustworthy records. It is sometimes abbreviated GDocP to distinguish it from good distribution practice. FDA's drug cGMP data integrity guidance describes the importance of complete, consistent, and accurate information.

A common teaching aid is **ALCOA**: attributable, legible, c



ontemporaneous, original or a true copy, and accurate. Attributable means the record identifies who performed an activity. Contemporaneous means information is recorded when the activity occurs. A true copy preserves the content and meaning of the original, including relevant context.

The expanded expression ALCOA plus also emphasizes completeness, consistency, endurance, and availability. These principles guide sound practices; they do not replace the requirements that apply to a specific record.

For paper records, use the approved form or notebook and a permanent writing method specified by the procedure. Make entries readable, identify the sample or batch, include units, and use a clear date format. Record times when they matter to the activity. Do not pre-record results, backdate entries, sign for another person, or use unofficial scraps as a substitute for required records.



Correct an error without hiding the original entry. A typical paper correction uses a single line through the error, the correct information, and the person's initials or signature and date. Add the reason when it is not obvious or when the procedure requires it. Do not erase, use correction fluid, or

remove a page to conceal an error.

Electronic corrections must preserve the original information and the history of the change through appropriate controls and audit trails. A correction is permitted when justified and traceable; an unrecorded alteration is not. **Report** missing data, late entries, or errors through the approved process. A late entry must identify when it was actually made and the source of the information rather than pretending to be contemporaneous.

Use the approved convention for blank or inapplicable fields. For example, enter N/A with any required explanation rather than leaving an ambiguous blank. Never invent a result to complete a form. Repeated tests, failed runs, deviations, and invalidated results must be retained and assessed as required; selecting only favorable results undermines data integrity.

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13.4: Signatures and Independent Verification



A signature or initial has a defined meaning. It may identify the person who performed a step, the person who independently checked it, the person who reviewed a record, or the person who approved a decision. These actions are different and should have separate fields where needed.

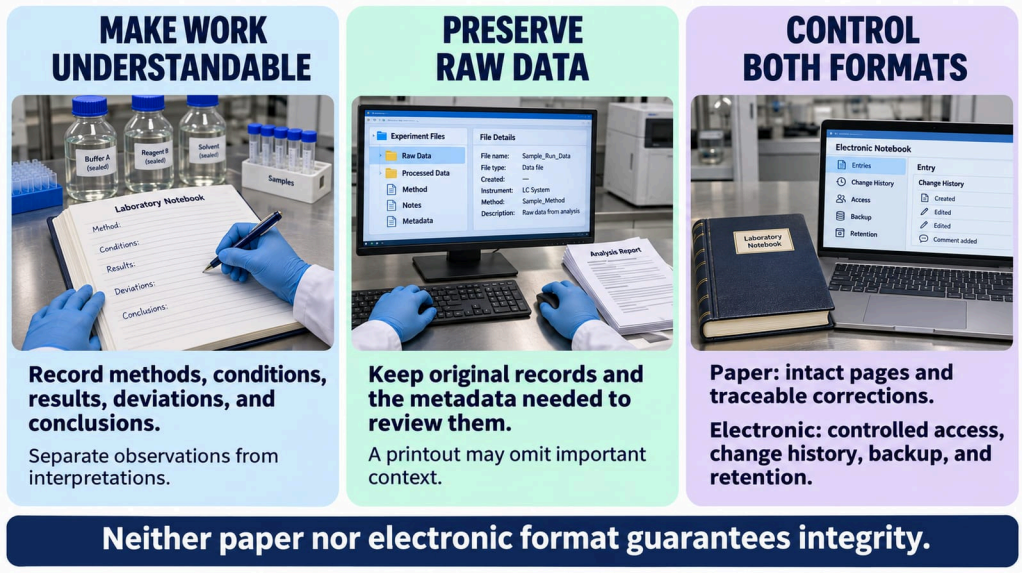
Independent verification must be performed by a suitably qualified person using the method and timing required by the procedure and applicable regulation. Some steps require observation as the activity occurs; others permit checking records or calculations afterward. Do not sign a witness field simply because a coworker says the work was correct.

For finished pharmaceuticals, regulations address independent checks of master records and identification of people performing, supervising, or checking significant batch steps. Specific requirements vary with the activity and permitted automated controls. There is no general rule that every laboratory entry needs a supervisor's signature.

Electronic signatures must identify the individual and have an appropriate link to the record. Shared credentials or an unverified typed name do not provide the same assurance as a controlled electronic signature. Follow the organization's procedures and applicable Part 11 requirements

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13.5: Laboratory Notebooks



Laboratory notebooks record research plans, methods, observations, data references, calculations, and interpretations. A paper notebook may be assigned to an individual; an electronic laboratory notebook may support individual or shared project work. Both need clear attribution and traceability.

Record enough detail for another qualified person to understand and, where feasible, reproduce the work. Include the purpose, relevant background, sample and reagent identifiers, equipment, method version, actual conditions, results, deviations, and conclusions. Distinguish a direct observation from an interpretation. Support conclusions with evidence and describe important limitations.

Raw data are the original records and information needed to reconstruct and evaluate the activity. They may include handwritten observations, instrument signals, electronic files, and associated **metadata**. Metadata explain context, such as who acquired a result, which method was used, and when a change occurred.

Protect original data and retain justified corrections. A printout is not always a complete substitute for the original electronic record. For example, an analytical file may contain processing settings or audit-trail information that is absent from a printed graph. The retention approach must preserve the information needed to understand and review the work.

For a paper notebook, keep pages intact and follow the approved approach for numbering, attachments, unused space, signatures, and review. For an electronic notebook, use controlled access, suitable change history, backup, and retention arrangements. Neither format automatically guarantees integrity.

Notebooks may support publications, regulatory submissions, or intellectual property matters. Inadequate records can make work difficult to defend or reproduce. Consequences depend on the facts and applicable rules; an untidy notebook does not automatically result in loss of a patent or a criminal penalty. Honest errors must be corrected transparently, while deliberate falsification is a serious matter.

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13.6: Standard Operating Procedures

A **standard operating procedure (SOP)** gives approved instructions for a recurring activity. SOPs can address equipment use, cleaning, sampling, testing, data review, record control, or other work. They promote consistency, support training, identify required controls, and explain how to respond when something goes wrong.

A useful SOP is clear enough for qualified personnel to follow. Use direct instructions and numbered steps when sequence matters. State relevant acceptance criteria, required records, safety precautions, and escalation steps. An SOP reduces avoidable variation but does not guarantee success under every condition.

Personnel familiar with the activity should contribute to drafting and review. Appropriate technical and quality personnel approve the document according to assigned responsibilities.



Review SOPs at defined intervals and when changes, investigations, or new requirements indicate a need.

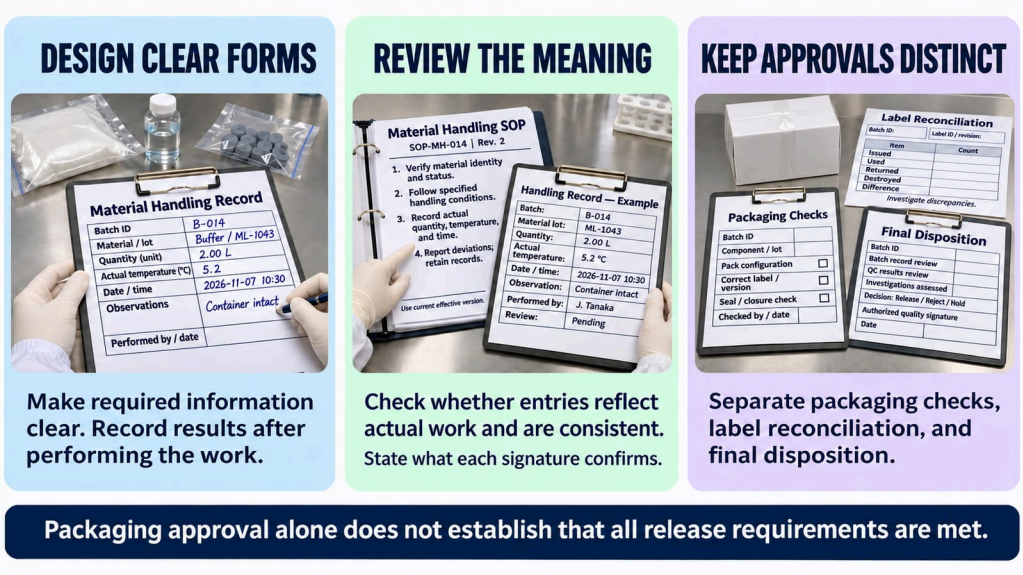
Do not allow an SOP to accommodate unspecified equipment changes without evaluation. Define approved alternatives where appropriate, and use change control when a proposed change could affect results or product quality. Train personnel before the revised procedure becomes effective when required.

Typical SOP components include a descriptive title; a unique identifier; revision and effective date; preparation, review, and approval information; purpose; scope; responsibilities; materials and equipment; precautions; calculations where needed; numbered instructions; acceptance criteria; records to complete; references; and revision history.

Only the effective, approved version should be used for current work. Withdraw obsolete working copies and prevent unintended use. Retain controlled historical versions as required so earlier work can still be interpreted.

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13.7: Forms, Protocols & Reports



A form provides a consistent way to record required information. It may capture material lot numbers, quantities, temperatures, times, observations, calculations, and signatures. A good form makes the needed information clear without encouraging someone to fill in results before performing the work.

Completing or initialing a field does not by itself prove that a procedure was followed correctly. Records must reflect actual work, and review should assess the meaning and consistency of the entries. Critical checks and authorization fields should state what the signer is confirming.

A revised packaging authorization example appears in the practice forms at the end of this workbook. It separates packaging checks from final disposition and provides space to reconcile labels. A packaging approval is not automatically evidence that all other release requirements have been met.

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13.8: Reports

A report explains completed work, its results, and the conclusions the evidence supports. It identifies the purpose, methods, people or roles involved, relevant dates, deviations, findings, and limitations. The amount of detail depends on the intended audience and requirements.

Management summaries may be shorter than regulatory or technical reports, but important limitations must remain visible. Supporting records should be traceable. Not every internal report is public, and regulatory access depends on the type of record and applicable authority.

In the Biotechnology Program, follow your instructor's directions for laboratory and research reports. A project may involve sequence analysis, a presentation, or submission to a public database when assigned. Do not assume every course requires a cloning project or GenBank submission.

Scientific reports communicate methods and evidence so others can evaluate the work and build on it. Their purpose is to report results honestly, not to persuade readers to accept a preferred hypothesis regardless of the data.

A typical scientific report includes the following sections. Course, journal, and workplace formats may differ.

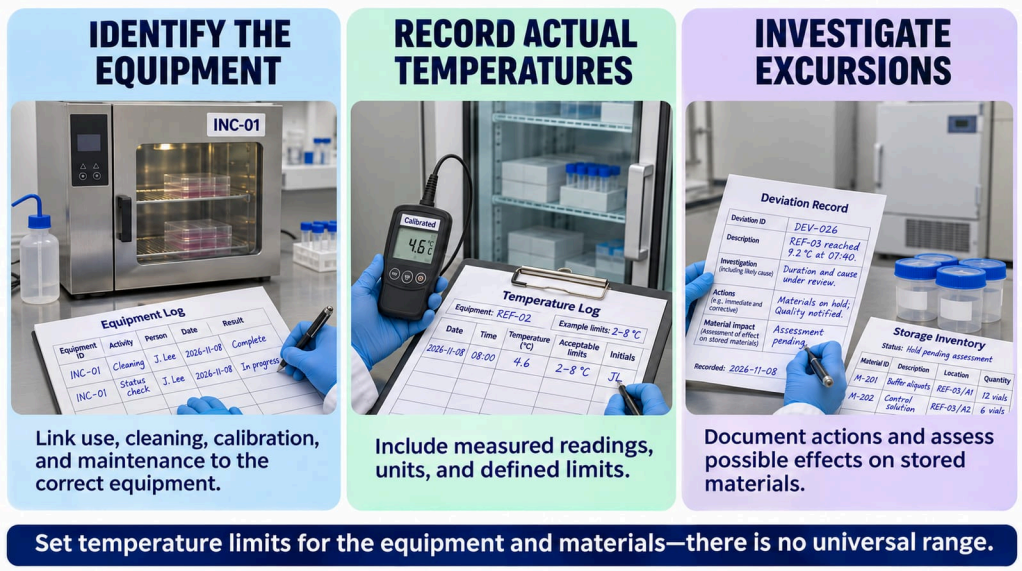
- Title — State the subject and purpose clearly.
- Abstract — Summarize the question, approach, major results, and conclusion. The required structure and length vary.



- Introduction — Explain the problem, relevant background, and objective or hypothesis.
- Materials and methods — Provide sufficient detail to evaluate and reproduce the work where feasible. Identify important changes to referenced methods.
- Results — Present findings clearly in text, tables, or figures. Reports often summarize data; the complete underlying records must remain available as required. Do not assume every raw observation belongs in a graph.
- Discussion — Interpret the findings, compare them with relevant evidence, address limitations, and explain alternative interpretations where appropriate.
- Conclusion — State what the results support and what remains uncertain. Evidence may support or fail to support a hypothesis; it rarely proves it absolutely. Statistical failure to reject a null hypothesis does not establish that the null hypothesis is true.
- References — Cite sources in the text and provide enough information for readers to locate them.

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13.9: Equipment and Instrument Logbooks



Equipment logs document relevant use, status, cleaning, calibration, maintenance, repair, and problems. They may be paper or electronic. Identify the equipment uniquely and connect the entry to the relevant activity, person, date, and result. The procedure determines which events must be recorded.

Temperature logs are used for equipment such as refrigerators, freezers, and incubators. Record actual readings with units, defined acceptable limits, and any required minimum or maximum readings. Investigate excursions and document actions and potential effects on stored materials. A log with only the headings Time 1 and Time 2 is insufficient if it does not clearly capture the measured temperatures.

A temperature log example appears in the practice forms. Its blank limits must be set for the equipment and materials; there is no single acceptable temperature range for all storage units.

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13.10: Instrument and Computer Records

Instrument records may include printouts, original electronic data, processing methods, calculations, system logs, and audit trails. Identify the instrument, sample or batch where relevant, date and time, operator, and method. Preserve relationships between these records.

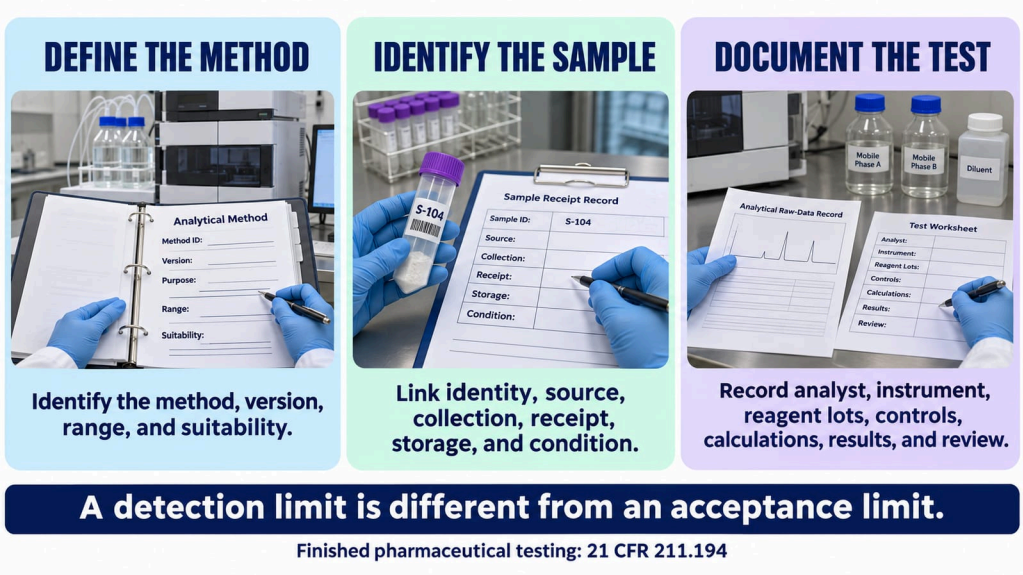
Attach paper outputs securely or store them in a controlled location referenced by the notebook or test record. Identify attachments so they can be matched to their source if separated. Protect fading or fragile outputs through an appropriate verified copy process while retaining what the applicable requirements demand.

Automated monitoring can provide continuous information about temperatures or other conditions. A data stream is useful only when the system is suitable, time settings are controlled, relevant alarms are addressed, and records are reviewed. A lack of an alarm is not proof that every condition remained acceptable.

Computer systems can control instruments, acquire and analyze data, manage samples, store procedures, and support review. Appropriate controls include access permissions, unique user accounts, validated or otherwise suitably assured operation, backups, recovery arrangements, and protection against unauthorized changes. Electronic documentation is compatible with regulated work when the applicable controls are in place.

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13.11: Analytical Laboratory Documentation



Analytical records describe the sample, test method, work performed, and result. An environmental laboratory may measure water pH or turbidity; a clinical laboratory may measure blood components; a pharmaceutical QC laboratory may assess drug potency or impurities. Applicable requirements differ, but results need adequate supporting evidence.

Method information can include the method identifier and version, test purpose, relevant measurement range and limits, source, suitability, and verification or validation information. A detection limit is different from an acceptance limit; specify which limit is being reported.

Sample information includes a unique identifier, source, collection method and collector, collection and receipt times where relevant, storage, condition, and disposition. Link the tested portion to the original sample.

Performance information includes the test date, analyst, instrument, reagents and lots, method, raw data, calculations, controls, results, and review. For finished pharmaceutical testing, 21 CFR 211.194 describes laboratory record requirements.

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13.12: Identification Systems and Labels

Identification systems distinguish materials, products, samples, equipment, and documents. A lot number identifies a defined lot or batch; it is not necessarily unique to each individual container. Numbers may be numeric or alphanumeric. The company's controlled system determines who assigns them and how duplication is prevented.

Retain links between internal receipt identifiers and supplier lot numbers. An internal number must not erase the supplier's identity or make it impossible to trace the material. Document identifiers and equipment identifiers serve different purposes and should follow clear conventions.

Labels communicate identity, status, handling, storage, safety, or use information. Required content depends on the item and applicable rules. A laboratory solution label may include its name, concentration, preparation date, preparer, expiration or retest date where justified, and storage conditions. Ingredient sources may be linked through preparation records rather than printed on every label.

Control label versions and issuance where required. Reconcile labels and investigate discrepancies as appropriate to the activity. Incorrect labels can cause serious errors even when the contents meet specifications.



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13.13: Chain of Custody

Chain of custody documents possession and handling of a sample from collection through receipt, transfer, testing, storage, and final disposition. It can be important for legal evidence, environmental testing, investigations, and other work requiring documented accountability.

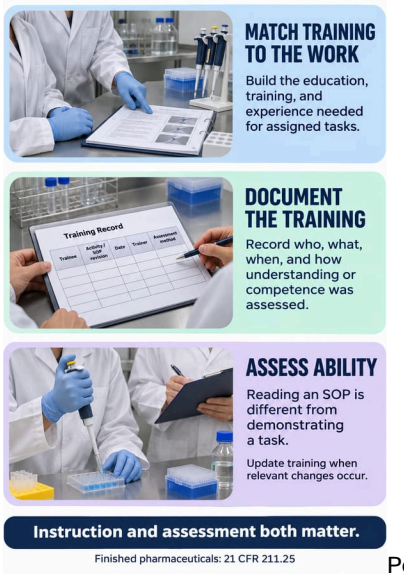
Assign a unique sample identifier and record relevant transfers, dates and times, people, locations, condition, and seal information where applicable. A tracking record and a formal chain-of-custody record are related, but their required detail may differ.

A missing transfer entry can make it difficult to show who had a sample or how it was stored. That can weaken confidence in the result.

A chain-of-custody example appears in the practice forms. Adapt its fields to the study, contract, and legal requirements.

