Cleaning and Sanitation
Training Outcome of the Module:

Cleaning and sanitation programs are an important part of GMP, as they protect products from environmental contamination and cross-contamination with other materials or product. These programs are also designed to protect us from the effects of hazardous materials.

At the end of the module, you will be able to:

- Define the meaning of the words "cleaning" and "sanitation"
- Recognize why you need to clean before you sanitize
- Identify the GMP requirements for documenting cleaning and sanitizing activities
- Explain the reasons why you must use only approved cleaning and sanitizing materials
- Explain why cleaning and sanitation prevents product contamination

International GMP rules

Outside the US, almost all regulatory agencies have standardized and harmonized to the EU GMP rules and guidance for medicinal products. Some countries, such as Canada, still maintain a country-specific code of GMP, which is very similar to the EU GMP rules.

In this training program, we use the term International GMP rules" to refer to the group or rules, guidance, and codes that are based on the EU GMPs. If there are specific differences that are relevant to the module, it will be indicated as such.
For almost 20 years, it has been a basic GMP requirement that all cleaning steps in a pharmaceutical plant be documented accurately, and also validated to prove they work. Once the steps are validated, employees must only follow the approved procedure.

**What do the GMP rules say?**

**US FDA CFR 211**

**Subpart D - Equipment**

Sec. 211.67 Equipment cleaning and maintenance.
(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:
(1) Assignment of responsibility for cleaning and maintaining equipment;
(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
(4) Removal or obliteration of previous batch identification;
(5) Protection of clean equipment from contamination prior to use;
(6) Inspection of equipment for cleanliness immediately before use.
(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.

**International GMPs**

**Ch. 5 Production:**

5.19 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

(e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

(g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

**Overview**

Some kinds of contamination are often difficult to detect by physical inspection. The claim: "It looks clean, therefore it must be clean" is not necessarily true. Laboratory testing for potential contaminants is generally not practical, economical, nor reliable.

Cleaning and sanitation are both needed to reduce potential contamination. Contamination could negatively impact the end product if it is present in the manufacturing facility or on production equipment.

- Chemical contamination
- Environmental contamination
- Biological contamination
### GOOD TO KNOW - STERILE PRODUCTS

For sterile products, production must be done cleanrooms protected by High Efficiency Particulate Air (HEPA) air filters. Cleanroom requirements are very strict in these areas and are usually associated with positive room pressures (overpressure) to protect the areas from external airborne contamination. Usually 99.97% of all airborne particles above 0.5 microns are excluded by the HEPA filters.

### GOOD TO KNOW - POTENT PRODUCTS AND CROSS-CONTAMINATION

The prevention of cross-contamination is particularly important when the factory produces products such as steroids, hormones, antibiotics, cytotoxic products and some potentially pathological biological materials.

These materials, even in minute amounts, may have a significant effect on the body, and it is important to isolate them from the environment during manufacture, and remove their residues from equipment during cleaning.

If you manufacture any of these products, ensure that you are fully aware of the rules for handling and cleaning. Wear the protective gear provided.

### TYPES OF CONTAMINATIONS

**Chemical contamination**

Chemical contamination occurs when product becomes contaminated with other materials or products. This can potentially occur when different products are processed in the same equipment, or when materials such as cleaning agents and lubricants come into contact with products or product surfaces.
The way to avoid chemical contamination is by following written cleaning procedures exactly. Often the steps and conditions in the procedures have been validated to ensure they are effective.

Changing the steps or conditions may make the cleaning ineffective.

### Environmental contamination

Different areas of manufacturing within the facility carry different levels of contamination risk to the product.

In areas where product is exposed to the environment, for example, in the dispensary, formulation areas, and bottle filling rooms, there is a higher risk of contamination. Air control is required (usually filtered), and frequent cleaning of the facility and environmental monitoring are recommended.

In other areas, such as in secondary packaging or in material storage areas, the product isn’t exposed to the environment, so there is a lower risk of contamination. Less environmental air control is necessary, the frequency of cleaning is reduced, and environmental monitoring is minimal.

### Biological contamination

"Biological contamination" refers to contamination by bacteria, yeasts, moulds, viruses, or any other microorganisms that may be present in product. This also can include residues from dead micro-organisms or endotoxins, which can contaminate injectable products.
The origins of biological contamination are varied, but include the environment, personnel, raw materials, contaminated water, and poorly cleaned or wet equipment.