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13.14: Training Records



Personnel must have the education, training, and experience needed for their assigned work. For finished pharmaceuticals, 21 CFR 211.25 addresses training in relevant operations and cGMP, including continuing training at sufficient frequency.

Record who was trained, the activity or document and revision, the date, the trainer where applicable, and the method used to assess understanding or competence. Reading an SOP and demonstrating the ability to perform a task are not the same assessment.

Managers and qualified trainers conduct training under the organization's assigned responsibilities, while quality personnel provide appropriate oversight. The regulation does not assign every training task to one universal job title. Training must match the work and be updated when relevant changes occur.

The training record example provides space for both instruction and assessment. Additional skills can support professional development, but training does not automatically guarantee higher pay.

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13.15: Master and Completed Batch Records

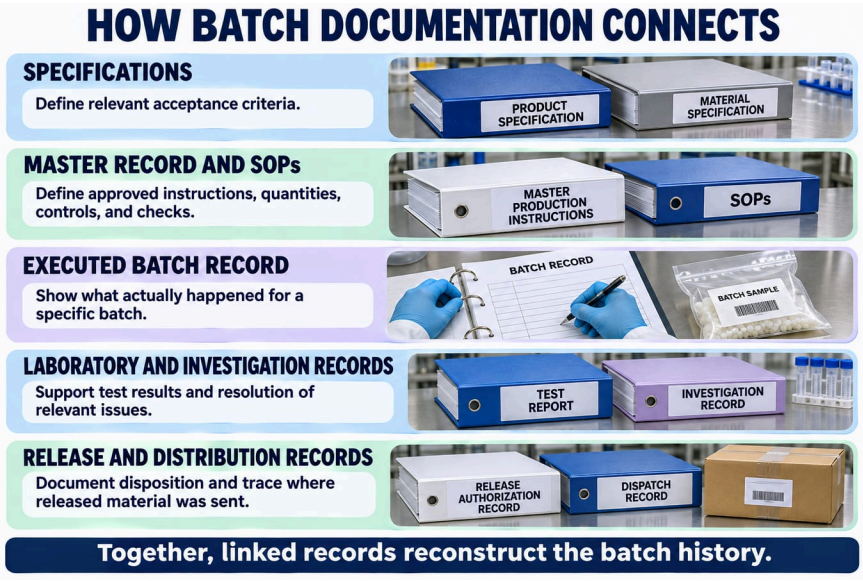
For finished pharmaceuticals, 21 CFR 211.186 addresses master production and control records. A **master batch record (MBR)** is a commonly used term for the approved instructions and information used to ensure batch-to-batch consistency. It is prepared for each product and batch size and independently checked as required.

A master record typically defines ingredients and quantities, specifications, equipment or equipment requirements, processing instructions, in-process controls, expected yields, packaging and labeling, precautions, and required checks. It may reference controlled SOPs.



A **batch production record (BPR)** documents one actual batch. Under 21 CFR 211.188, it includes an accurate reproduction of the appropriate master record, checked for accuracy, dated, and signed, together with complete production and control information. The approved master and the executed batch record have different purposes.

Issue the correct controlled record for use, whether paper or electronic. Operators enter actual information as work occurs. Significant steps identify the people performing and, where required, supervising or independently checking them. Do not sign a step before performing or verifying it.



Batch records can identify equipment; dates and

times; component names, quantities, and lot numbers; in-process results; area and line checks; actual and theoretical yields; label specimens and reconciliation; samples taken; and relevant signatures or other identification. Record applicable process limits and actual observations with units.

Supporting records may include deviations and investigations, laboratory results, environmental records, instrument files, and referenced SOPs. Records can be stored in linked systems if the complete history remains controlled and readily retrievable.

For covered finished drug batches, 21 CFR 211.180 generally requires specified batch-associated production, control, and distribution records to be retained at least one year after batch expiration. Certain exempt OTC products without expiration dating have a three-year period after distribution. Other record categories or legal obligations may require longer retention.

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13.16: Regulatory Submissions and Product Release

Regulatory submissions provide information required by an agency for a defined purpose. An investigational new drug application (IND), for example, contains relevant nonclinical, manufacturing, and clinical information for a proposed human investigation. An effective IND is not marketing approval, and applicable IRB and participant-protection requirements must also be met.

Before batch release, the authorized quality unit reviews appropriate production and control records, including packaging and labeling records, to determine whether established requirements have been met. Relevant discrepancies and failures must be investigated. The quality unit's approval or rejection authority is described in 21 CFR 211.22; production record review is addressed in 211.192.

Production, laboratory, and other staff may review records within their responsibilities. Regulations do not prescribe a universal sequence involving three directors followed by an independent Regulatory Affairs Director. The company must define qualified roles and adequate authority for its operations.

A release authorization records the batch, disposition, approving person, date, and relevant conditions or references. A **certificate of analysis (CoA)** generally reports specified tests and results. A certificate of conformity or release certificate may state conformity or release status. Their names and content vary, and a CoA is not automatically a substitute for the required release decision.

Packaging authorization must identify its scope. Approval to package or repackage a product does not itself authorize final shipment. Follow the applicable release process and investigate relevant complaints through the assigned quality system responsibilities.

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13.17: Electronic Documentation



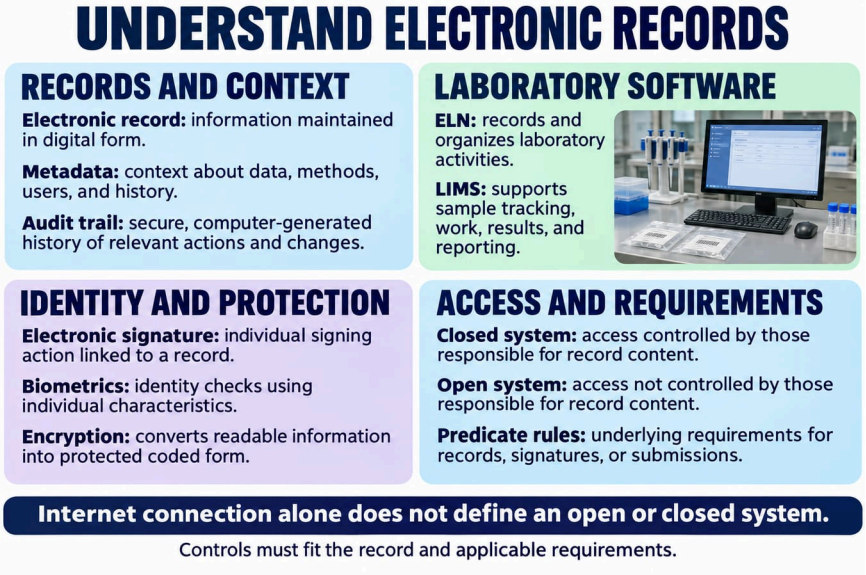
Biotechnology organizations may use paper, electronic, or hybrid records. Each system must preserve required information and support accurate review and retrieval. In a hybrid system, define which record is authoritative for each activity and how paper and electronic portions are connected.

21 CFR Part 11 sets criteria for the trustworthiness and reliability of covered electronic records and signatures. Its applicability depends on underlying record requirements and how electronic records or submissions are used. It does not automatically apply to every computer file in every laboratory [6].

FDA's 2003 scope-and-application guidance describes its interpretation and enforcement approach. Guidance does not eliminate the underlying requirements to retain accurate and complete records. Review applicable **predicate rules**, Part 11, and current guidance together.

A compliant system involves more than a software label. Evaluate intended use, suitable validation, access controls, audit trails where required, record protection, copies, retention, signatures, and personnel practices. Retain relevant metadata and the ability to review the complete record for the required period.

- Audit trail — A secure, computer-generated history that records relevant actions and changes with dates and times. Its content and review must be appropriate to the record and applicable requirements.
- Biometrics — Methods of verifying identity using measurable individual characteristics.



- Closed system — A system in which access is controlled by the people responsible for the electronic records' content. It is not defined merely by whether the computer connects to the internet.
- Electronic laboratory notebook (ELN) — Software used to record and organize laboratory activities and associated information.
- Electronic record — Information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
- Electronic signature — An individual's electronic signing action that is linked to a record and intended to serve as a legally binding equivalent of a handwritten signature when applicable requirements are met.
- Encryption — A process that converts readable information into a protected coded form. It is one security control, not a complete documentation system.
- Laboratory information management system (LIMS) — Software that supports activities such as sample tracking, work assignment, results management, and reporting.
- Metadata — Information that describes data and their context, including relevant methods, users, dates, and processing history.
- Open system — A system in which access is not controlled by the people responsible for the electronic records' content. Additional controls may be needed to protect the records.
- Predicate rules — The underlying requirements that call for records, signatures, or submissions, such as applicable cGMP regulations.

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13.18: Managing Changes in Documentation



Controlled procedures support consistency while change control enables justified improvement. A change must be assessed before implementation for its effect on product quality, safety, data integrity, validation, training, and regulatory commitments. Not every affected person must personally approve every change; the required reviewers and approvers follow defined responsibilities.

A document change request may be initiated by anyone permitted under the procedure. It identifies the current document, proposed revision, reason, impact, approvals, effective date, distribution, and training. Different organizations use different names for this record.

Document-control personnel release the approved revision and prevent unintended use of obsolete working copies. Retain historical versions and change records as required. Do not destroy completed records simply because their associated instructions have been revised.

A change notice can include the request identifier; date; initiator; document title and revision; existing and proposed wording; scientific or business justification; impact assessment; affected departments and linked documents; training and validation actions; approvals; implementation date; and confirmation that actions were completed. Cost can be included when relevant but does not replace a quality impact assessment.

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13.19: Storage Retention and Retrieval



Protect records against loss, damage, unauthorized access, and inappropriate alteration. Use suitable facilities and systems, access controls, backups, recovery plans, and periodic checks of readability and retrieval. There is no universal rule that every file must be in a locked fireproof room or that every electronic record must be retained forever.

Define retention periods by record type using applicable regulations, contracts, policies, and legal holds. Do not assume a universal five-year period. Do not destroy records while an applicable investigation, legal hold, or other obligation requires preservation.

Electronic archiving must preserve meaning and accessibility as software and storage systems change. A backup supports recovery but is not necessarily a complete archive. Migration or conversion needs appropriate verification so records, relationships, and relevant metadata remain usable. Records should be retrievable for authorized review, inspections, investigations, and other required uses. A good archive preserves the evidence needed to reconstruct activities; it is more than a storage location.

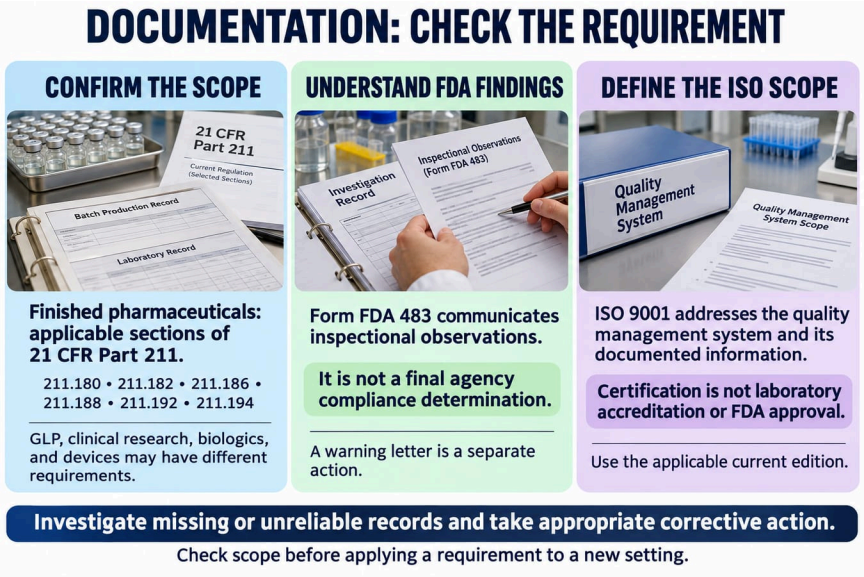
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13.20: Documentation Requirements and Oversight

For finished pharmaceuticals, review the applicable sections of 21 CFR Part 211, including 211.180, 211.182, 211.186, 211.188, 211.192, and 211.194. GLP, clinical research, biological products, and devices have additional or different requirements. Always check the scope of a requirement before applying it to a new setting.

FDA may issue Form FDA 483 to communicate inspectional observations. It is not a final agency determination of compliance. A warning letter is a separate action and does not automatically follow every Form 483. Missing, unreliable, or falsified records can be significant findings that require prompt investigation and appropriate corrective action.

ISO 9001 also requires suitable documented information for the QMS and evidence of its operation. The required detail depends on the organization and applicable requirements. ISO 9001 certification concerns the defined management system scope; it is not laboratory accreditation or FDA approval. ISO currently lists ISO 9001:2026. Historical quotations from ISO 9001:2008 should not be presented as the current requirements.



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13.21: Chapter Summary

Quality documentation connects instructions, actual work, and the evidence used to make decisions. Directive documents explain what should be done. Data collection records show what happened. Commitment documents describe policies, responsibilities, and quality arrangements. Together, they help employees perform work consistently, investigate problems, and protect the people who use biotechnology products.

Trustworthy records must preserve both results and their context. The ALCOA principles describe records that are attributable, legible, contemporaneous, original or a true copy, and accurate. ALCOA plus adds completeness, consistency, endurance, and availability. Employees should record information when work occurs, identify who performed it, and preserve all relevant results. Corrections must remain traceable and must not hide the original entry. Missing information must be reported and addressed honestly rather than replaced with invented data.

Different documents support different activities. A standard operating procedure (SOP) provides approved instructions for a recurring task. A protocol plans a study or defined evaluation. A laboratory notebook records methods, observations, calculations, and interpretations. Equipment logs, analytical records, labels, and chain-of-custody records connect results to the materials, instruments, methods, and people involved. Training records should distinguish participation in training from evidence that an employee can perform the assigned work.

Master batch records define approved production instructions and controls. Completed batch records document what actually happened for individual batches. Supporting laboratory data, investigations, label reconciliation, and other linked records help reviewers reconstruct the batch history. Performing a step, independently verifying it, reviewing a record, and authorizing release are different responsibilities. A signature must accurately represent the action taken. Completed packaging checks or a certificate of analysis alone do not establish that all release requirements have been met.

Paper, electronic, and hybrid systems all need appropriate controls. Electronic records may include raw data, metadata, processing information, and audit trails that a printout does not preserve. Unique user accounts, controlled access, suitable system assurance, and recovery arrangements help protect records. Part 11 applicability depends on the records and underlying requirements involved; it does not automatically apply to every laboratory computer file.

Document control ensures that employees use effective, approved instructions. Change control assesses proposed revisions and their effects on quality, training, related documents, and other commitments before implementation. Obsolete working copies must be controlled, while required historical instructions and completed records remain available. Retention and archiving arrangements must preserve readable, retrievable evidence for the applicable period.

Good documentation is a shared responsibility. Clear forms and procedures help employees record work accurately, while careful review identifies gaps and inconsistencies. Reliable records support sound decisions, reduce repeated work, and help organizations respond to quality concerns with evidence.

Key Terms

Quality documentation	Traceability	Directive document
Data collection record	Commitment document	Good documentation practice (GDocP)
Data integrity	ALCOA	ALCOA plus
Contemporaneous recording	True copy	Independent verification

Standard operating procedure (SOP)	Protocol	Laboratory notebook
Raw data	Metadata	Audit trail
Equipment log	Lot number	Chain of custody
Training record	Competence	Master batch record (MBR)
Batch production record (BPR)	Label reconciliation	Release authorization
Certificate of analysis (CoA)	Electronic record	Electronic signature
Electronic laboratory notebook (ELN)	Laboratory information management system (LIMS)	Predicate rules
Document control	Change control	Record retention

Review Questions

1. What are the three main purposes of quality documentation?

2. How do directive documents, data collection records, and commitment documents differ?

3. What does each letter in ALCOA represent, and what additional principles does ALCOA plus emphasize?

4. How should an employee correct a mistaken entry in a paper record without hiding the original information?

5. How does an SOP differ from a protocol?

6. What is the difference between raw data and metadata?

7. What information does a chain-of-custody record capture?

8. How does a training acknowledgment differ from evidence of competence?

9. How does a master batch record differ from a completed batch production record?

10. How do performing, independently verifying, reviewing, and authorizing an activity differ?

11. What is an audit trail, and why might a printed result be an incomplete electronic record?

12. How do document control, change control, and record retention help preserve reliable information?

Apply Your Knowledge

The following situations are hypothetical teaching scenarios.

1. A technician records a freezer temperature as −20 °C but immediately realizes the display read −12 °C. The approved range

is –25 °C to –15 °C. A coworker suggests erasing the entry and recording the usual temperature. Describe how the technician should correct the record and respond to the out-of-range reading. What evidence would help assess the possible effects on stored materials?

2. A laboratory receives a sample with the correct identifier and an intact seal, but its chain-of-custody record has no entry for an overnight transfer. Explain what is known and what remains uncertain. What information should staff seek, how should they document the gap, and what should they consider before relying on the test results?

3. An analyst finds an old printed SOP beside an instrument after completing a test. The current revision changed a sample preparation step. Describe how the team should determine which instructions were used and assess the affected work. Propose actions to prevent unintended use of obsolete copies while preserving the historical record.

4. A laboratory plans to delete original instrument files after printing the final graphs. The files contain processing settings and an audit trail that do not appear on the printouts. Explain why the printouts may be insufficient. Propose a retention approach that preserves relevant data, context, access, and the ability to review the work later.

5. An employee signed a form confirming that she read a revised SOP, but her first independent run shows that she misunderstood a critical calculation. Explain why the signature alone does not establish competence. Propose an assessment and follow-up plan that supports the employee and provides evidence of readiness for the assigned work.

6. A batch record contains all required signatures, but label reconciliation shows 500 labels issued, 470 used, 20 returned, and 5 destroyed. A supervisor asks the quality reviewer to authorize shipment because the product passed its tests. Calculate the unexplained label difference. Explain what the team should investigate and why signatures and passing results alone do not resolve the release decision.

Temperature Monitoring Log

Practice form — Adapt and approve this example before workplace use. Complete entries as work occurs. Follow the applicable SOP for corrections, signatures, and review.

Form ID _____ Revision _____ Page ___ of ___

Equipment ID _____ Description _____

Location _____ Temperature unit _____ SOP _____

Approved acceptable range _____ Reading schedule _____

Emergency contact _____ Phone _____

Record actual temperature values. Document excursions, actions, and affected materials; do not change limits to make an out-of-range value acceptable.

Date	Time	Temperature	Initials	Within limits	Action or incident reference

Comments and follow-up _____

_____

Reviewed by _____ Date _____ Follow-up complete _____

Sample Chain of Custody Record

Practice form — Adapt and approve this example before workplace use. Complete entries as work occurs. Follow the applicable SOP for corrections, signatures, and review.

Form ID _____ Revision _____ Page ___ of ___

Sample ID _____ Description _____

Submitter _____ Contact _____

Source or collection location _____

Collected by _____ Collection date and time _____

Quantity and unit _____ Container or seal ID _____

Required storage and transport conditions _____

Shipment method _____ Received date and time _____

Received by _____ Condition and seal status _____

Initial storage location _____ Related test request _____

Transfer History

Date and time	Released by	Received by	From and to location	Purpose and condition

Quantity used or remaining _____ Unit _____

Final disposition _____ Date and time _____

Authorized by _____ Performed by _____

Related records or discrepancies _____

SOP Training and Competence Record

Practice form — Adapt and approve this example before workplace use. Complete entries as work occurs. Follow the applicable SOP for corrections, signatures, and review.

Form ID _____ Revision _____ Page ___ of ___

Employee _____ Job title _____

Department _____ Supervisor _____

Training topic _____ Start date _____

Document revisions must match the versions used for training. Record the assessment separately from attendance or reading acknowledgment.

SOP ID and title	Revision	Training date	Method and trainer	Assessment and result

SOP ID and title	Revision	Training date	Method and trainer	Assessment and result

Methods may include reading, discussion, demonstration, or supervised practice. Describe the method actually used and the evidence of competence.

Assessment evidence or reference _____

_____

Authorized activities and any limits _____

Retraining or follow-up needed _____

Employee acknowledgment _____ Date _____

Trainer or assessor _____ Date _____

Authorization by _____ Date _____

Packaging Work Order and Disposition Record

Practice form — Adapt and approve this example before workplace use. Complete entries as work occurs. Follow the applicable SOP for corrections, signatures, and review.

Form ID _____ Revision _____ Page ___ of ___

Work order ID _____ Product _____ Batch or lot _____

Batch record reference _____ Packaging SOP and revision _____

Packaging configuration _____ Quantity and unit _____

Label identifiers and revisions _____

Line clearance reference _____ Approved by _____ Date ____

Label type	Required	Issued	Used	Returned	Destroyed	Difference
Product label						
Shipping label						

Explain discrepancies and reference investigations _____

_____

Product packaged by _____ Date and time _____

Label identity and placement checked by _____ Date and time _____

Closure or seal checked by _____ Date and time _____

Actual packaged quantity _____ Unit _____ Reconciliation reference _____

Packaging review

Reviewed by _____ Date _____ Open issues _____

Final disposition

Status _____ Release or hold reference _____

Authorized quality approver _____ Date and time _____

Complete this authorization only after the applicable release requirements have been met. Packaging checks alone do not establish final product release.

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14: QUALITY SYSTEMS IN THE LABORATORY AND PRODUCTION FACILITY

Learning Objectives

After completing this chapter, you should be able to:

- Identify the people, procedures, equipment, and controls needed for a reliable laboratory quality system.
- Explain how facilities, equipment, and incoming materials support cGMP manufacturing.
- Describe how specifications and suitable test methods are established.
- Explain the investigation of an out-of-**specification** result and the limits on **retesting**.
- Distinguish **calibration**, **verification**, qualification, and validation.
- Describe the process validation life cycle and the roles of IQ, OQ, equipment PQ, and process performance qualification.

Reliable products depend on reliable laboratory results, suitable materials, controlled processes, and trained people. This workbook explains how these elements work together and how an organization investigates results that fail to meet requirements. It also distinguishes equipment **qualification** from the ongoing process of **validation**.

14.1: General Principles and Laboratory Management

14.2: Facilities and Equipment in Production

14.3: Handling Raw Materials and Components

14.4: Example - Material Specification Fields

14.5: Establishing Specifications

14.6: Processes and In Process Controls

14.7: Example of a Mammalian Cell Culture Process

14.8: Out of Specification Results

14.9: Change Control and Emergency Actions

14.10: Designing a Controlled Manufacturing Process

14.11: Calibration Verification Qualification and Validation

14.12: Process Validation Across the Life Cycle

14.13: Process and Analytical Method Validation

14.14: Example - Testing a Bioreactor Temperature Control System

14.15: Sterilization Validation as an Example

14.16: Maintaining Control and Handling Unplanned Events

14.17: Workplace Hazards in Biotechnology

14.18: Choosing and Checking Exposure Controls

14.19: Mock Audit of Sample Receiving

14.20: Chapter Summary

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14.1: General Principles and Laboratory Management



Laboratory results must be trustworthy and useful for their intended purpose. A **quality system** supports suitable methods, competent personnel, controlled equipment, accurate records, and review of results. Pharmaceutical QC laboratories must meet applicable cGMP requirements. ISO standards may also be relevant, but ISO 9000 is not a universal laboratory testing requirement. ISO/IEC 17025 addresses the **competence** of testing and **calibration** laboratories.

Three important foundations are trained personnel with appropriate skills, clearly assigned responsibilities, and adequate supervision. These foundations need support from sufficient staffing, suitable facilities, reliable supplies, written procedures, and management commitment.

Training must be documented and matched to the work. New analysts need instruction and an appropriate assessment of competence before working independently. Experienced analysts also need continuing training, including training on revised methods and equipment. Attendance alone does not demonstrate competence.

Laboratory personnel must be able to report results honestly, including failures and uncertainty. Managers must not pressure analysts to invent, conceal, or change results to obtain a preferred outcome. Data must remain attributable, complete, accurate, and traceable. Concerns should be reported through defined quality and escalation processes.

For a teaching example, imagine an assay indicates that a tablet batch contains less active ingredient than its lower acceptance limit. A supervisor asks an analyst to enter a passing result. The analyst must preserve the actual data, decline to falsify the record, and report the concern through the quality system. The result requires investigation, not a replacement number. This hypothetical example illustrates the need for honest reporting and prompt escalation.

Equipment must be suitable for its intended use and appropriately maintained, calibrated, verified, or qualified. New equipment is not automatically better or more suitable than an existing instrument. Decisions to replace equipment should consider its capability, reliability, support, and risks to the work.

The National Institute of Standards and Technology (NIST) provides measurement science and reference resources. **Metrological traceability** links a measurement result to a stated reference through a documented, unbroken chain of calibrations, each contributing to **measurement uncertainty**. It is not simply a sticker or a claim that equipment is NIST certified.

Control environmental conditions when they can affect results or product quality. Relevant factors can include temperature, humidity, vibration, airborne particles, microbial **contamination**, and lighting. Define appropriate limits, monitoring, and actions for the work rather than assuming every laboratory needs identical controls.

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14.2: Facilities and Equipment in Production

A facility must support manufacture of products that meet applicable quality requirements. Not every pharmaceutical product is sterile. Nonsterile products still require appropriate contamination controls, while sterile products require additional controls suited to their processing strategy.

Facility layout, personnel practices, material flow, cleaning, and storage should reduce contamination, **cross-contamination**, and **mix-ups**. Contamination means unwanted material is present. Cross-contamination involves transfer from another product or material. A mix-up occurs when the wrong material, product, label, or instruction is used; it is a different type of error.

Control the status and movement of sterile and nonsterile items. Protect exposed product and critical operations. Keep accepted, quarantined, and rejected materials distinguishable through appropriate physical segregation or other adequately controlled systems. The correct approach depends on the risks and applicable requirements.

Housekeeping and sanitation programs should keep the facility clean and control pests. Environmental monitoring should be appropriate to the product and process. Monitoring cannot replace a well-designed facility and effective contamination prevention.

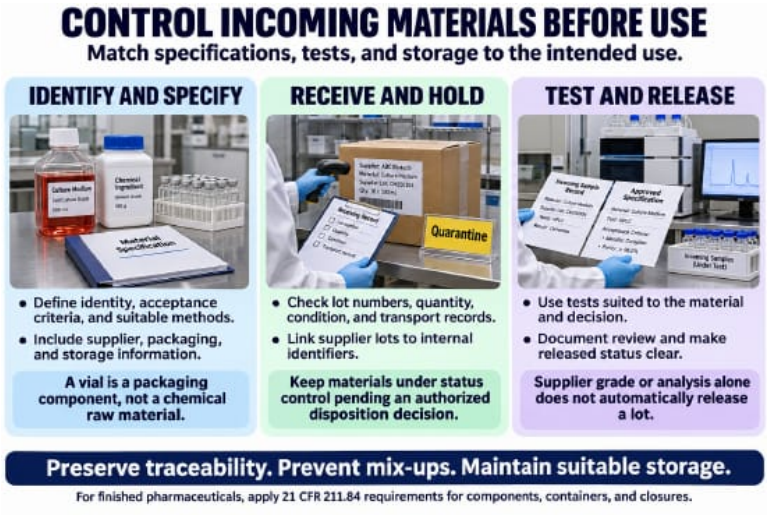
Equipment and instruments must have sufficient capacity and accuracy for the task. Establish maintenance, calibration, cleaning, operating, and malfunction procedures. Equipment status should be clear to users, and failures should be reported promptly. Evaluate whether an equipment problem could have affected previously generated data or manufactured material.

A freezer may operate near −80 °C, and a refrigerator may have a defined refrigerated range, but actual limits must be established for the equipment and stored materials. A display reading alone does not prove that every location in a storage unit is within range. Mapping, monitoring, alarms, and calibration may be needed according to the intended use.

Steam sterilization depends on effective saturated steam contact, temperature, exposure time, air removal, and the load. Pressure supports the required steam conditions; it is not an independent guarantee of sterilization. Common steam sterilization temperatures include 121 °C and 132 °C, but cycle settings and exposure times must be validated for the sterilizer, load, and application. Follow the approved cycle and manufacturer's instructions.

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14.3: Handling Raw Materials and Components



Incoming resources may include active ingredients, excipients, culture media, gases, containers, closures, and other components. These categories are related but have different functions and testing needs. A vial is a packaging component, not a chemical raw material.

A material **specification** defines the required identity, characteristics, **acceptance criteria**, and methods or references used to assess conformity. Compendia and other standards, such as USP–NF, the British Pharmacopoeia, the Food Chemicals Codex, or ACS reagent specifications, may help define requirements. The appropriate grade depends on intended use; appearing in a catalogue with a recognized grade does not by itself qualify a supplier or release a lot.

Materials need an identifier, a clear description, relevant quality criteria, approved methods, suitable packaging, storage conditions, and supplier information. Chemical formula and molecular mass are useful when applicable, but they do not describe every biological material or packaging component.



At receipt, inspect and document the shipment, supplier identity, lot numbers, quantity, condition, and any required temperature or transport information. Maintain links between supplier lot numbers and internal identifiers. Hold materials under defined status controls until the authorized quality unit makes a disposition decision.

For finished pharmaceutical manufacturing, 21 CFR 211.84 requires each lot of components, containers, and closures to be withheld from use until appropriately sampled, tested, or examined and released. Components require at least one identity test,

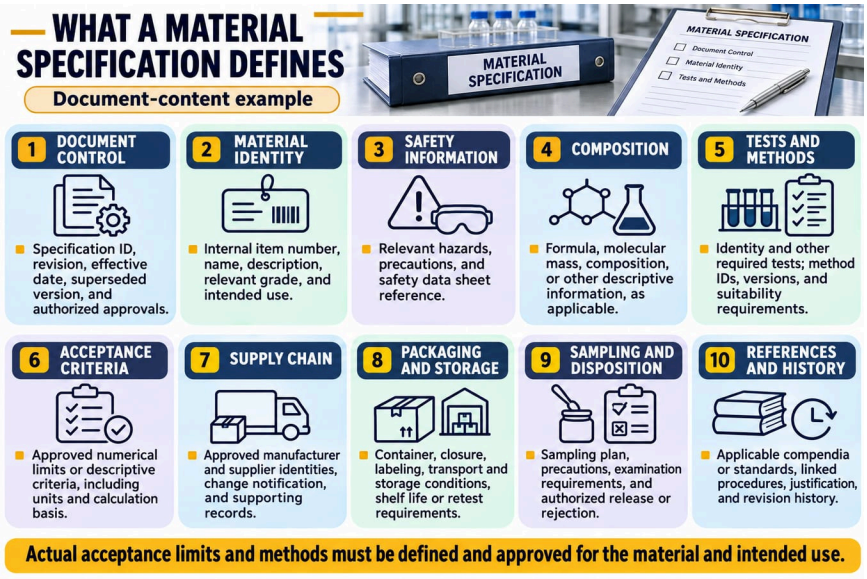
using a specific identity test where one exists. Reliance on a supplier's analysis for certain other attributes is permitted only when the applicable conditions are met, including establishing the reliability of supplier results at appropriate intervals.

Choose tests based on the material, relevant risks, and required attributes. Methods may include chromatography, spectroscopy, physical tests, or biological assays. It is not a general requirement or necessarily appropriate to test an incoming material using the same method as the finished product. A method must be suitable for the sample and intended decision.

Prevent mislabeling and mix-ups, preserve traceability, maintain suitable storage, and ensure that released status is clear before use. Control hazards, moisture sensitivity, temperature requirements, shelf life, and retest periods where applicable. Investigate damaged containers or other evidence of a possible problem.

Example Material Specification Fields

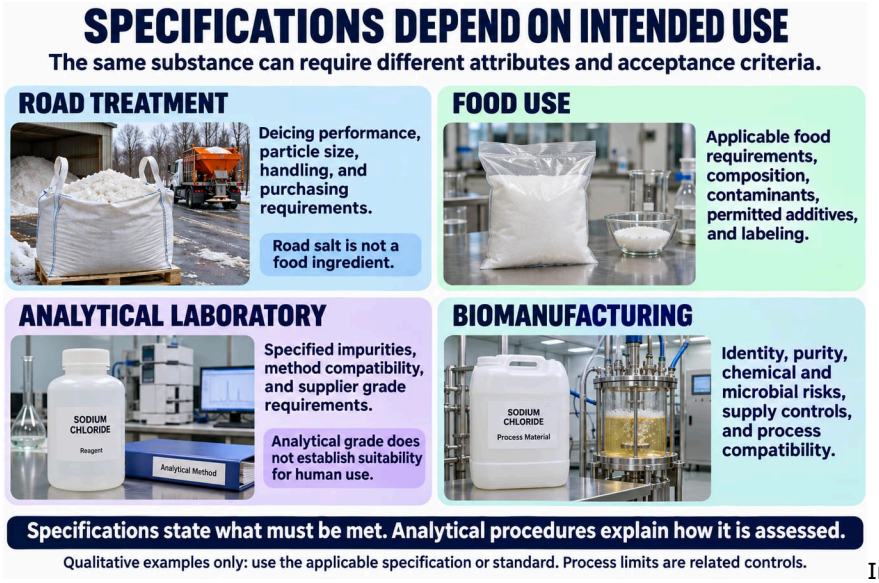
This is a document-content example. Actual acceptance limits and methods must be defined and approved for the material and intended use.



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14.4: Example - Material Specification Fields

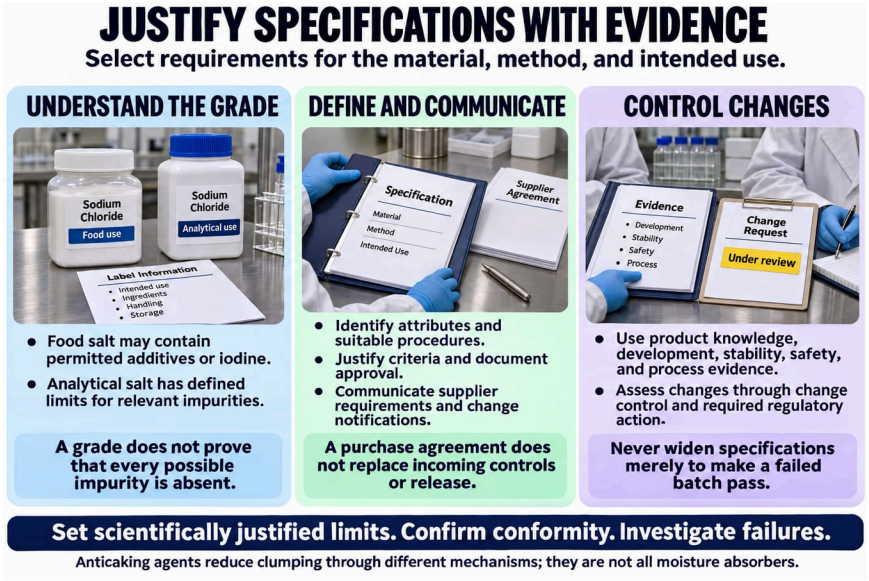
Specifications define the attributes and acceptance criteria a material or product must meet. Tests and analytical procedures explain how those attributes are assessed. Manufacturing instructions and process limits are related controls, but they are not all interchangeable with finished-product specifications.



Intended use determines what matters. For example, sodium chloride used for road treatment, food, or analytical chemistry can have different requirements for purity, contaminants, additives, moisture, and particle size. The comparison below is qualitative. It does not establish universal limits for a grade or substitute for a supplier specification or applicable standard.

Food-grade salt may contain permitted anticaking agents or added iodine, depending on the product. Anticaking agents reduce clumping through different mechanisms; they are not all simply moisture absorbers. Analytical-grade salt has defined limits for relevant impurities, not proof that every possible metal is absent. The acceptable impurity level depends on the method and intended use.

For a biomanufacturing process, select a grade and specification justified for that process. Supplier agreements and purchasing



controls should communicate relevant requirements, including changes that need notification. A purchase agreement does not replace incoming controls and release decisions.

Establishing specifications involves identifying necessary attributes, selecting suitable analytical procedures, justifying acceptance criteria, documenting approval, and confirming that the requirements are met. Product knowledge, development data, stability, safety, regulatory commitments, and process capability can all inform this work.

Limits set too loosely may fail to protect quality. Limits set without adequate justification may reject suitable material or hide weaknesses in development. Specifications must not be widened merely to make a failed batch pass. Proposed changes require scientific justification, **change control**, and any required regulatory action.

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14.5: Establishing Specifications

Specifications define the attributes and acceptance criteria a material or product must meet. Tests and analytical procedures explain how those attributes are assessed. Manufacturing instructions and process limits are related controls, but they are not all interchangeable with finished-product specifications.

Intended use determines what matters. For example, sodium chloride used for road treatment, food, or analytical chemistry can have different requirements for purity, contaminants, additives, moisture, and particle size. The comparison below is qualitative. It does not establish universal limits for a grade or substitute for a supplier specification or applicable standard.

Intended use	**Examples of attributes to evaluate**
Road treatment	Fitness for deicing, particle size, handling, and the relevant purchasing requirements. Road salt is not a food ingredient.
Food use	Compliance with applicable food requirements, composition, contaminants, permitted additives, and labeling for the product.
Analytical laboratory use	Specified impurity limits, method compatibility, and supplier grade requirements. Analytical grade does not automatically establish suitability for human use.
Biomanufacturing	Justified identity, purity, relevant chemical and microbial risks, supply controls, and compatibility with the specific process.

Food-grade salt may contain permitted anticaking agents or added iodine, depending on the product. Anticaking agents reduce clumping through different mechanisms; they are not all simply moisture absorbers. Analytical-grade salt has defined limits for relevant impurities, not proof that every possible metal is absent. The acceptable impurity level depends on the method and intended use.

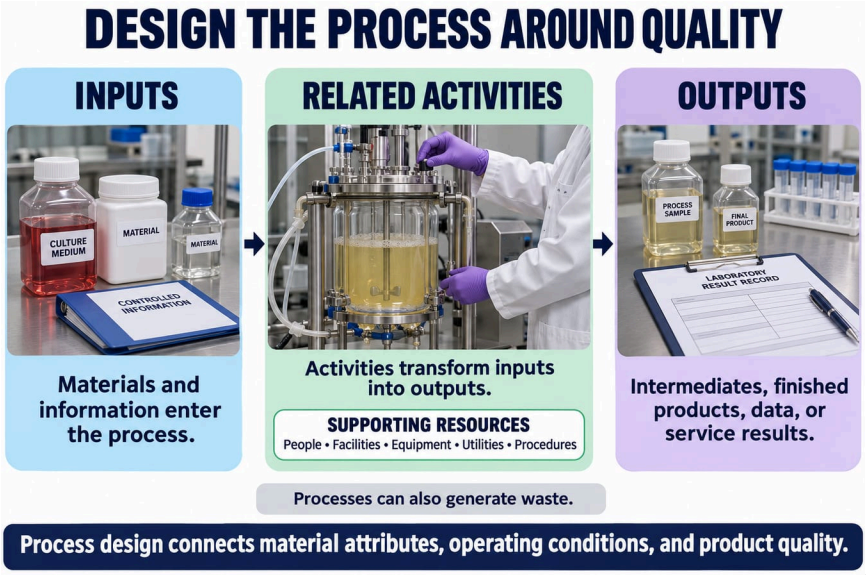
For a biomanufacturing process, select a grade and specification justified for that process. Supplier agreements and purchasing controls should communicate relevant requirements, including changes that need notification. A purchase agreement does not replace incoming controls and release decisions.

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14.6: Processes and In Process Controls



A process uses inputs and related activities to produce outputs. Inputs can include materials and information. Resources include personnel, facilities, equipment, utilities, and procedures. Outputs can be an intermediate, a finished product, data, or another service result.

Process design should consider the relationship between material attributes, operating conditions, and product quality. Not every input becomes desired product; processes also generate waste, by-products, or unused material. Suitable efficiency is important, but consistent quality and patient protection remain central requirements.