While cleaning reduces biological contamination, sanitizing agents play an important role in killing micro-organisms.

GOOD TO KNOW - VISUAL EVIDENCE OF CONTAMINANTS

Visual inspection of products is easy and inexpensive, but it is often labor-intensive and unreliable. Although obvious contaminants can be seen, there may be microscopic contaminants in the product, such as microbial, particulate, and product chemical residues, which are all difficult and expensive to detect once they are inside product.

The aim in good cleaning and sanitation practices is to prevent contamination arising in the first place, rather than try to detect it once it is present.

These two ampoules are actually contaminated. However, you cannot see this with the naked eye. It’s important to know that not all contamination in medicinal products can be seen, and in many cases, cannot be detected in laboratory testing.
What is cleaning?

Cleaning is the removal of visible and microscopic contamination by dirt, extraneous material, or product residues by mechanical or physical means. Cleaning is usually followed first by visual inspection, and then by laboratory testing to verify that the cleaning continues to be effective.

Effective cleaning usually requires the use of cleaning agents such as detergents and solvents, which are used under specified conditions of pH, temperature, time and solvent concentration.

A concern with cleaning is whether or not the cleaning agent itself will have a negative effect on the life of the equipment or on the quality of the product.

What is sanitation?

Sanitation is the reduction of microbiological contamination. It is usually achieved by the use of chemicals. However, it can also be achieved by hearing and even vigorous mechanical action, such as scrubbing. (Note: Cleaning may result in a partial reduction of the microbial load.)

If sanitizing chemicals are used, it may be necessary to remove the sanitizers' residues by further cleaning. It is therefore very important to use the specified amount of sanitizing agent.
There are several factors that determine how effective sanitizing will be. These include:

- the number and types of microbes
- the type of material containing the microbes
- the concentration, temperature, and pH of the sanitizing agent
- the length of time you sanitize for

**Note:** It is impossible to sanitize a dirty surface. The surfaces must first be thoroughly cleaned.

### Types of sanitizing agents

Different sanitizing agents will be effective only in certain circumstances.

<table>
<thead>
<tr>
<th>TYPE OF SANITIZING AGENTS</th>
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<tbody>
<tr>
<td><strong>Sanitizer</strong></td>
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<tr>
<td>Proper use results in bacteria reduction of &gt;99.9% if used on pre-cleaned surfaces. Pre-cleaning is always required in order to reduce bioload and dirt.</td>
</tr>
</tbody>
</table>
**Disinfectant**
Proper use results in 100% kill of vegetative bacteria, target viruses and target fungi. Pre-cleaning may or may not be required, but it is considered a pre-requisite.

**Sterilant**
Proper use results in 100% kill of all microorganisms, including bacterial spores. Pre-cleaning is always required in order to reduce bioload and dirt.

**Sporicide**
Proper use results in 100% kill of all bacterial spores.

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**GOOD TO KNOW - WHAT DOES PROPER USE MEAN?**

Proper use means using the agent under specific conditions to ensure they are optimally effective. The conditions of use are described in written procedures.

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**GOOD TO KNOW - "STERILISATION" VS. "SANITATION"**

**Sterilization** means the total elimination of any living organisms, usually by heat or chemical means, of any living organisms.

**Sanitation** means the reduction in microbial load (the bio burden) by chemical means. The end result of sanitation does not guarantee the complete absence of micro-organisms.
The majority of chemical and physical agents in use will clean and sanitize and/or disinfect but not sterilize.

### GOOD TO KNOW - COMMON SANITIZERS

- 70% v/v alcohol (for surfaces)
- Quaternary ammonium compounds (QUATs)
- Phenolics
- Sporicides (for killing spores)
- Chlorines (such as hypochlorite)
- Hydrogen peroxide/peracetic acids
- Sodium hydroxide (cleaning & partial sanitizing)

You should be familiar with your company agents and only use approved agents in the nominated strengths.

### GMP rules and cleaning

The GMP rules are very explicit regarding the requirement to clean and sanitize equipment and the manufacturing facility.