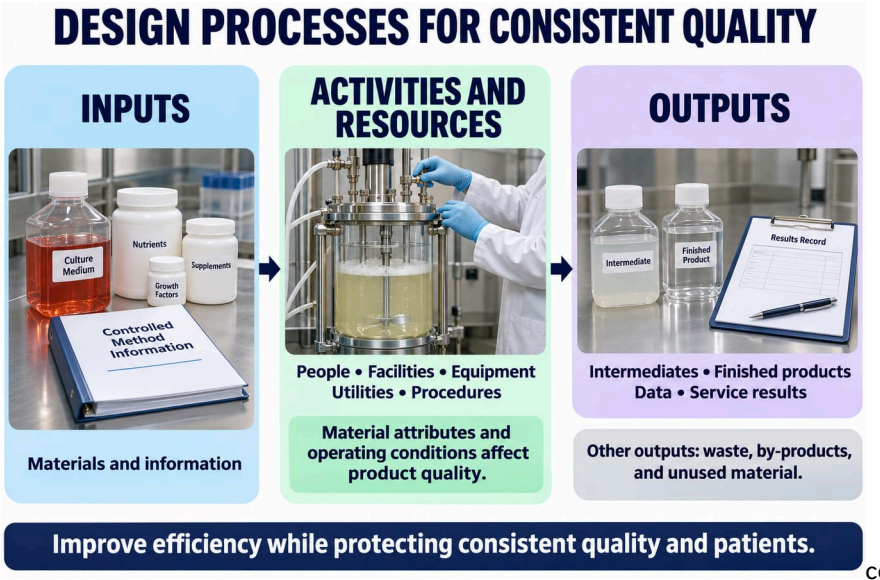
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14.7: Example of a Mammalian Cell Culture Process

Consider a hypothetical process using a recombinant mammalian cell line to produce a therapeutic protein. Cells grow in a controlled bioreactor, and the protein is later recovered and purified. This example focuses on cell culture rather than the complete downstream process.

Inputs include a qualified cell bank or inoculum, culture medium, supplements where needed, process gases, and other defined materials. Many modern processes use serum-free or chemically defined media; fetal bovine serum is not a universal requirement for mammalian cell production.

Activities include preparing medium, assembling and preparing the culture system, inoculating the bioreactor, adding feeds, monitoring the culture, controlling conditions, and harvesting at the defined stage. Resources include the bioreactor, utilities, instruments, trained operators, and approved instructions.



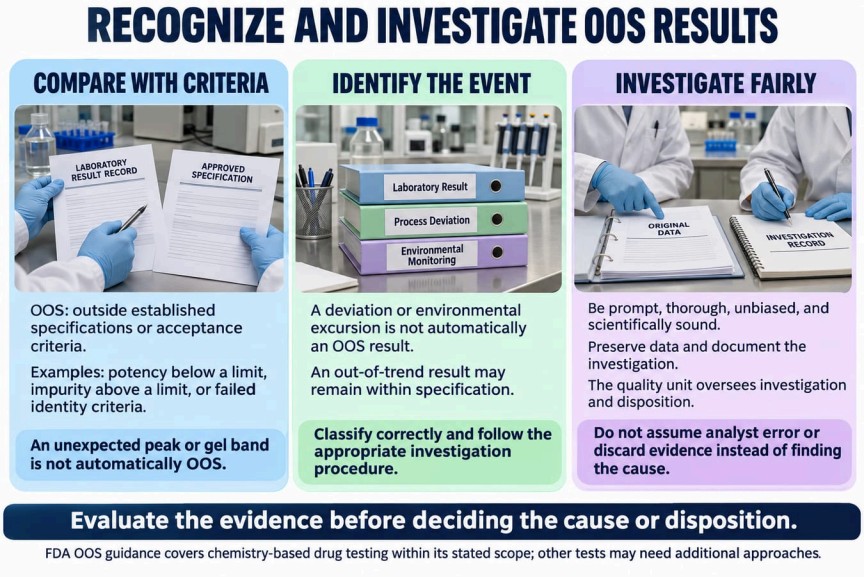
Operators may monitor temperature, pH, dissolved oxygen, viable cell density, nutrients, metabolites, and product-related measurements as appropriate. These measurements help determine whether the culture remains within the established control strategy.

For example, a pH excursion may affect cell growth, viability, or product attributes. The response must follow approved limits and procedures. Adjusting pH does not erase the excursion or demonstrate that the batch was unaffected. Record the event and evaluate its effect.

A **critical process parameter** is one whose variability can affect a **critical quality attribute** and therefore needs appropriate control. Not every measured value is critical. Use development evidence and risk assessment to identify the controls that matter and the actions needed when limits are exceeded.

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14.8: Out of Specification Results



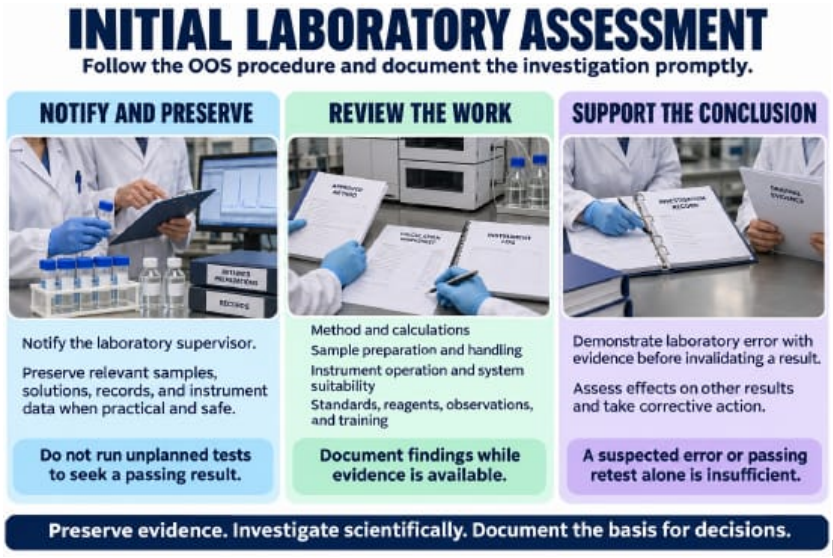
An **out-of-specification (OOS) result** falls outside established specifications or acceptance criteria. FDA's OOS guidance addresses chemistry-based testing of drugs within its stated scope, including applicable in-process laboratory tests. Other test types may need different or additional investigation approaches.

A process **deviation**, an environmental monitoring excursion, or an unusual trend is not automatically the same as an OOS laboratory result. All may need investigation, but the procedure should identify the type of event correctly. An **out-of-trend result** can remain within specification while differing meaningfully from expected performance.

Examples include a potency result below its approved lower limit, an impurity above its limit, or an identity test that fails its predefined criteria. An extra gel band or a large chromatographic peak is not automatically OOS without knowing the method, expected result, and acceptance criteria. Unexpected observations still require appropriate evaluation.

An OOS investigation should be prompt, thorough, unbiased, scientifically sound, and documented. Do not assume the analyst caused the failure, and do not discard the batch or data as a substitute for finding the cause. The quality unit oversees appropriate investigation and disposition under the quality system.

Initial Laboratory Assessment



Notify the laboratory supervisor promptly and follow the OOS procedure. Preserve relevant samples, preparations, solutions, records, instrument data, and other evidence when practical and safe. Do not continue unplanned testing in the hope of producing a passing result.

The analyst and supervisor review the method, calculations, sample preparation, instrument operation, system suitability, standards, reagents, and relevant records. They also consider sample handling, observations made during testing, training, and possible equipment problems. Document the investigation while evidence is available.

A demonstrated laboratory error may justify invalidating a result, but the explanation must be supported by evidence. A suspected error or a passing retest alone is insufficient. Evaluate whether the identified problem could affect other results and implement appropriate corrective action.

Full Investigation

If the initial assessment does not establish a clear laboratory cause, expand the investigation to manufacturing and other



relevant activities. Define the problem, responsibilities, investigation plan, affected batches, and evidence needed. The quality unit should assess the complete record before deciding disposition.

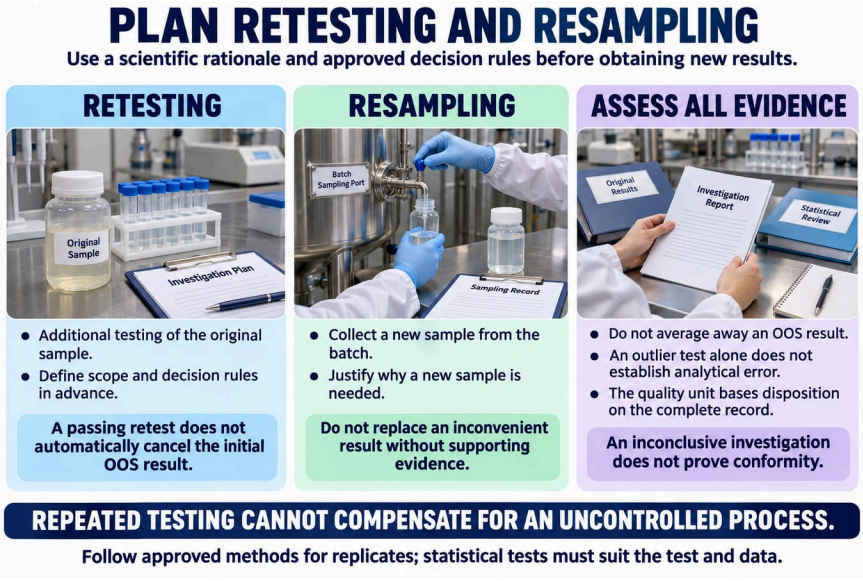
Review materials, processing and packaging records, equipment, sampling, storage, transport, methods, and relevant trends. Examine whether the event is isolated or could affect other batches or products, including material already distributed. Preserve all relevant results, including failed and invalidated results and the justification for any invalidation.

The investigation report should summarize findings, supported causes or remaining uncertainty, impact assessment, batch disposition, **corrective and preventive actions** (CAPA), and follow-up. A conclusion of human error alone is inadequate without examining why the error occurred and whether system weaknesses contributed.

Retesting Resampling and Statistical Tests

Retesting uses additional testing of the original sample. **Resampling** collects a new sample from the batch. Either action needs a scientific rationale and an approved investigation plan. Define the scope and decision rules before obtaining the new results rather than adding tests until the outcome is favorable.

A passing retest does not automatically cancel the initial OOS result. Consider all relevant data and the investigation findings. Resampling may be justified when evidence shows that the original sample was unrepresentative or improperly prepared, but it must not be used simply to replace an inconvenient result.



Do not average an OOS result with passing results to hide variability or create a passing result when the method does not permit that approach. Follow established methods for replicate measurements and report results appropriately.

Statistical outlier tests are not mandatory for every OOS investigation and cannot by themselves establish an analytical error. Their suitability depends on the test and data. They must not be used to discard a valid chemical result solely because it is unusual.

An inconclusive investigation does not prove that the batch meets requirements. The authorized quality unit must make a scientifically justified disposition based on the entire record and applicable obligations. Testing a product repeatedly cannot compensate for an uncontrolled process.

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14.9: Change Control and Emergency Actions

An investigation can reveal opportunities to improve, but the failure itself is not a benefit. Change control provides a structured way to assess and approve changes without introducing unintended risks. Evaluate effects on product quality, safety, process performance, analytical methods, validation, documents, training, and regulatory commitments.



Assign reviewers according to the change and its risks. Manufacturing, engineering, materials, QC, QA, and regulatory staff may contribute, but not every change needs approval from every department. Define the required approvals in the quality system.

Document the reason, proposed actions, impact assessment, supporting studies, required approvals, implementation plan, and effectiveness checks. Complete necessary studies and training at the appropriate stage. A change record should link affected specifications, procedures, equipment, and validation records.

In an emergency, personnel should follow approved safety and response procedures, stop unsafe work, protect people, and secure equipment or material within their authority. Escalate promptly and record actions. Emergency action does not provide unrestricted authority to improvise a new manufacturing process or bypass quality release decisions.

After the event, investigate the deviation, assess product and data effects, and determine whether a permanent change is needed. Follow change control for that permanent change and any regulatory requirements that apply.

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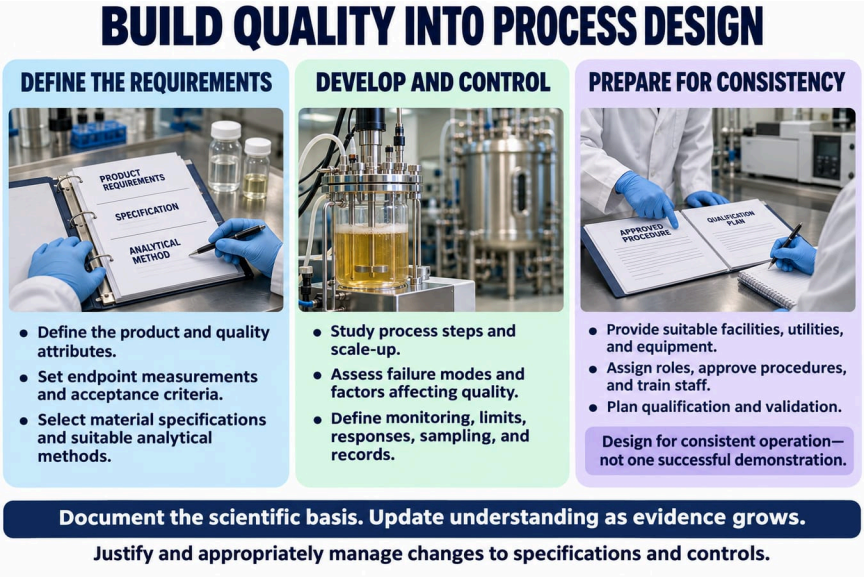
14.10: Designing a Controlled Manufacturing Process

Define the intended product and relevant quality attributes. Identify the endpoint measurements and acceptance criteria that show whether requirements have been met. Establish suitable material specifications and analytical methods.

Develop process steps through scientifically sound studies, and evaluate how the process changes during scale-up. Assess foreseeable failure modes and identify the parameters and material attributes that affect quality. Establish an appropriate control strategy, including monitoring, limits, response procedures, sampling, and records.

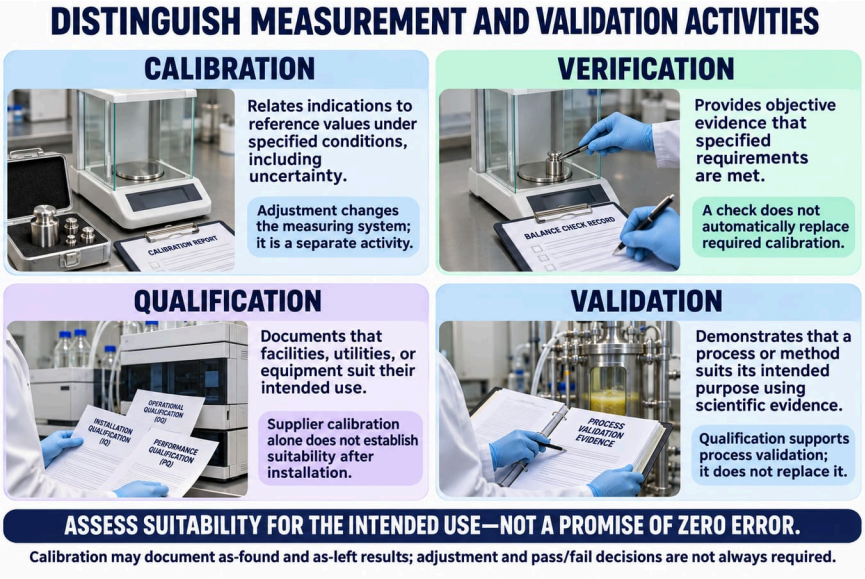
Provide suitable facilities, utilities, and equipment. Define responsibilities, write and approve necessary procedures, train personnel, and plan qualification and validation. The design must support consistent operation, not only one successful demonstration.

Document the scientific basis for decisions and update process understanding as evidence grows. Some specifications and controls evolve during development, but changes must be justified and managed appropriately.



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14.11: Calibration Verification Qualification and Validation



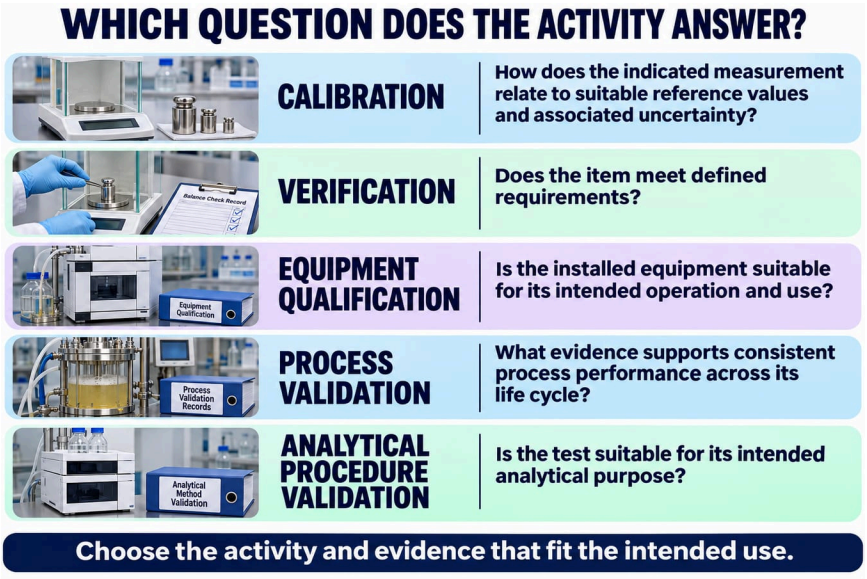
Calibration establishes a relationship between a measurement indication and reference values under specified conditions, including relevant measurement uncertainty. It may identify bias or support a correction. Adjustment changes the measuring system and is a separate activity, even when performed during the same service visit.

A calibration report may include results before and after adjustment, often called as-found and as-left results. Not every calibration requires adjustment or a pass/fail decision. A company must assess whether the uncertainty and performance are suitable for the intended measurement.

Verification provides objective evidence that specified requirements are met. A balance check using a suitable weight or a pipette performance check may be verification activities. Their adequacy depends on the procedure, acceptance criteria, reference, and intended use. Verification does not automatically replace required calibration.

Qualification documents that facilities, utilities, or equipment are suitable for their intended use. The scope may include design review and installation, operational, and performance qualification. Use qualified personnel and appropriate evidence rather than assuming that a supplier's initial calibration proves suitability after shipment and installation.

Validation demonstrates that a process or method is suitable for its intended purpose using scientifically justified evidence. It is not proof of zero error under every imaginable condition. Equipment qualification supports process validation but does not replace it.



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14.12: Process Validation Across the Life Cycle



Installation qualification (IQ) checks that equipment and supporting systems are installed according to approved requirements. Evidence may include identity, model and serial number, location, materials of construction, utilities, wiring and connections, drawings, manuals, and relevant calibration or maintenance arrangements.

Operational qualification (OQ) evaluates operation over intended operating ranges. It may challenge controls, alarms, interlocks, functions, and relevant limits. Acceptance criteria and test conditions should be justified for the equipment and use.

Equipment performance qualification (equipment PQ) evaluates reliable performance for the intended use under representative conditions, such as defined loads or operating patterns. Its relationship to **process qualification** depends on the system and validation strategy.

For a steam sterilizer, installation checks address the unit and utilities; operational checks evaluate relevant controls and operation; load-specific studies assess effective steam penetration and exposure for the intended loads. The location most difficult to sterilize must be determined through evidence, not assumed to be a particular chamber corner.

An equipment file should include its unique identifier; manufacturer, model, and serial number; receipt and installation information; intended use; qualification evidence; relevant calibration; instructions; maintenance; training or procedure references; and a history of failures, repairs, modifications, and status decisions.

If a measuring instrument is found outside acceptance criteria, control its use and investigate the effect on previous measurements and products. Adjustment or recalibration may be needed, followed by appropriate checks. Full revalidation is not automatically required for every calibration issue; the impact assessment determines the necessary action.

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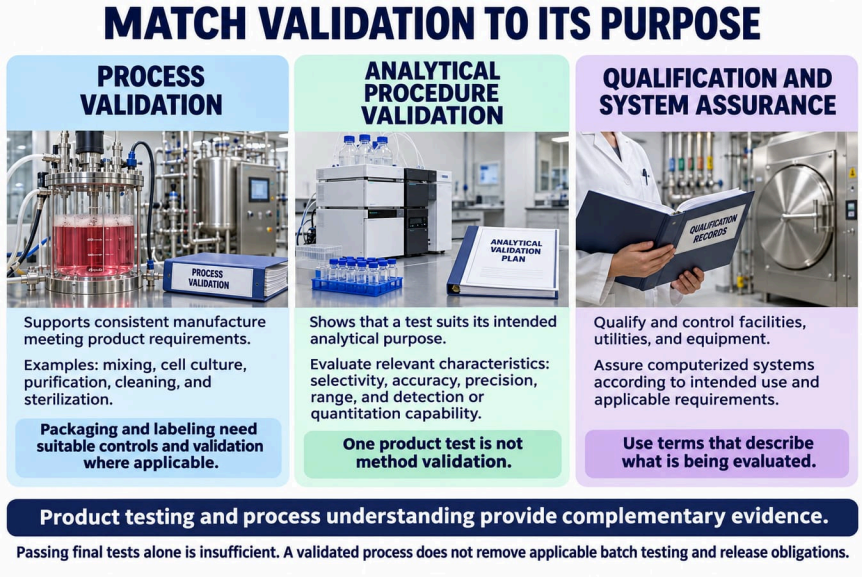
14.13: Process and Analytical Method Validation

Process validation concerns consistent manufacture of a product meeting its requirements. Examples include appropriate validation of mixing, cell culture, purification, cleaning, and sterilization processes. Packaging and labeling operations also require suitable controls and validation where applicable to the activity and risks.

Analytical procedure validation concerns whether a test is suitable for its intended purpose. Depending on the procedure, relevant characteristics can include specificity or selectivity, accuracy, precision, range, and detection or quantitation capability. Method validation does not mean merely testing a raw material or finished product once. FDA's ICH Q2(R2) guidance provides a framework for analytical procedure validation.

Facilities, utilities, and equipment such as HVAC systems, pharmaceutical water systems, autoclaves, and freeze dryers require appropriate qualification and control. Computerized systems need assurance suited to their intended use and applicable requirements. Use terminology and scope that describe what is actually being evaluated.

Product testing and process understanding provide complementary evidence. Passing final tests alone cannot establish that a poorly controlled process is consistently suitable. At the same time, a validated process does not remove applicable batch testing and release obligations.

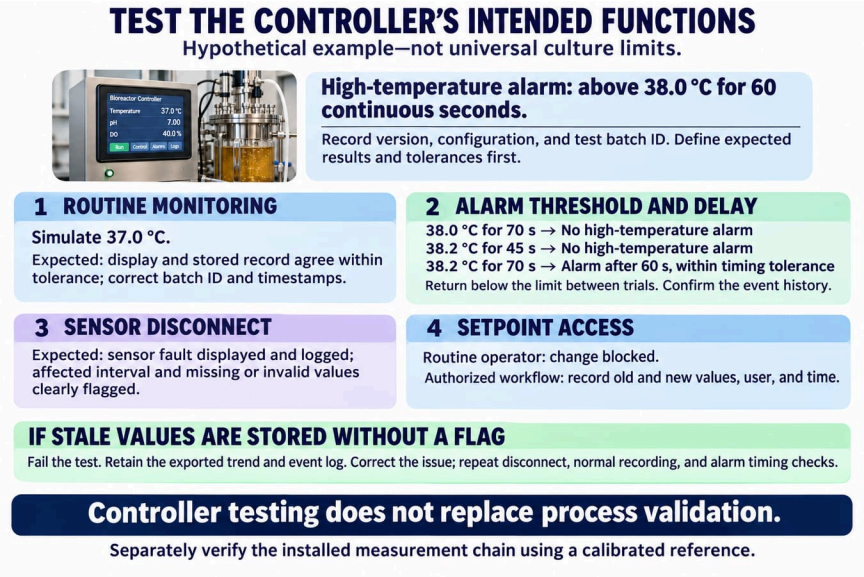


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14.14: Example - Testing a Bioreactor Temperature Control System

A manufacturing team intends to use a computerized controller to monitor a bioreactor, record temperatures against the correct batch identifier, and alert operators if temperature stays above a defined limit. For this hypothetical test, the alarm is set to trigger above 38.0 °C after 60 continuous seconds. The values are example acceptance criteria for the controller.

Record the controller version, configuration, and test batch identifier. Use an approved simulation or test setup to supply known temperature inputs. Define the expected alarm, timing, and record behavior before testing. Use a separate check with a calibrated reference to verify the installed measurement chain.Suppose the controller shows the sensor fault but continues storing the last valid value without flagging it. Mark the test as failed and retain the exported trend and event log. After the team corrects the issue, repeat the disconnect test and check normal recording and alarm timing. Passing these tests supports use of the controller for the defined functions. Separate process validation evidence is needed to show that the manufacturing process consistently produces acceptable product.



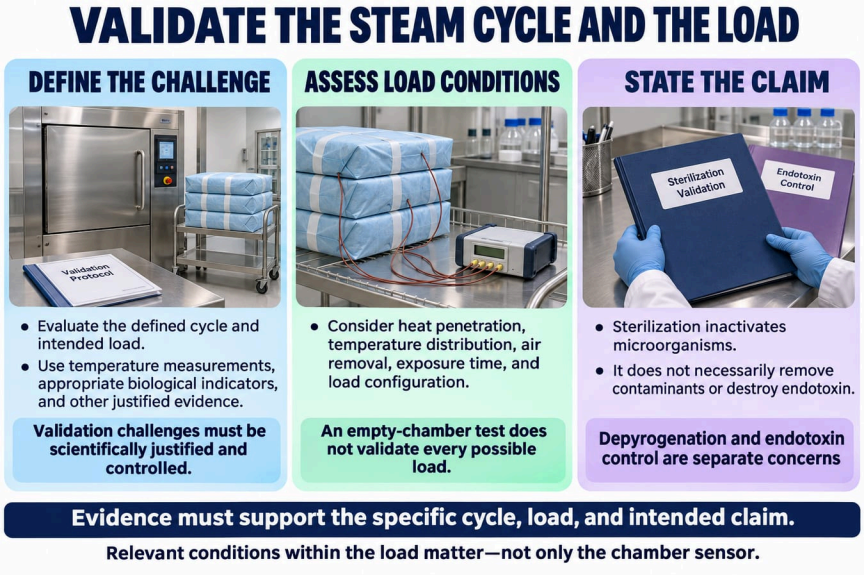
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14.15: Sterilization Validation as an Example

Steam sterilization validation evaluates the defined cycle and load, including conditions that are difficult to sterilize. Studies can use temperature measurements, appropriate biological indicators, and other evidence to assess the process. Challenges must be scientifically justified and controlled; they are not an instruction to introduce harmful organisms into routine production equipment.

Successful treatment depends on conditions at relevant locations within the load, not only at a chamber sensor. Temperature distribution, heat penetration, air removal, exposure time, and load configuration can matter. A successful empty-chamber test alone does not validate every possible load.

Sterilization inactivates microorganisms; it does not necessarily remove contaminants or destroy endotoxin. Depyrogenation and endotoxin control are separate concerns. The protocol must state the intended claim and the evidence needed to support it.



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14.16: Maintaining Control and Handling Unplanned Events

Continue to monitor process performance after qualification and PPQ. Changes in materials, equipment, software, facilities, methods, or process settings require assessment. Additional qualification, validation, studies, or regulatory action may be needed according to the potential effect. Not every change automatically requires full revalidation.

A deviation is a departure from an approved instruction, requirement, or expected condition. A **nonconformity** is a failure to meet a requirement and can involve a material, product, process, document, or system. OOS describes a particular test result outside its criteria. These terms are related but have different scopes.

Control potentially affected material while the issue is assessed. Document the event, immediate actions, investigation, cause where supported, impact on other batches or data, disposition, and CAPA when needed. Evaluate effectiveness rather than assuming that retraining alone fixes every problem.

Possible dispositions include release when justified and permitted, rejection, return, destruction, or appropriately authorized reprocessing. The available options depend on the product and requirements. Raw materials are not automatically returned, and a product must not be reprocessed merely to avoid an unfavorable result without an approved, justified approach.

Good planning and validation reduce risk but cannot guarantee that unplanned events never occur. A reliable quality system detects problems, responds appropriately, preserves accurate evidence, and uses what is learned to maintain control.



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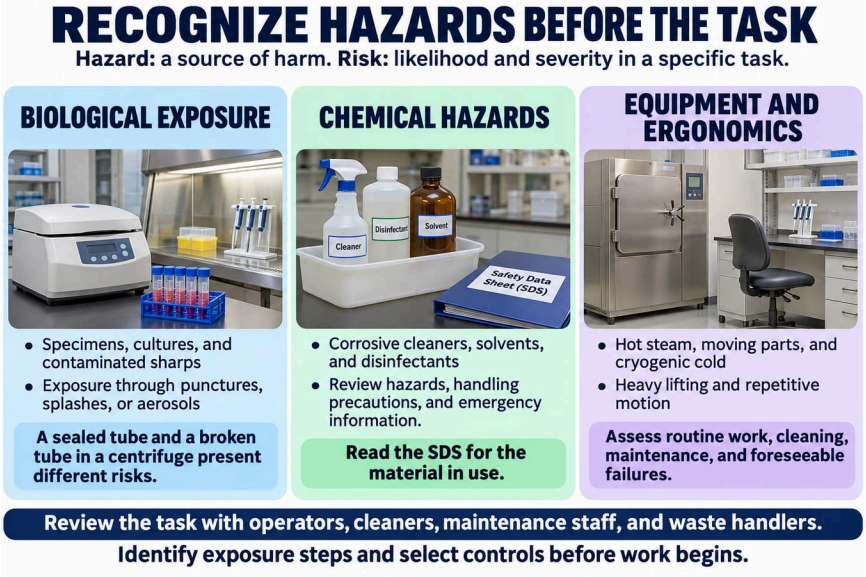
14.17: Workplace Hazards in Biotechnology

A hazard is something that can cause harm. Risk depends on how likely harm is during a specific task and how serious the consequences could be. A sealed culture tube and the same tube after it breaks in a centrifuge present different risks. Before work begins, identify the materials and equipment involved, the steps that can expose people, and the controls needed for routine work, cleaning, maintenance, and foreseeable failures.

Recognizing Hazards and Exposure Routes

Biological hazards include potentially infectious specimens, cultures, and contaminated sharps. Pipetting, mixing, or centrifuging can create droplets or aerosols. A puncture, a splash to the eyes or mouth, or breathing an aerosol can expose a worker. Chemical hazards include corrosive cleaners, solvents, and disinfectants. Review the safety data sheet (SDS) for the material's hazards, handling precautions, and emergency information.

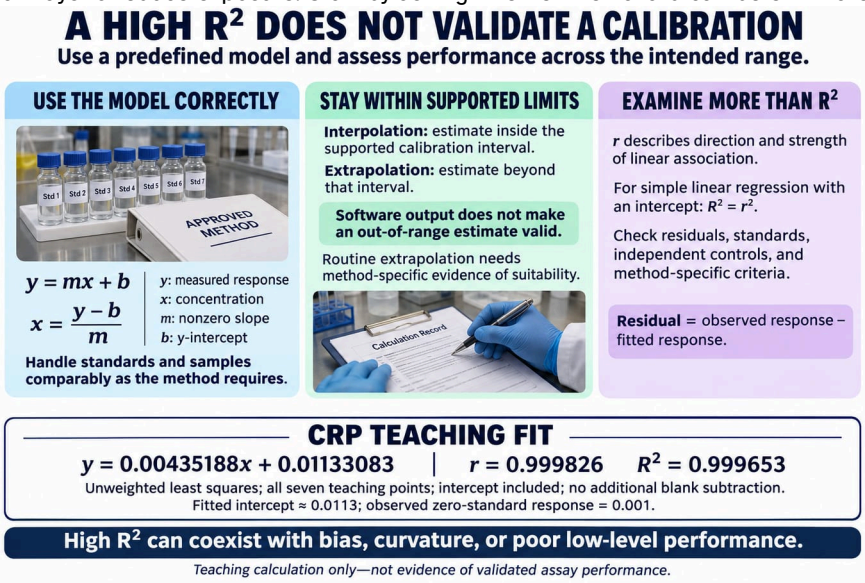
Equipment can also injure workers. An autoclave can expose someone to hot steam, a mixer has moving parts, and a cryogenic liquid can cause cold injury. Lifting heavy containers or repeating a pipetting motion can strain muscles and joints. Walk through the task with the people who perform it. Include workers who clean the area, repair the equipment, or remove waste.



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14.18: Choosing and Checking Exposure Controls

The hierarchy of controls helps teams select ways to reduce exposure. Start by asking whether the hazard can be eliminated. If it is needed, consider a safer substitute and check what risks the substitute introduces. Engineering controls isolate workers from the hazard. Administrative controls specify how work is performed, and personal protective equipment (PPE) protects the person wearing it. A task may need several controls at once.



Worked Example Choosing Controls for a Centrifuge Task

A technician needs to centrifuge cell culture samples. The team identifies a possible exposure if a tube leaks or breaks during the run. It checks whether the step is necessary and whether the same work can be done with less hazardous material. If the step must remain, the team assesses whether compatible sealed rotors or safety cups can reduce aerosol release and where the containers should be opened under the approved procedure.

The procedure specifies how to select and inspect tubes, balance loads, and respond to suspected breakage. Staff demonstrate the procedure before working independently and use PPE selected for the task. Supervisors check that the containers and seals are in good condition and observe whether workers can use the controls correctly. A new rotor, sample type, or procedure is a reason to reassess the risk.

Matching Controls to the Hazard

A chemical fume hood can control exposure to hazardous vapors when suitable for the work. A biological safety cabinet can provide containment for biological work when the cabinet type and setup are appropriate. Select the equipment for the hazards involved with help from environmental health and safety (EHS) staff. Review waste handling as part of the same assessment. Identify the waste stream at the point of use, segregate incompatible materials, and follow the facility's approved labeling, storage, and disposal procedures.

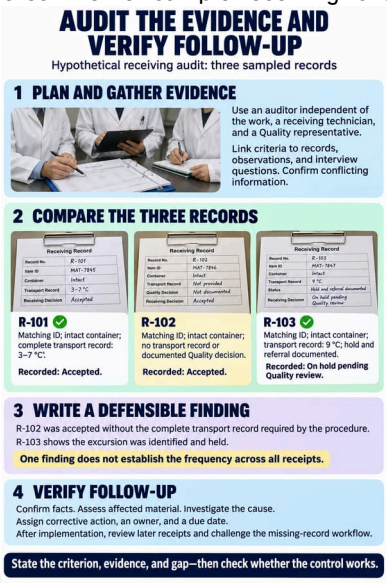
EHS Practice Reviewing a Change Before Work Begins

A laboratory replaces capped tubes with a different tube design for centrifuging cell culture samples. Before adopting the change, identify how a leak or break could expose people during loading, unloading, or cleanup. Compare the proposed tubes and closure with the equipment and procedure requirements. Identify an engineering control, a work practice, and task-appropriate PPE that the team should assess with EHS. State how the supervisor would verify that the controls are in place and what would trigger a review. Use the centrifuge example and the existing hierarchy of controls as your starting points.

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14.19: Mock Audit of Sample Receiving

In this exercise, an internal audit team evaluates whether sample receiving follows a fictional approved procedure. The scope



starts when shipments arrive and ends when samples are accepted or placed on hold. The criteria require a matching ID, an intact container, and a complete 2–8 °C transport record before acceptance. The procedure also requires staff to document any hold and refer it to Quality. These criteria apply to this exercise.

1. Plan the audit. Assign an auditor who did not perform the work, a receiving technician, and a Quality representative. Prepare a checklist that links each criterion to a record, observation, or interview question. Identify the three records below as the audit sample.

2. Gather evidence. Ask the technician to describe what happens when the transport record is missing. Compare the response with the procedure and the completed records. Confirm any conflicting information with the technician or Quality representative before writing a finding.3. Write the finding. State the criterion, the evidence, and the gap. A defensible finding is that R-102 was accepted without the complete transport record required by the procedure. R-103 shows that an excursion was identified and held. One finding in this sample does not establish how often the gap occurs across all receipts.

4. Close the audit and verify follow-up. Present the evidence and confirm factual accuracy with the audited team. Ask the process owner to assess affected material, investigate the cause, propose corrective action, and set a due date. For example, if the form allows acceptance without a transport record ID, the team could revise that decision field and train staff. After implementation, sample later receipts and challenge the workflow with a missing record to verify that the control works.

Deliverables. Prepare a one-page audit plan, a completed checklist, one finding supported by the sample, and a follow-up plan naming the owner, due date, and effectiveness evidence.

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14.20: Chapter Summary

Reliable laboratory results and consistent production depend on a connected quality system. Competent personnel, clear responsibilities, suitable facilities, controlled equipment, approved procedures, and honest reporting all contribute. Management must provide the resources and support employees need to report problems accurately. A quality system examines evidence and process weaknesses rather than assuming that an analyst caused every failure.

Materials and equipment must be suitable for their intended use. Incoming materials need clear identification, traceable lot information, appropriate storage, and defined status controls before use. Specifications establish required attributes and acceptance criteria, while suitable methods determine whether those criteria are met. Supplier information supports these decisions but does not automatically replace required incoming controls. Facility layout, cleaning, maintenance, and material flow help prevent contamination, cross-contamination, and mix-ups.

Process controls connect operating conditions to product quality. In a cell culture process, temperature, pH, dissolved oxygen, and other measurements can help operators recognize changes. Critical process parameters need appropriate control because their variability can affect critical quality attributes. Correcting an operating condition does not erase an excursion or establish that the product was unaffected. Employees must record the event and evaluate its impact.

An out-of-specification (OOS) result falls outside established specifications or acceptance criteria. It requires a prompt, documented, scientifically sound investigation. An initial laboratory assessment examines methods, calculations, sample preparation, instruments, reagents, and other evidence. If no clear laboratory cause is established, the investigation expands to manufacturing and other relevant activities. A passing retest alone does not invalidate the original result. Retesting and resampling need justified plans, and all relevant data must remain available for review.

Calibration, verification, qualification, and validation answer different questions. Calibration relates measurement indications to reference values and associated uncertainty. Verification provides evidence that defined requirements are met. Qualification evaluates whether facilities, utilities, or equipment are suitable for their intended use. Validation uses scientific evidence to establish suitability of a process or method for its intended purpose. Equipment qualification supports process validation but does not replace it.

Process validation continues across the product life cycle. Process design develops the process and its control strategy. Process qualification evaluates the design through suitable facilities, utilities, and equipment, followed by process performance qualification (PPQ). Continued process verification uses routine production data to confirm ongoing control. Installation qualification (IQ), operational qualification (OQ), and equipment performance qualification (PQ) address equipment suitability; they are not the entire process validation life cycle.

Validation protocols define the purpose, conditions, sampling, methods, and acceptance criteria before execution. Reports evaluate the complete results and any deviations. Changes and unplanned events require impact assessment, appropriate investigation, and authorized decisions about affected materials or products. Monitoring and effectiveness checks help determine whether corrective actions work. These practices support reliable results, consistent products, and patient protection.