Since most residues cannot be seen nor reliably tested for, the company’s standard procedures and cleaning records are relied upon as evidence of cleaning.
## GMP Rules for Cleaning

<table>
<thead>
<tr>
<th>Cleaning Procedure</th>
<th>Cleaning validation</th>
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<tbody>
<tr>
<td>GMP requires the cleaning procedures to be fully documented in written procedures. These procedures are initially validated (shown to be effective) specifically for an item of equipment or an area. Once validated, the procedures are then published and used.</td>
<td>All cleaning procedures should be validated (shown to be effective) under specific conditions of use. These conditions of use are specified in the written procedure. If employees alter the conditions of use, the cleaning methods may be &quot;invalidated&quot; and may not be effective. For example, it would seem logical that adding more sanitizer than the procedure requires</td>
</tr>
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</table>
would make cleaning faster or better. This is not always the case. Adding additional sanitizer may alter the pH of the cleaning agent and make it less effective.

The relevant GMP rules are to only clean under validated conditions, and to follow procedures exactly.

### Cleaning conditions

The written procedures describe the required conditions under which cleaning is optimal. These conditions may include a range of the following:

- strength of the cleaning or sanitizing agent (e.g. 2.0% v/v)
- the type of water or solvent to be used
- the pH of the cleaning agent
- the temperature of the water to be used
- how much to dismantle equipment before cleaning commences
- the contact or residence time for the sanitizing agent on the surface
- what agents to use to clean off the sanitizing agent
- what standard of water to use in the final rinse (GMP, for example, requires purified or water for injection as the final rinse).
**Cleaning records**

One essential GMP rule is the keeping of detailed cleaning records. Cleaning records provide not only proof that cleaning took place, but also provide evidence of the cleaning outcomes, for example, that the surfaces are visually clean, or the results of rinse water tests. The records must also identify who did the cleaning and when, and must be signed.

For automatic cleaning procedures such as clean in place (CIP), the cycle conditions are usually automatically monitored and the conditions recorded. Cycle conditions may include the temperature, flow rate, time, concentration of solvent, and solvent agitation time. Often CIP systems have alarms when something goes wrong.

The completed and signed records should be attached to the records, since they provide the only real evidence that cleaning has occurred.

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**What must be cleaned?**

- The facility must be regularly cleaned. Particular emphasis is placed on areas or rooms where product is processed.

- Particular emphasis is placed on the effective cleaning of all equipment in contact with product, and must be cleaned according to validated and detailed procedures.

- All equipment in processing areas not in contact with product needs regular cleaning in order to prevent buildup of dust and dirt.
WHAT MUST BE CLEANED

The inside of the factory should be regularly cleaned, but particular attention should be paid to the processing and storage rooms. The floors, surfaces, benches, walls and ceilings should undergo cleaning at defined intervals.

Cleaning and sanitation also applies to any equipment that is in contact with the product during manufacture, such as production and packaging equipment, transfer lines and tanks, and storage containers and drums.

Protecting yourself

One of the most overlooked reasons for cleaning is to protect yourself.

Chemicals may cause adverse reactions in people if they are continuously exposed to them.

Regular and thorough cleaning, wearing protective garments, and abiding by correct handling procedures eliminate this problem.
These operators are preparing to dean a dispensary used to weigh out powders.

- They are wearing hair nets.
- They are wearing protective gloves and face masks.
- They are wearing disposable gowns.
- They are checking the procedure to verify if the chemical residues may need special handling.

While your company may not use all these specific precautions, it's important to ensure you follow the written procedure and protect yourself when cleaning.

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Part II: Facility Cleaning

Most production facilities are multi-use, that is, on any given day, different products will be simultaneously processed, but never in the same rooms. The primary means of preventing cross-contamination in multi-use facilities are the air controls (sometimes called HVAC).

Room pressures serve a couple of functions. They contain dust within a room, and prevent the dust from getting into other rooms (negative pressure). Room pressures also exclude outside air containing dust, dirt and microbial particles from entering a facility (positive pressure). If these pressures are lost, then there is potential risk of contamination. No amount of laboratory testing could
overcome this problem, since the laboratory cannot possibly devise tests for all possible contaminants.