Key Terms

Quality system	Competence	Metrological traceability
Specification	Acceptance criteria	Quarantine
Contamination	Cross-contamination	Mix-up
In-process control	Critical process parameter	Critical quality attribute

Out-of-specification (OOS) result	Out-of-trend result	Laboratory assessment
Root cause	Retesting	Resampling
Corrective and preventive action (CAPA)	Change control	Calibration
Measurement uncertainty	Verification	Qualification
Validation	Installation qualification (IQ)	Operational qualification (OQ)
Equipment performance qualification (PQ)	Process design	Process qualification
Process performance qualification (PPQ)	Continued process verification	Analytical procedure validation
Validation protocol	Deviation	Nonconformity

Review Questions

1. What people, resources, and controls support a reliable laboratory quality system?

2. How do contamination, cross-contamination, and mix-ups differ?

3. What information and status controls help ensure that incoming materials are suitable before use?

4. How does a specification differ from an analytical test method?

5. How does a critical process parameter relate to a critical quality attribute?

6. What is an OOS result, and how does it differ from an out-of-trend result?

7. What evidence should an initial laboratory assessment of an OOS result examine?

8. How does retesting differ from resampling, and why does either need scientific justification?

9. How do calibration, verification, qualification, and validation differ?

10. What are the purposes of IQ, OQ, and equipment PQ?

11. What are the three stages of the process validation life cycle, and where does PPQ fit?

12. What should a validation protocol define before execution, and what should its final report evaluate?

Apply Your Knowledge

The following situations are hypothetical teaching scenarios.

1. A cell culture facility receives a new lot of culture medium with a supplier certificate reporting passing results. The shipment arrived above its specified transport temperature, and production staff want to use it immediately to avoid a delay. Describe how the team should control the lot, review the shipment and supplier evidence, and determine whether it is suitable. Explain why a passing certificate alone does not resolve the temperature concern.

2. A drug assay has an approved acceptance range of 95.0–105.0% of label claim. The initial result is 92.0%, followed by unplanned retests of 98.0% and 99.0%. A supervisor proposes averaging all three results to report a passing value. Explain why this approach is not justified simply because the average passes. Describe the laboratory assessment, possible wider investigation, and evidence needed for a scientifically sound disposition decision.

3. A laboratory installs a new balance. The supplier provides a calibration certificate, but staff have not evaluated its performance at the laboratory's location or with the quantities they routinely weigh. Explain what the certificate establishes and what remains to be assessed. Distinguish relevant calibration, verification, and qualification activities, including possible effects of environmental conditions.

4. A steam sterilizer passes an empty-chamber test. Production then changes to a tightly packed load of larger containers, and a manager assumes the earlier test covers the new load. Explain why that assumption is incomplete. Propose the evidence and load-related conditions that should be evaluated through change control and appropriate qualification or validation. Explain why sterilization alone does not establish endotoxin removal.

5. A therapeutic protein process completed its initial PPQ work successfully. Months later, routine data show gradually decreasing cell viability and changing product measurements, although finished batches still meet specifications. Explain why the team should examine the trend. Identify material, equipment, process, and analytical information to review, and describe how continued process verification and change control should guide any response.

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15: QUALITY ASSAYS

After completing this chapter, you should be able to:

- Describe the roles of the sample, method, reference materials, calibration standards, and controls in an assay.
- Explain how sampling and sample preparation can affect a result.
- Distinguish accuracy, precision, bias, and random variation, and calculate basic measures of performance.
- Explain selected analytical method validation characteristics.
- Organize data in labeled tables and suitable graphs.
- Use an appropriate calibration equation to estimate an unknown within the validated range and account for dilution.

An **assay** is a procedure used to evaluate a defined characteristic of a sample. Examples include identity, concentration, biological activity, or a particular impurity. **Specificity** is usually a performance characteristic of a method rather than a property being measured in a product.

A **quantitative assay** reports a numerical value, such as concentration. A **qualitative assay** reports a category, such as detected or not detected under defined conditions. Some assays are semiquantitative and provide an estimate or range rather than a precise numerical result.

For example, a cholesterol test can report a concentration. Many routine urine pregnancy tests detect human chorionic gonadotropin (hCG) and report a qualitative result according to a threshold. A negative result does not prove that no hCG is present; the level may be below the test's detection capability or the sample may have been collected too early.

Assays support research, development, manufacturing, and quality control. They may measure an active ingredient, detect contamination, evaluate degradation, or help determine whether a material meets specifications. A laboratory purity or **potency** test does not by itself establish clinical efficacy in patients.

15.1: Categories of Quality Tests

15.2: Selecting and Establishing a Method

15.3: The Sample

15.4: Sample Preparation and Recovery

15.5: Reference Materials Standards and Controls

15.6: Analytical Method Validation

15.7: Measurement Error and Accuracy

15.8: Precision

15.9: Detection and Quantitation Limits

15.10: Specificity and Selectivity

15.11: Calibration Model Linearity and Range

15.12: Robustness and Intermediate Precision

15.13: System Suitability

15.14: Organizing Quantitative Data

15.15: Graphs

15.16: Standard Curves and Linear Regression

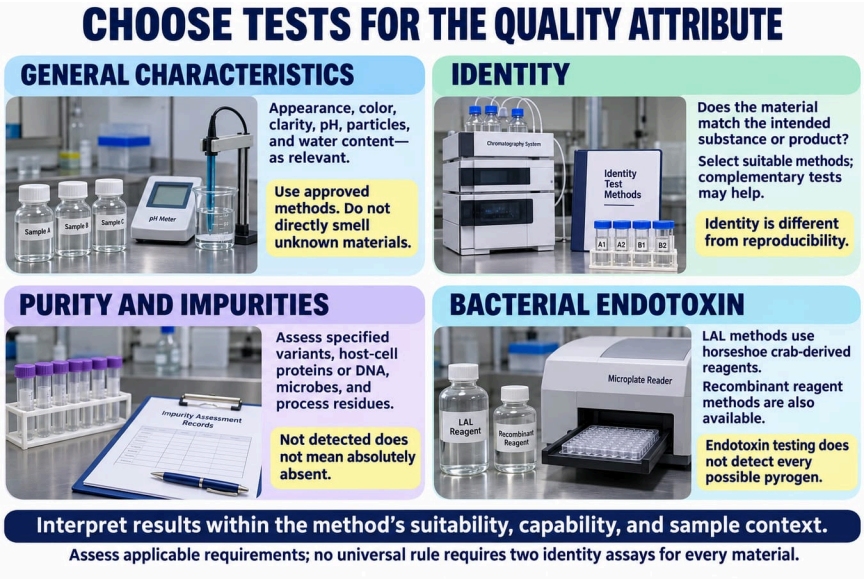
15.17: Unknown and Dilution Example

15.18: Chapter Summary

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15.1: Categories of Quality Tests

General characteristics include appearance, color, clarity, pH, visible particles, and water content where relevant.

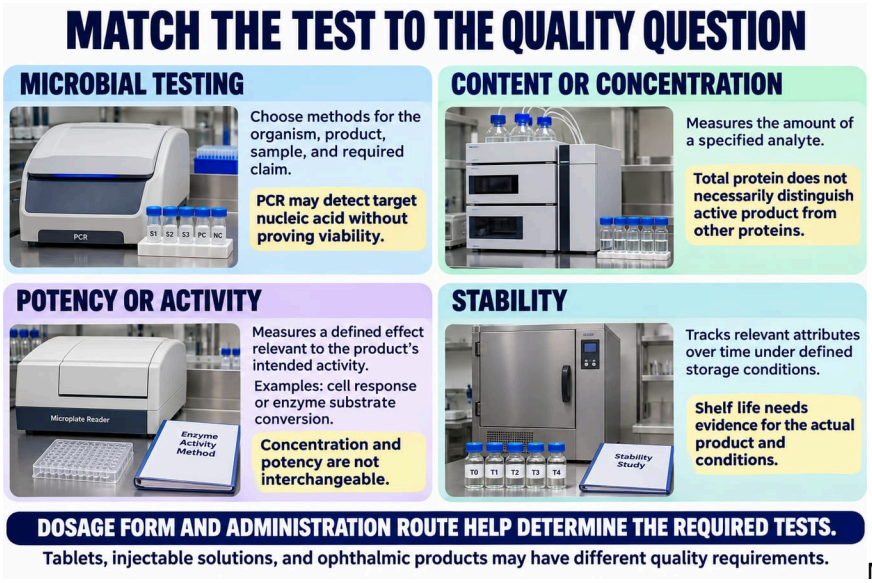


Use approved methods and precautions; direct smelling of an unknown material is not a routine instruction for assessing odor.

Identity tests determine whether the material is the intended substance or product. Methods may include chromatography, mass spectrometry, peptide mapping, sequencing, spectroscopy, immunological tests, or nucleic acid methods. Complementary methods can strengthen identification, but there is no universal rule requiring two assays for every material. Confirming identity is different from demonstrating **reproducibility**.

Purity and impurity tests assess specified unwanted materials. Examples include product-related variants, **residual** host-cell proteins or DNA, microbial contamination, and process residues. Absence of a detected impurity is a statement about the method and sample, not proof that the material is absolutely pure.

Bacterial endotoxin testing detects endotoxin associated with Gram-negative bacteria. Limulus amebocyte lysate (LAL) methods use a biological reaction from horseshoe crab-derived reagents. Depending on the method, detection may involve gel formation, turbidity, or a color change. Recombinant reagent methods are also available; USP Chapter 86 provides additional techniques using nonanimal-derived reagents. Applicable requirements and method suitability must be assessed. Endotoxin is one type of pyrogen, so an endotoxin test does not detect every possible pyrogen.



Mycoplasma tests may use nucleic acid amplification or other suitable methods. Microbial and viral testing approaches depend on the organism, product, sample, and required claim. A PCR result can indicate target nucleic acid without necessarily demonstrating a viable organism.

Content or concentration tests measure the amount of a specified analyte in raw materials, intermediates, or finished products. Suitable methods can include chromatography, spectrophotometry, or other validated approaches. A total protein measurement does not necessarily distinguish active product from inactive protein or contaminants.

Potency or biological activity tests measure a product's ability to produce a defined effect relevant to its intended activity. A cell-based bioassay may assess a response to a biological medicine; an enzyme assay may assess conversion of a substrate. Potency is not limited to measuring an effect directly in a patient, and concentration and potency are not interchangeable.

Stability studies evaluate whether a product maintains relevant attributes within specifications over time under defined storage conditions. Measurements can include potency, content, degradation products, physical changes, microbial quality, and container-closure effects. Degradation kinetics may support understanding, but shelf-life conclusions require appropriate evidence for the actual product and conditions.

The dosage form and route of administration help determine which tests are needed. A tablet, an injectable solution, and an ophthalmic product do not necessarily have the same quality requirements.

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15.2: Selecting and Establishing a Method

Methods may come from scientific publications, company development, recognized standards, or compendia. Examples of sources include USP–NF, the British Pharmacopoeia, the European Pharmacopoeia, EPA methods, and AOAC INTERNATIONAL methods. Select the method for the intended sample, analyte, concentration range, and decision.

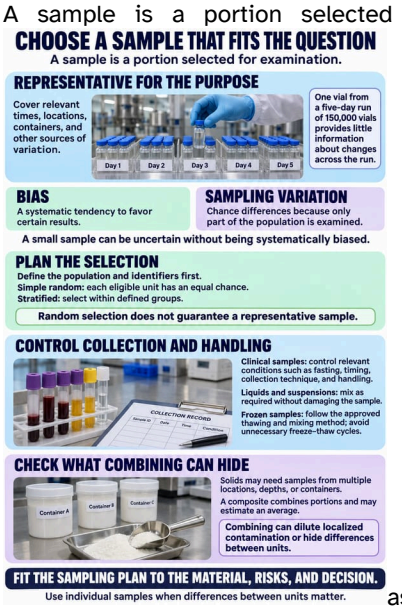
A published or compendial procedure is not automatically suitable for every sample or laboratory. Verify applicable compendial procedures under actual conditions of use and perform validation or additional studies where required. New or modified methods need evidence supporting their intended use. Follow the applicable regulation, compendium, and method requirements.

An SOP should describe sampling, storage, preparation, test execution, standards, controls, calculations, acceptance criteria, permitted repeats, handling of unexpected results, and records. Do not perform unplanned repeat tests simply to obtain a preferred result.

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15.3: The Sample

A sample is a portion selected for examination. Its value depends on how well it supports the question being asked. A **representative sample** reflects relevant characteristics of the material or population for that purpose. Random selection can reduce selection **bias**, but randomness alone does not guarantee that a particular sample is representative.



Bias is a systematic tendency for selection or measurement to favor certain results. **Sampling variation** is the chance difference that occurs because only part of a population is examined. A small sample can have high uncertainty without necessarily being systematically biased.

For example, one vial selected from a five-day production run of 150,000 vials provides little information about changes across the run. Selecting only an easily reached vial from the beginning adds a selection problem. A justified plan might cover relevant times, locations, containers, or other sources of variability. The plan must fit the material, risks, and decision rather than relying on a fixed percentage for every situation.

Clinical samples also depend on collection conditions. A blood result may be affected by fasting, collection time, posture, exercise, collection technique, or sample handling. The appropriate sampling procedure defines which conditions need control for the analyte and purpose.

Simple random sampling gives each eligible unit an equal chance of selection. Other valid approaches include stratified sampling, which selects units within defined groups such as production periods or storage locations. A statistician can help design plans for complex or high-risk decisions.

For individuals or containers, define the population and identifiers before selection and use an appropriate random procedure. For an area, a numbered grid may support selection, but access, sample size, and spatial variation must also be considered. Avoid substituting convenient locations without documenting the effect on the plan.

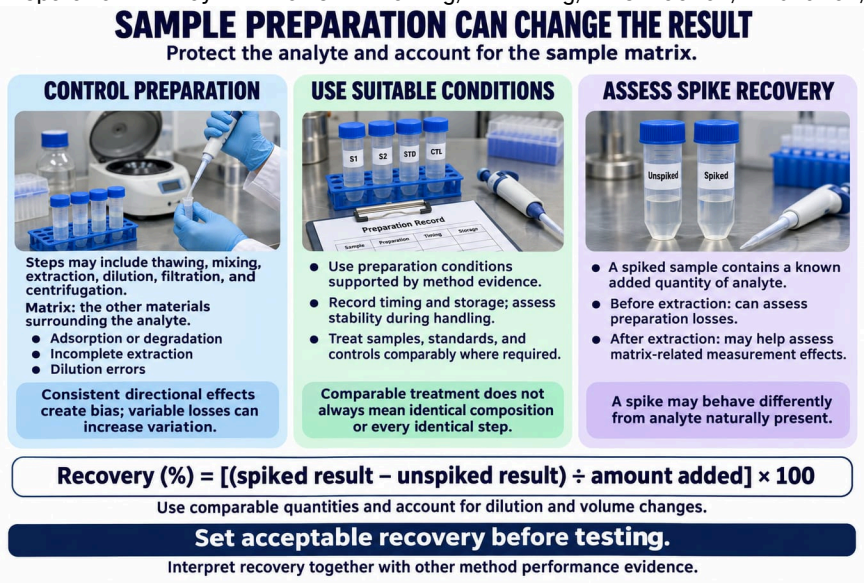
For a liquid or suspension, mix sufficiently to distribute the target material without damaging it or changing the measurement. Mix frozen samples after thawing as the approved method requires; avoid unnecessary freeze-thaw cycles. Do not assume that every biological sample should be fully thawed and mixed in the same way.

For solids, the plan may require samples from multiple locations, depths, or containers. A composite sample combines portions and can estimate an average property, but it may dilute a localized contaminant or hide variability. Use individual samples when the decision requires information about differences between units.

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15.4: Sample Preparation and Recovery

Preparation may involve thawing, mixing, extraction, dilution, filtration, centrifugation, or removal



of interfering substances. Each step can affect the target analyte and the sample **matrix**, the other materials surrounding it. Adsorption, degradation, incomplete extraction, or dilution errors can change the result.

A preparation effect is systematic when it creates a consistent directional bias. Variable loss can also increase random variation. Use preparation conditions shown to be suitable, document timing and storage, and assess stability during handling.

Prepare samples, standards, and controls consistently where the method requires comparable treatment. They need not always have identical composition or every identical preparation step. Appropriate matrix matching, independent controls, and correction approaches depend on the method and validation evidence.

A **spiked sample** contains an added known quantity of analyte. A recovery study compares the measured increase with the amount added, accounting for the analyte already present. Adding a spike before extraction can assess preparation losses, while adding it afterward may help assess matrix-related measurement effects. A spike does not always behave exactly like analyte naturally present in the sample.

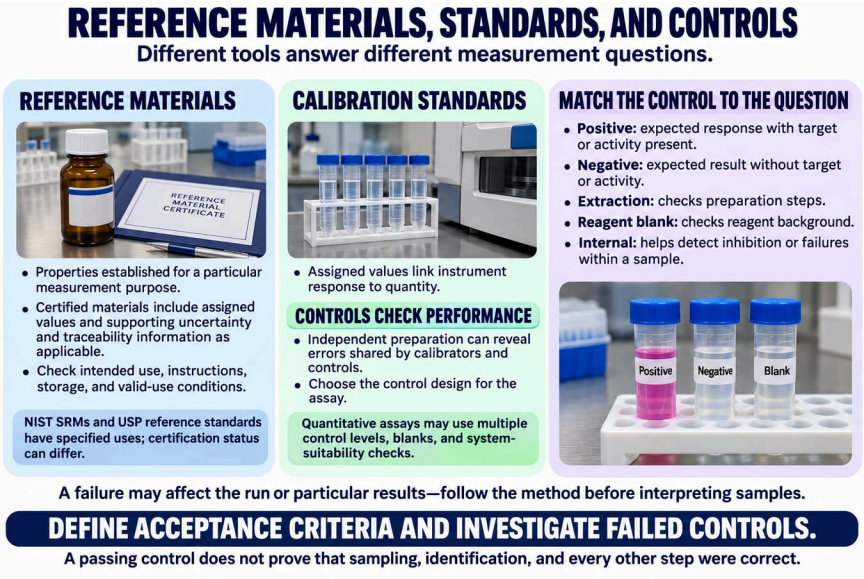
Recovery (%) = [(result for spiked sample – result for unspiked sample) / amount added] × 100

All quantities must be expressed on a comparable basis, with relevant dilution and volume changes included. Define acceptable recovery before testing and interpret it together with other method performance evidence.

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15.5: Reference Materials Standards and Controls

A **reference material** has properties sufficiently well established for a particular measurement purpose.



A certified reference material includes specified documentation, assigned property values, and associated uncertainty and traceability information as applicable. Not every reference material is a highly purified chemical.

NIST provides Standard Reference Materials (SRMs) for many measurement applications. USP also supplies reference standards for specified compendial uses. Check the intended use, certificate or instructions, storage, expiration or valid-use conditions, and handling requirements. Do not assume every reference standard from every source has the same certification status.

A **calibration standard** has an assigned value used to establish the relationship between response and quantity. A control checks whether the test system performs acceptably. One material can sometimes serve more than one purpose, but independent control preparation can reveal errors that would be missed if the same mistake affected both calibrators and controls.

Choose controls appropriate to the assay. Qualitative tests often include positive and negative controls. Quantitative assays may use control samples at low, middle, or high levels, blanks, system-suitability tests, or other checks. There is no single control design that applies unchanged to every assay.

A **positive control** should give the expected response when the target or activity is present. It may be qualitative or have a known concentration. A **negative control** should give the expected result in the absence of the target or relevant activity. Depending on the method, this might be a matrix blank, a reagent blank, or a no-template control.

An extraction control assesses preparation steps; a reagent blank checks background introduced by reagents; and an internal control can help detect inhibition or other failures within individual samples. These controls answer different questions and are not necessarily interchangeable.

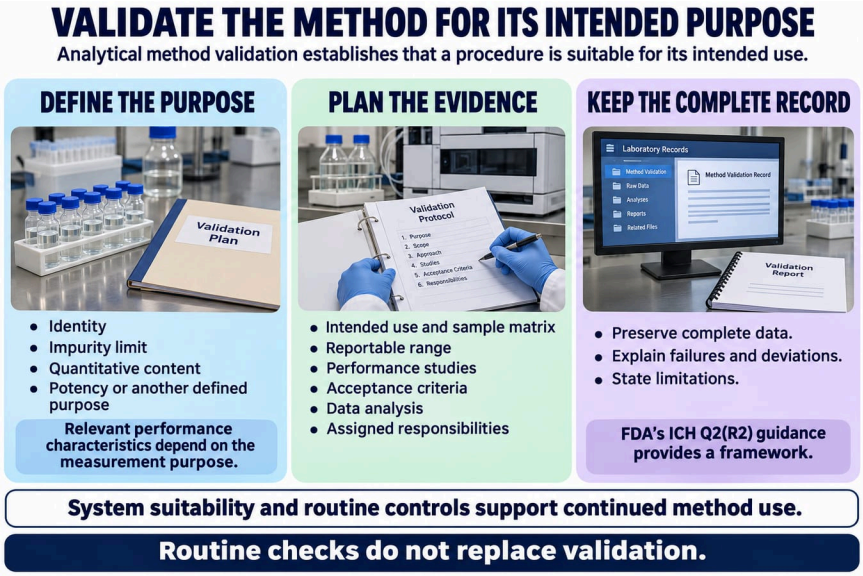
Define control acceptance criteria and what to do when they fail. A failed control may invalidate a run or affect particular results, depending on the method and cause. Investigate before interpreting affected samples. A passing control does not prove that sampling, identification, and all other steps were correct.

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15.6: Analytical Method Validation

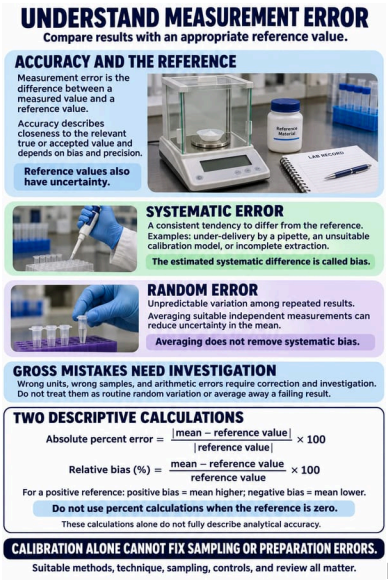
Analytical method validation establishes that a procedure is suitable for its intended purpose using defined performance characteristics. The relevant characteristics depend on whether the method is used for identity, an impurity limit, quantitative content, potency, or another purpose. FDA's ICH Q2(R2) guidance provides a current framework.

The validation plan should define the intended use, sample matrix, **reportable range**, performance studies, acceptance criteria, data analysis, and responsibilities. Preserve the complete data and explain failures, deviations, and limitations. **System suitability** and routine controls support continued use but do not replace validation.



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15.7: Measurement Error and Accuracy



Measurement error is the difference between a measured value and a reference value. A true value is generally not known exactly, so an accepted reference value and its uncertainty often provide the practical basis for comparison. **Accuracy** describes closeness to the relevant true or accepted value and depends on both bias and **precision**.

Gross mistakes include recording the wrong unit, using the wrong sample, or making an arithmetic error. Such events require correction and investigation. They should not be treated as routine random variation.

Systematic error creates a consistent tendency for results to differ from the reference. Examples include a pipette that consistently delivers too little, an inappropriate calibration model, or incomplete extraction. The estimated systematic difference is often called bias.

Random error causes unpredictable variation among repeated results. Averaging suitably independent measurements can reduce uncertainty in the mean, but it does not eliminate systematic bias. It also does not justify averaging away a failing result contrary to the approved method.

Good technique, suitable calibration, validated methods, representative sampling, effective controls, and appropriate review all support accurate results. Calibration alone cannot correct errors caused by unsuitable sampling or sample preparation.

One useful descriptive calculation is absolute percent error of the mean. It summarizes the difference between a replicate mean and a nonzero reference value; it is not a complete measure of analytical accuracy.

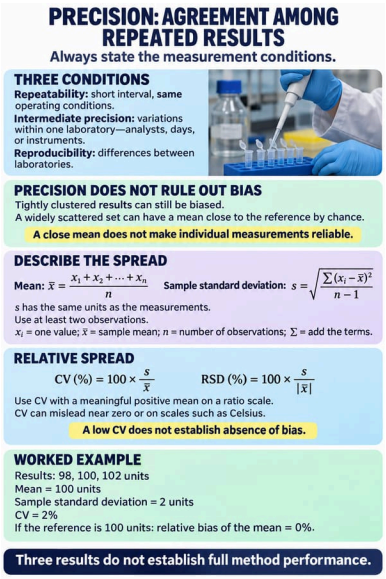
Absolute percent error = |mean − reference value| / |reference value| × 100

Relative bias (%) = (mean − reference value) / reference value × 100

Relative bias retains direction for a positive reference value. A positive value indicates that the mean is higher than the reference; a negative value indicates that it is lower. Percent-based calculations are inappropriate when the reference is zero.

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15.8: Precision



Precision describes agreement among repeated measurements under stated conditions. **Repeatability** concerns a short interval under the same operating conditions. **Intermediate precision** considers variations within a laboratory, such as different analysts, days, or instruments. Reproducibility concerns differences between laboratories.

A tightly clustered set of results can still be biased. Conversely, a highly variable set can have a mean close to the reference by chance. A close mean alone does not establish that individual measurements are reliable.

The **sample standard deviation**, written s, describes the spread of observations around their mean. Its units match those of the original measurements. For a sample of n observations, the usual calculation uses n – 1 in the denominator. Population standard deviation is conventionally written σ and uses the population mean and population size; it should not be mislabeled on a sample formula.

Mean: $\bar{x} = (x_1 + x_2 + \ldots + x_n) / n$

Sample standard deviation: $s = \sqrt{[\Sigma(x_i - \bar{x})^2 / (n - 1)]}$

Here, x_i is one observed value, $\bar{x}$ is the sample mean, n is the number of observations, and Σ means to add the indicated terms. At least two observations are needed to calculate this sample standard deviation.

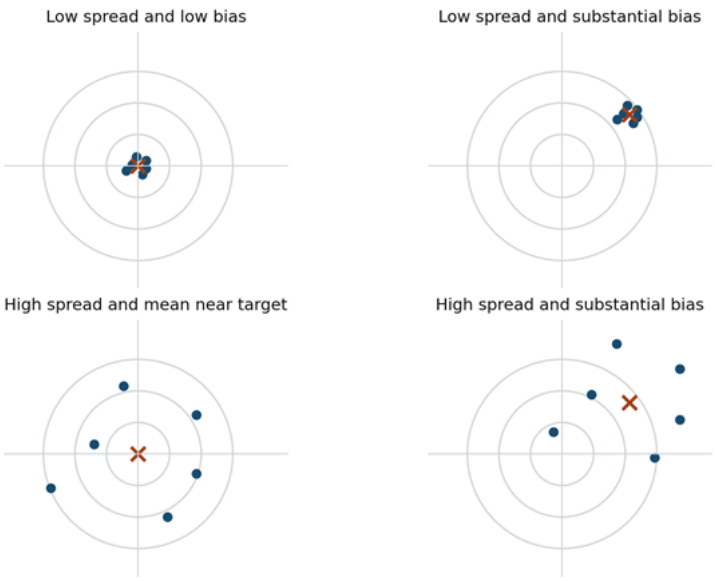
The **coefficient of variation (CV)** is a measure of relative spread, not the difference between one observation and the mean. For positive ratio-scale measurements, CV is often reported as a percentage. Relative standard deviation (RSD) uses the absolute mean in the denominator.

$CV\ (\%) = 100 \times s / \bar{x}$ for a meaningful positive mean

$RSD\ (\%) = 100 \times s / |\bar{x}|$

CV can be misleading when the mean is near zero or when zero is arbitrary, as on the Celsius temperature scale. A low CV does not establish absence of bias.

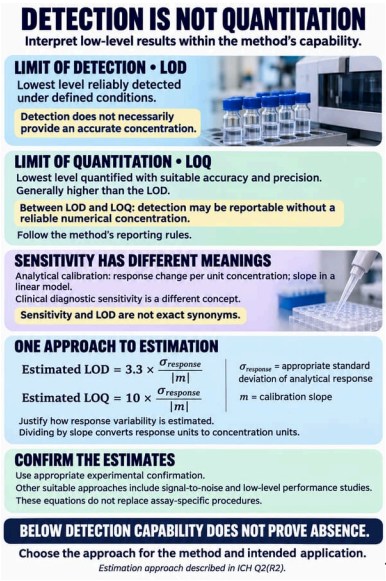
For example, measurements of 98, 100, and 102 units have a mean of 100, a sample standard deviation of 2, and a CV of 2%. If the reference value is 100 units, the mean has 0% relative bias. Three results alone do not establish the full performance of a method.



Conceptual illustration of bias and precision. The center is the reference, blue points are repeated results, and the orange cross marks their mean. A mean close to the target does not make widely scattered individual results reliable. These simulated points illustrate concepts, not assay data.

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15.9: Detection and Quantitation Limits



The **limit of detection (LOD)**, also called the detection limit, is the lowest level that can be reliably detected under defined conditions, without necessarily being quantified accurately. A result below this capability should not be described as proof that the analyte is absent.

The **limit of quantitation (LOQ)** is the lowest level that can be quantified with suitable accuracy and precision. It is generally higher than the detection limit. Results between these levels may support detection without a reliable numerical concentration, according to the method's reporting rules.

The term sensitivity can refer to different concepts. In analytical calibration, it often refers to the change in response per unit change in analyte concentration, represented by the slope for a linear model. Clinical diagnostic sensitivity is a different concept. Avoid treating sensitivity and LOD as exact synonyms.

LOD and LOQ can be evaluated using suitable approaches such as signal-to-noise, low-level performance studies, or the response standard deviation and calibration slope. One approach described in ICH Q2(R2) uses the following estimates:

Estimated LOD = 3.3 × σresponse / |m|

Estimated LOQ = 10 × σresponse / |m|

In these equations, σresponse is an appropriate standard deviation of the analytical response and m is the calibration slope. The choice and estimation of response variability must be justified. Dividing by the slope converts response units to concentration units. Simply multiplying a blank's standard deviation by 3 or 10 does not generally yield a concentration limit.

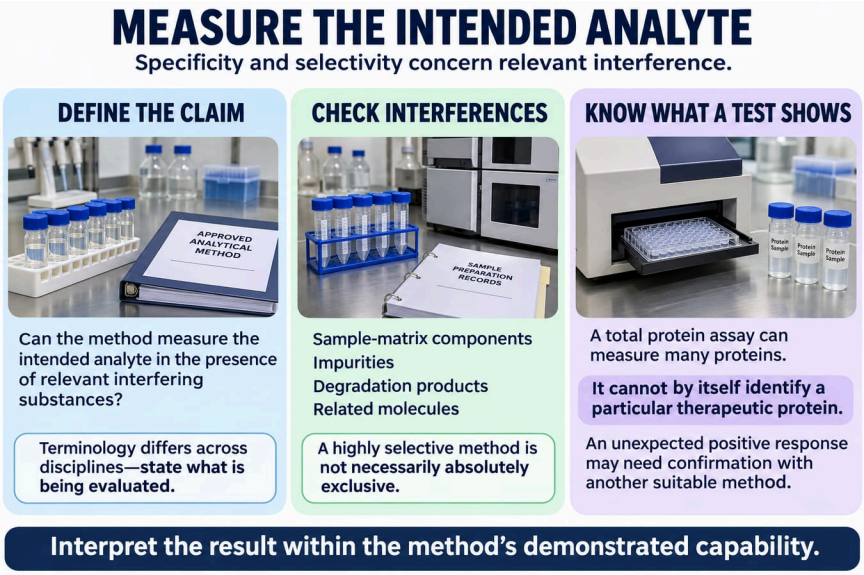
Calculated estimates need appropriate experimental confirmation. These equations are not universal substitutes for the procedure specified for a particular assay or regulatory application.

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15.10: Specificity and Selectivity

Specificity or selectivity concerns measuring the intended analyte in the presence of relevant interfering substances. Possible interferences include sample-matrix components, impurities, degradation products, and related molecules. The terms are used with some differences across disciplines; define the claim being evaluated.

A method may be highly selective without being absolutely exclusive. An unexpected positive response may require confirmation with another suitable method. A total protein assay, for example, may measure many proteins and cannot by itself identify a particular therapeutic protein.



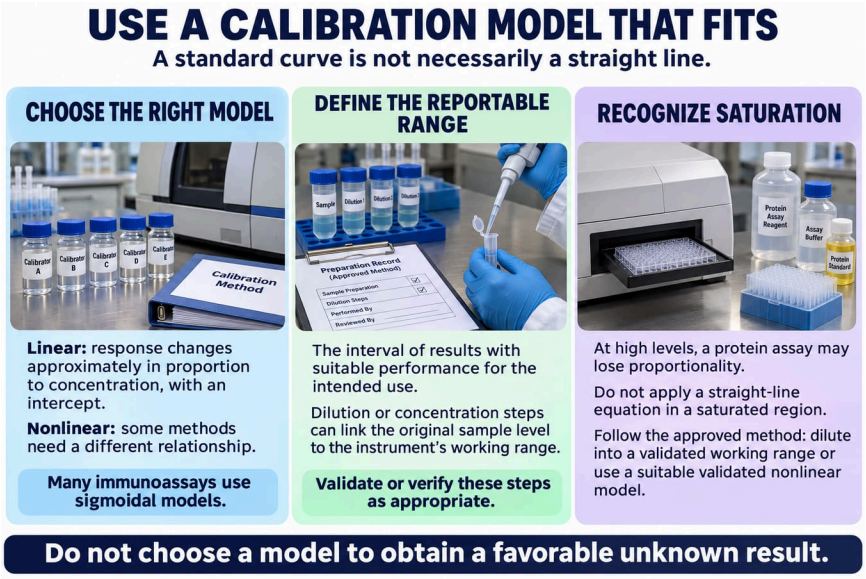
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15.11: Calibration Model Linearity and Range

A linear calibration model describes a response that changes approximately in proportion to concentration, allowing for an intercept. A method may instead require an appropriate nonlinear model. Many immunoassays use sigmoidal calibration models, so a standard curve is not necessarily a straight line.

The reportable range is the interval of results over which the procedure provides suitable performance for its intended use. Relevant dilution or concentration steps can connect a sample's original level to the instrumental working range. Validate or verify those steps as appropriate.

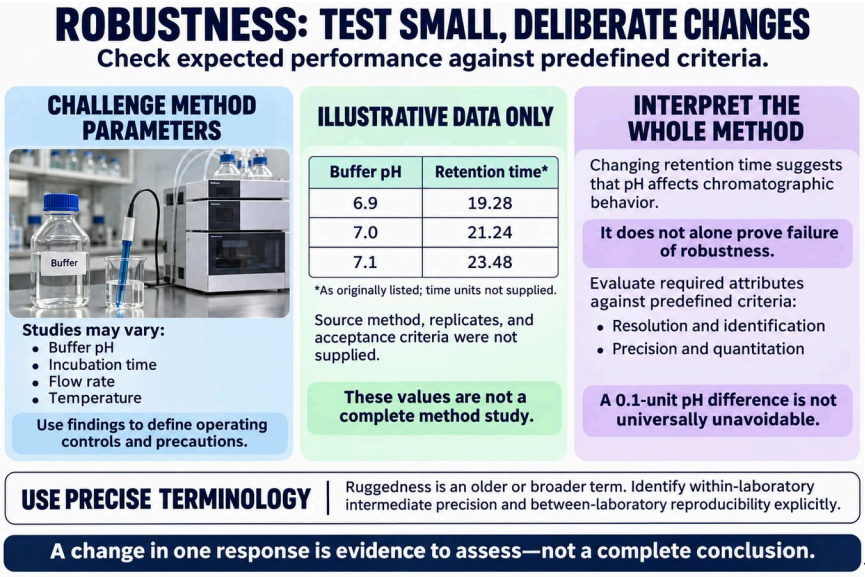
A protein assay can lose proportionality at higher levels. Do not use a straight-line equation in a saturated region. Depending on the approved method, dilute into a validated working range or use a suitable, validated nonlinear model. Do not choose a model merely because it gives a favorable value for an unknown.



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15.12: Robustness and Intermediate Precision

Robustness evaluates whether a procedure meets expected performance despite small, deliberate changes in method parameters. Studies might vary buffer pH, incubation time, flow rate, or temperature. They help define suitable operating controls and precautions.



The original workbook gives the following pH and retention-time values. No source method, time unit, replicate information, or acceptance criteria were supplied, so they are retained only as an illustrative teaching dataset.

Time units were not specified in the supplied source. Treat the values as illustrative rather than as a complete method study.

The changing retention time suggests that pH affects this chromatographic behavior. It does not by itself prove that the complete method fails robustness. Evaluate the required attributes, such as resolution, identification, precision, or quantitation, against predefined criteria. Suitable instruments and procedures can control pH to the precision needed; a 0.1-unit difference is not universally unavoidable.

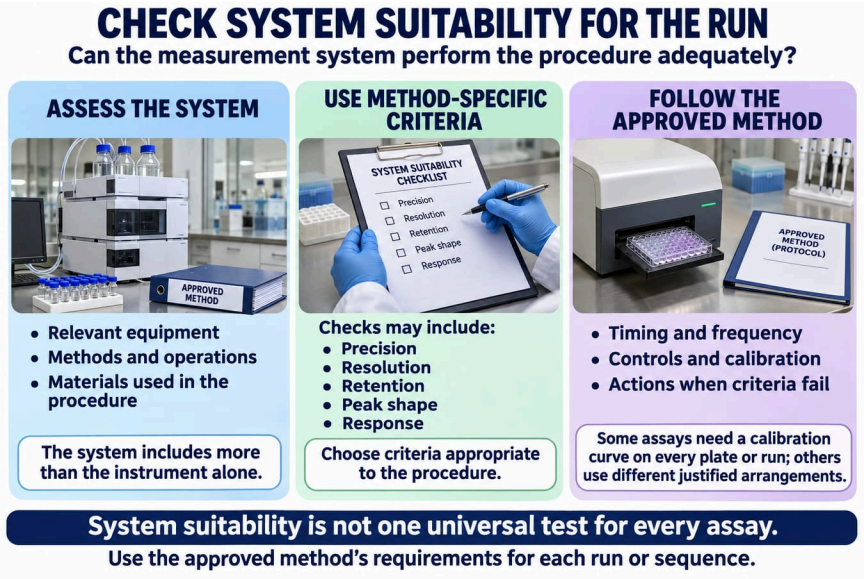
Ruggedness is an older or broader term often used for performance across normal operating variations. In current pharmaceutical validation discussions, identify within-laboratory intermediate precision and between-laboratory reproducibility explicitly rather than treating all these terms as exact synonyms.

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15.13: System Suitability

System suitability tests check whether the measurement system is capable of performing the procedure adequately for a run or sequence. Depending on the method, checks may involve precision, resolution, retention, peak shape, response, or other criteria.

The system includes relevant equipment, methods, operations, and materials. Suitability testing is not limited to one reference standard before every type of assay. Follow the approved method for timing, frequency, controls, calibration, and actions when criteria fail. Some assays require a calibration curve on every plate or run; other procedures use different justified arrangements.



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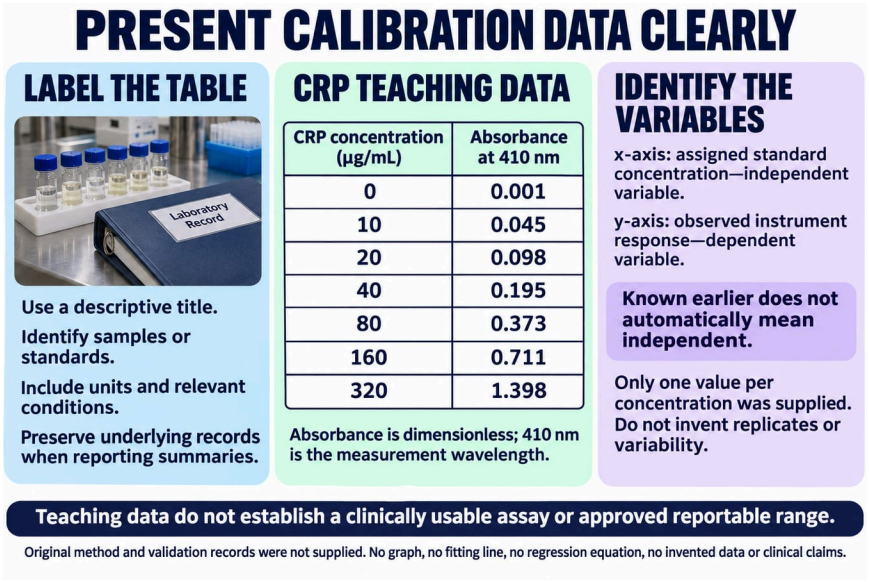
15.14: Organizing Quantitative Data

A table presents values in labeled rows and columns. Include a descriptive title, sample or standard identifiers, units, relevant conditions, and any information needed to interpret the values. Preserve underlying records even when a table reports means or other summaries.