**What do the GMP rules say?**

**US FDA CFR211**

*Subpart C–Buildings and Facilities*

*Sec. 211.46 Ventilation, air filtration, air heating and cooling.*

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production, In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

**International GMPs**

**Ch 5 - Production**

5.19 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:  
a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;  
b) providing appropriate air-locks and air extraction;  
c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
d) keeping protective clothing inside areas where products with special risk of cross contamination are processed;
e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
f) using "closed systems" of production;
g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Overview

Cleaning is a technical task. When you are cleaning, it is important to:

- Wear the same clothing as in the processing areas.
- Make sure you are trained in all written cleaning procedures,
- Use only specified cleaning agents,
- Maintain appropriate cleaning records.

GOOD TO KNOW - EXCLUDING CONTAMINATION FROM THE FACTORY

There are a number of ways to exclude external environmental contamination from the factory.

Dust, dirt, particles and bacteria can enter the factory via people, the air, packaging that is introduced from outside, or by transfer of pallets, equipment, forklifts, etc., that move regularly from outside the factory to inside.

GMP rules require that all entries to production rooms have air barriers and/or separating rooms that exclude air, require people to gown, or require the clean-down of all items that have been transferred from outside the facility to inside. Central to this is the GMP rule that requires the closing of external doors at all times when not in use.
GMP ISSUES WHEN CLEANING

- Take note of hard to reach places. As soon as air rushes through a dirty vent, there is a good chance or dirt and dust tailing into whatever is below.

- An open window presents an excellent opportunity for airborne contaminants, dirt, or pests to enter the production facility. Ensure that windows (and doors) are closed at all times.

- Dress standards should be the same for cleaning as for product manufacture.

- A mop and bucket left standing about can lead to microbial contamination. Additionally, poor quality equipment makes for a poor qualify job. Mops with wooden handles can easily harbor unwanted bacteria or fungal life, and should not be used.

- Particular care needs to be taken when cleaning around drains. Leaving the drain like this will quickly lead to widespread re-contamination of the facility.

Cleaning the facility

When cleaning the facility, you should pay particular attention to:

- High-traffic areas

- Doorknobs, switches, and other areas commonly touched by personnel

- Outer packages and pallets in processing areas

- Difficult to clean areas, such as extraction ducts, wet areas, and open drains

- Exposed pipework and ledges
Cleanliness of starting material and equipment surfaces as they are moved from less clean areas to cleaner or classified areas

Always work from the cleanest areas to the dirtiest areas.

This means cleaning from top to bottom, and working towards the door.

Buildings and grounds

GMP covers all areas of the factory, not just your immediate workspace. Facility cleanliness include such factors as:

- keeping the building and gardens tidy
- wiping shoes upon entering buildings
- keeping external doors shut at all times (to stop dirt and discourage pests or birds from entering)
- not eating or drinking in manufacturing areas
- minimizing clutter in common areas and at individual work areas
- keeping waste bins closed
**Inward goods and product storage areas**

It is important to regularly clean warehouses where raw materials, labels, components and products are stored.

Rules for storage areas are:

- Protect receiving areas from the weather
- Inspect inward goods before acceptance and clean if necessary
- Store materials in a clean and dry condition
- Store materials off the floor and away from walls
Pest control

GMP requires that a manufacturing facility have:

- a nominated pest control officer
- specific instructions or agreements with pest control companies
- maps showing bait locations
- documentation of all pest control treatments

Environmental regulations and OH&S also require companies to protect personnel and the surrounding environment from the chemicals used in pest control programs.

An effective pest control program involves:

- keeping track of any sightings of pests between visits by the pest control companies
- assigning someone to accompany the pest control agent when they are on site
- having frequent waste collections
- using only approved pesticides

Part III: Equipment Cleaning

The cleaning of equipment, particularly equipment that has been (or will be) in contact with product, is one of the fundamental principles of GMP. It is almost certain that unclean equipment will in some way contaminate the next batch to be processed.

GMP rules worldwide place particular emphasis upon the effective, validated cleaning of all product contact equipment. The GMP rules also require that written procedures be available on how to clean and store such equipment.
During storage, it is possible for clean equipment to be re-contaminated if it is exposed to the environment (i.e. not fully covered over).

Another way that equipment can be contaminated on storage is by leaving equipment wet, which would support the growth of microbes.

**What do the GMP rules say?**

**US FDA CFR 211**

*Subpart D—Equipment*

Sec. 211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;
(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
(4) Removal or obliteration of previous batch identification;
(5) Protection of clean equipment from contamination prior to use;
(6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.
International GMPs

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

Prevention of cross-contamination in production

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing.