For calibration, the assigned standard concentration is commonly the independent variable on the x-axis, and the observed instrument response is the dependent variable on the y-axis. This convention describes the calibration design; a variable is not independent merely because it was known earlier in time.

The following CRP data are retained from the original workbook as a teaching example. The original method and validation records were not supplied. Therefore, these values do not establish a clinically usable CRP assay or an approved reportable range.

Absorbance is dimensionless; report the measurement wavelength separately or in the column heading. Record replicate observations and their variability when available rather than inventing replicates for a dataset that contains only one value per concentration.



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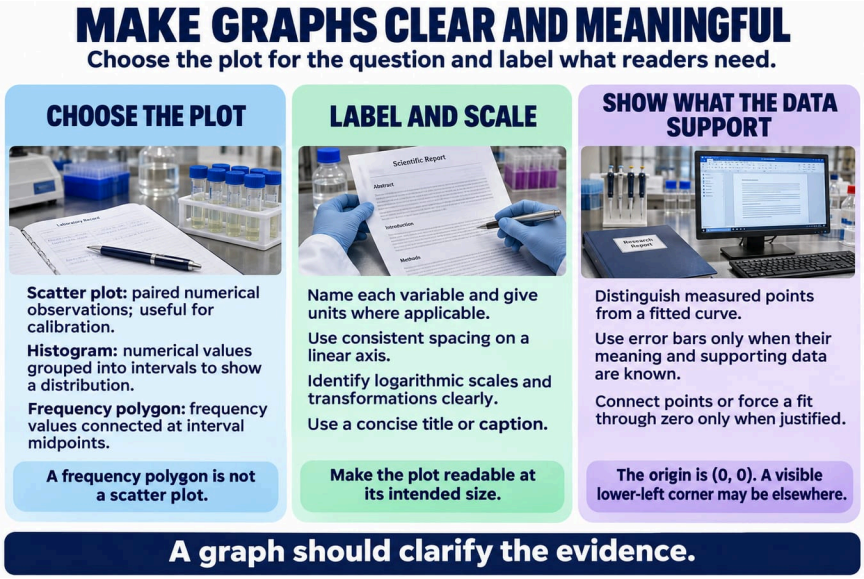
15.15: Graphs

A scatter plot displays paired numerical observations. It is useful for calibration data. A histogram groups numerical values into intervals to show a distribution. A frequency polygon connects frequency values at interval midpoints; it is not another name for a scatter plot.

Label axes with the variable and unit where applicable. Use a scale suited to the data, with consistent spacing on a linear axis. Logarithmic scales are useful in some applications, but the scale and transformation must be clear. A plot need not fill an entire page; it must be readable at its intended size.

Use a concise descriptive title or caption. Show measured points and distinguish them from any fitted curve. Include error bars only when their meaning and supporting data are known. Do not connect points or force the line through zero unless the method and analysis justify it.

The origin is the point (0, 0), but a graph may display only part of the coordinate plane. Its visible lower-left corner is not necessarily the origin.



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15.16: Standard Curves and Linear Regression

A calibration or standard curve relates assigned concentrations to measured responses. Use appropriate standards, blank treatment, sample preparation, and a predefined model. Standards and samples must be handled comparably as required by the method, with relevant matrix and timing effects controlled.

For a straight-line model:

$y = mx + b$

Here, y is the measured response, x is concentration, m is slope, and b is the y-intercept. For a nonzero slope, an unknown concentration is estimated by rearranging the equation:

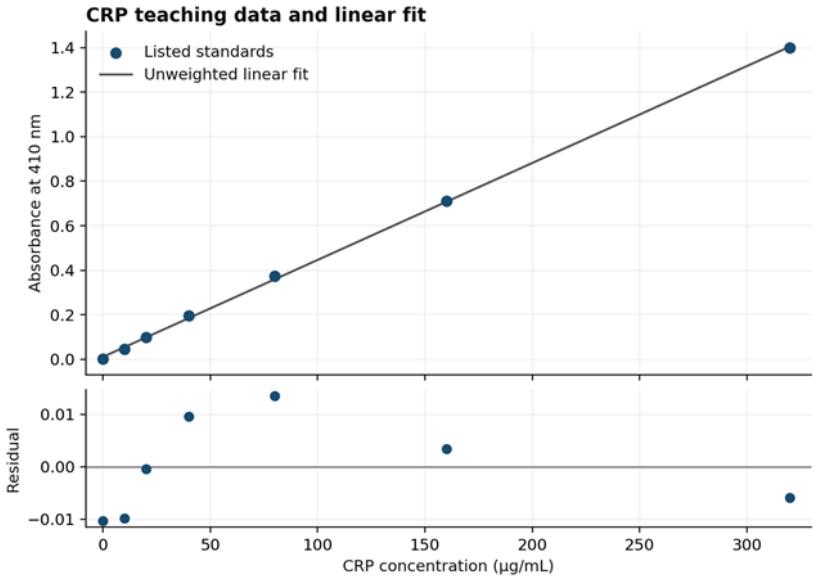
$x = (y - b) / m$

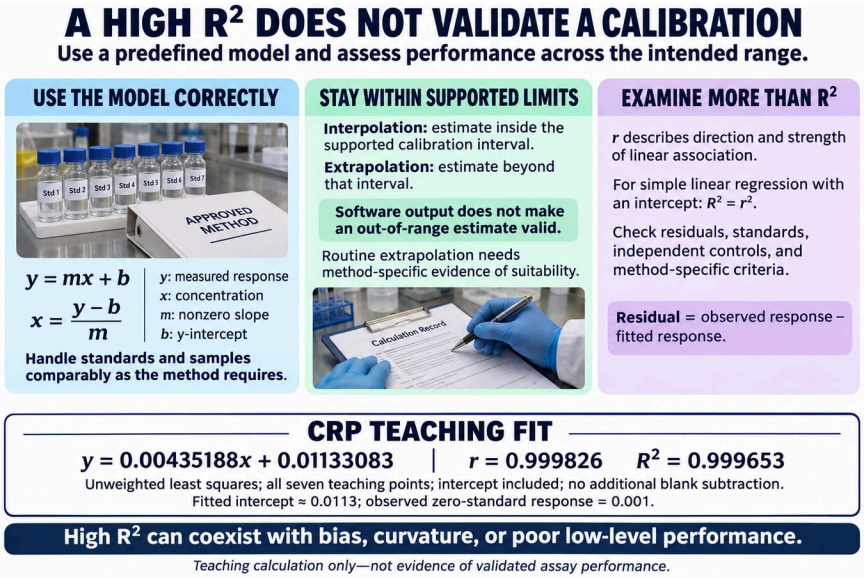
An estimate inside the supported calibration interval is **interpolation**. An estimate beyond that interval is **extrapolation** and is generally not justified for routine reporting unless the method specifically establishes its suitability. Numerical output from software does not make an out-of-range estimate valid.

An ordinary, unweighted least-squares fit to all seven CRP teaching points gives the following results. The calculation includes an intercept, uses the listed absorbances without additional blank subtraction, and is shown for instruction rather than as a validated model.

$y = 0.00435188x + 0.01133083$

$r = 0.999826 \quad R^2 = 0.999653$





Calibration points, fitted line, and residuals. Residuals are measured absorbance minus predicted absorbance. The fit is a teaching calculation; it is not evidence of validated assay performance.

The **correlation coefficient r** measures the direction and strength of a linear association and ranges from –1 to +1. For ordinary least-squares regression with an intercept, R^2 describes the fraction of response variation explained by the fitted model and normally lies between 0 and 1. In simple linear regression with an intercept, $R^2 = r^2$. These quantities are related but are not the same statistic.

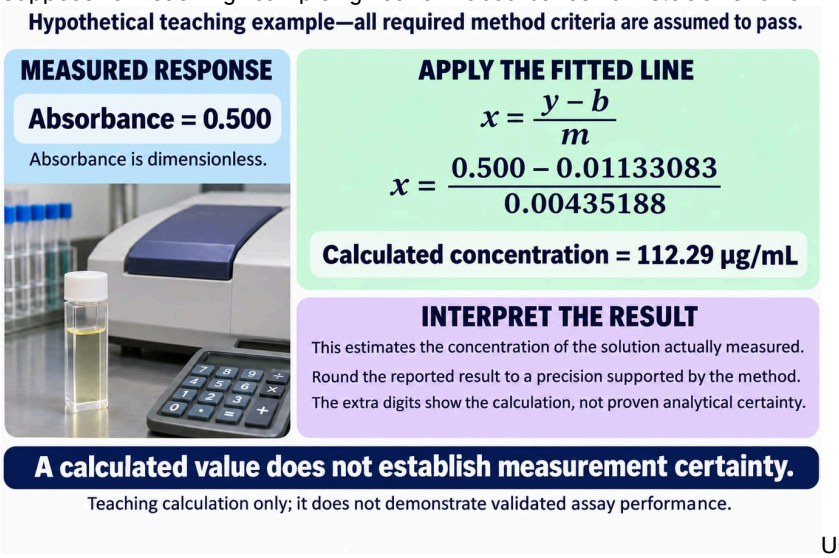
There is no universal rule that R^2 above 0.95 establishes an acceptable calibration. A high R^2 can coexist with bias, curvature, poor low-level performance, or inappropriate weighting. Inspect residuals, calibration standards, independent controls, and method-specific acceptance criteria. A residual is the observed response minus the fitted response.

For these teaching data, the high-concentration values strongly influence an unweighted fit. The fitted intercept is about 0.0113 even though the observed zero-standard response is 0.001. That difference illustrates why a high R^2 alone does not establish suitability across the entire concentration range.

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15.17: Unknown and Dilution Example

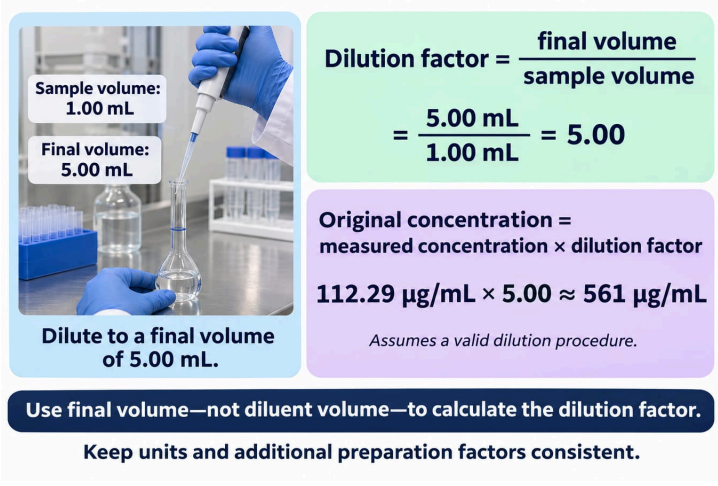
Suppose a teaching sample gives an absorbance of 0.500 and all required method criteria are assumed to pass.



Using the fitted line:

x = (0.500 − 0.01133083) / 0.00435188 = 112.29 µg/mL

This estimates the concentration of the solution actually measured. Report a rounded result appropriate to the method's precision; the extra digits here show the calculation, not proven analytical certainty.

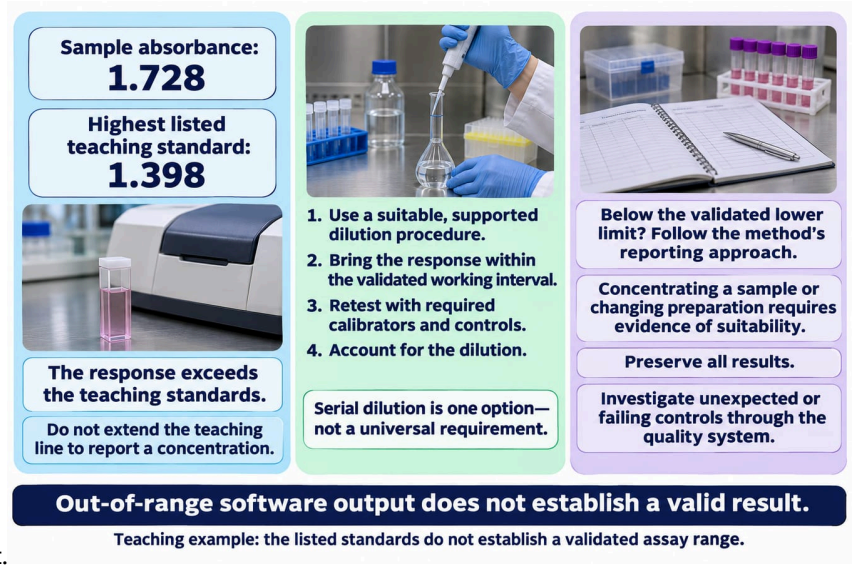


If the measured solution was prepared by diluting 1.00 mL of sample to a final volume of 5.00 mL, the dilution factor is 5.00. Under the assumed valid dilution procedure:

Original concentration = measured concentration × dilution factor

Original concentration = 112.29 × 5.00 ≈ 561 µg/mL

A dilution factor is final volume divided by sample volume, not diluent volume divided by sample volume. Keep the units and any



additional preparation factors consistent.

An absorbance of 1.728 exceeds the highest listed teaching standard response of 1.398. Do not report a concentration by extending this teaching line. Under a suitable method, dilute the sample to bring its response within the validated working interval, retest with required calibrators and controls, and account for the dilution. A serial dilution is one option, not a universal requirement.

Values below the validated lower limit also need the method's reporting approach; concentrating a sample or changing preparation cannot be assumed valid. Preserve all results and investigate unexpected or failing controls through the quality system.

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15.18: Chapter Summary

Quality assays provide evidence about a sample's identity, concentration, purity, biological activity, or other defined characteristic. Quantitative assays report numerical values, while qualitative assays report categories under defined conditions. The test must match the sample, intended use, and decision. Concentration and potency are different: measuring the amount of protein does not necessarily show how much of it is biologically active.

A reliable result begins with suitable sampling. A representative sample reflects the characteristics relevant to the question being asked. Sampling plans should address important differences across times, locations, or containers rather than selecting only convenient material. Sample preparation also matters. Mixing, extraction, storage, and dilution can introduce losses, interference, or errors. Recovery studies can help evaluate preparation and measurement effects, but their conclusions depend on how the study is designed.

Reference materials, calibration standards, and controls serve related but different purposes. Calibration standards establish the relationship between an assigned quantity and the measured response. Controls check whether the test system performs acceptably. Positive, negative, extraction, and internal controls address different possible problems. Staff must evaluate control failures before interpreting affected samples. Passing controls do not prove that sampling, labeling, or every other step was correct.

Analytical method validation provides evidence that a procedure is suitable for its intended purpose. Relevant characteristics include accuracy, precision, specificity or selectivity, range, and detection or quantitation capability. Accuracy concerns closeness to a relevant true or accepted value. Precision concerns agreement among repeated measurements. Tightly clustered results can still be biased, and a mean near the reference does not make widely scattered results reliable. Standard deviation and coefficient of variation describe spread, but neither alone establishes overall method suitability.

Detection and quantitation limits define different capabilities. A method may detect an analyte at a level too low for reliable numerical measurement. A result below the detection limit does not prove absence. Robustness studies examine performance after small, deliberate method changes, while system suitability checks whether the measurement system can perform adequately for a run or sequence. These checks support reliable testing but do not replace validation.

Clear tables and graphs help readers evaluate results. A standard curve relates assigned concentrations to measured responses. For a suitable linear model, $y = mx + b$, an unknown concentration can be estimated using $x = (y - b) / m$. Use the model only within its supported range and follow the method's preparation and reporting rules. A high R^2 alone does not establish an acceptable calibration; residuals, standards, independent controls, and relevant acceptance criteria also matter.

The calculated concentration usually describes the solution actually measured. When a valid dilution was performed, multiply that concentration by the dilution factor to estimate the original sample concentration. The dilution factor is final volume divided by sample volume. Preserve units, report appropriate precision, and avoid extending a curve beyond its supported range. Reliable assay decisions depend on the complete chain of evidence, from sampling through calculation and review.

Key Terms

Assay	Analyte	Quantitative assay
Qualitative assay	Identity test	Purity
Potency	Stability	Representative sample
Sampling bias	Sample matrix	Recovery

Reference material	Calibration standard	Positive control
Negative control	Internal control	Analytical method validation
Accuracy	Precision	Bias
Random error	Standard deviation	Coefficient of variation (CV)
Limit of detection (LOD)	Limit of quantitation (LOQ)	Specificity or selectivity
Robustness	System suitability	Reportable range
Standard curve	Linear regression	Residual
Interpolation	Extrapolation	Dilution factor

Review Questions

1. How does a quantitative assay differ from a qualitative assay?

2. How do identity, concentration, purity, and potency tests answer different questions about a product?

3. What makes a sample representative, and why might convenience sampling be unsuitable?

4. How can sample preparation affect an assay result, and what can a recovery study help evaluate?

5. How does a calibration standard differ from a control?

6. What do positive and negative controls help establish, and what should happen when a required control fails?

7. How do accuracy, precision, and bias differ?

8. What do standard deviation and coefficient of variation describe?

9. How does the LOD differ from the LOQ, and why does a result below the LOD not prove absence?

10. What are the purposes of robustness studies and system suitability tests?

11. Why is a high R^2 insufficient by itself to establish an acceptable standard curve?

12. How do you calculate an unknown concentration from $y = mx + b$ and then account for a valid dilution?

Apply Your Knowledge

The following situations and numerical values are hypothetical teaching examples, not approved assay methods or product specifications.

1. A facility fills vials over five days. An analyst selects six easily reached vials from the first hour and combines equal portions into

one sample for testing. Explain how this plan could miss changes across the production run or differences among vials. Propose a more suitable sampling approach and explain when separate samples would provide information that a composite sample could hide.

2. An assay plate has a smooth standard curve and a high R^2, but an independently prepared low-level control fails its predefined acceptance criterion. A coworker wants to report the sample results because the curve looks good. Explain why the curve alone is insufficient. Identify possible standard preparation, control preparation, matrix, and method problems to investigate before deciding which results can be interpreted.

3. A reference material has an assigned concentration of 100 units/mL. Method A gives results of 89, 90, and 91 units/mL. Method B gives 90, 100, and 110 units/mL. Calculate each mean, sample standard deviation, CV, and relative bias. Compare the precision and bias of the two sets. Explain why these three measurements per method are insufficient to establish complete method performance.

4. A method has an established LOD of 0.20 µg/mL and LOQ of 0.60 µg/mL. A sample produces a confirmed response consistent with analyte detection, but its estimated concentration is 0.35 µg/mL. Explain why reporting a precise concentration or reporting the analyte as absent would each overstate the evidence. Describe how the approved reporting rules and the purpose of testing should guide the next step.

5. A teaching assay uses the linear model $y = 0.0050x + 0.020$, where y is absorbance and x is concentration in µg/mL. Its supported working interval is 10–100 µg/mL. An analyst dilutes 1.00 mL of sample to a final volume of 5.00 mL and measures an absorbance of 0.320. Assuming all method criteria pass, calculate the measured solution's concentration, the dilution factor, and the original sample concentration. Then explain why an absorbance of 0.720 would require a different response rather than simply extending the line.

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