Overview

Equipment cleaning is critical to product quality. Cleaning is as much as a technical task as formulating, so it requires the same attention to detail and compliance to GMP.

The same principles apply for equipment cleaning as they do for facility cleaning:

- Follow all written cleaning SOPs,
- Maintain records of cleaning,
- Use only those cleaning agents that have been approved by QA,
- Store cleaning equipment in dry conditions, and clean the cleaning equipment regularly.

With equipment, a toggling system should identify the equipment cleaning status.

GOOD TO KNOW - WATER RESIDUE IN HOSES

A common problem in production areas is the cleanliness of transfer hoses. Transfer hoses can be a major source of microbial contamination if left wet on
storage. If a wet hose is reused later, it may then transfer bio burden back into the tank on the first flush through, causing microbial contamination of the next batch.

The specific GMP rules for hoses are:

- After cleaning, ensure that all hoses are detached from the equipment, and fully drained.
- Where possible, store hoses vertically away from wash bays.
- Keep hoses off the floor.
- Periodically sanitize, the hoses to keep them fresh.
- Flush the hoses before use, where possible.
- Where hoses are dedicated to a product, make sure that they are properly identified as such.

Equipment may have a number of areas where cleaning is difficult or where product residues tend to build up during processing. Move your mouse over the red circles in the diagram to see more information about these trouble spots.
Common and dedicated equipment

A common question regarding equipment cleaning is, "Does equipment have to be cleaned if it's going to be used again for the same product?"

The short answer is yes, however, the depth of cleaning may be different depending on whether or not the following batch is the same strength of the same product, a different strength of the same product, or a different product altogether. Each of these in turn will require more intensive cleaning.

<table>
<thead>
<tr>
<th>COMMON AND DEDICATED EQUIPMENTS</th>
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<tbody>
<tr>
<td><strong>COMMON EQUIPMENT</strong></td>
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<tr>
<td>is equipment that is used for more than one type of product. Common equipment must be completely cleaned, and sanitized if necessary, before every use, in order to prevent carryover of previous product to the next product.</td>
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<tr>
<td><strong>DEDICATED EQUIPMENT</strong></td>
</tr>
<tr>
<td>is equipment used to manufacture only one type of product, or for a run of batches (a campaign) of the same formulation. Cleaning requirements for dedicated equipment may be less than those for common equipment, provided the company has documented either the maximum number of batches or the maximum time that can elapse before complete cleaning must be done.</td>
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Cleaning validation

Cleaning validation sets out to prove that the documented cleaning procedure will consistently remove the previous product, remove the cleaning agent, and reduce the microbial population to a safe and acceptable level. Obviously then,
when companies handle potent or toxic drugs, equipment cleaning validation becomes a very important

Cleaning validation:

- defines the products that can be made in the equipment
- determines the maximum time allowed before the tank must be cleaned
- defines the cleaning agent to use, and its correct volume and concentration
- verifies the temperature of the cleaning process
- verifies the length of time needed for cleaning

Cleaning and sanitizing validation verifies that the specific cleaning procedure, under the specific conditions of cleaning described in the procedure, will be effective for a specific range of products in specific equipment. Any changes to these parameters may make the cleaning/sanitizing ineffective.

**GOOD TO KNOW - ORIGIN OF CLEANING VALIDATION**

The focus on cleaning validation commenced in the early 1990s, when the FDA published the Inspection Guide to Cleaning Validation.

This guidance was prompted by the increased manufacture of potent and new biotechnology products, that had high potency in low concentrations. Clearly
then, any of this product left on equipment could cause major contamination risks.

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<th>EQUIPMENT HOLD TIME</th>
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**POST-USE / PRE-CLEAN**

Once we have completed batch processing, there must be a maximum hold time between post-use and the commencement of cleaning. This is because over time, any residues will start to "bake" onto equipment surfaces and will be much harder to clean off. In addition, bio burden may start to grow.

It is required that procedures nominate and validate maximum allowable hold time. During cleaning, it is required to commence cleaning **before** the maximum hold time has elapsed.

**DURING THE CLEANING CYCLE (CONTACT TIME)**

During the cleaning cycle, procedures should specify a minimum hold time for contact of the cleaning agents and sanitizers with equipment surfaces.

This is because in order for cleaning and sanitizing agents to be effective, they must be in contact with the dirt and surface for a period of time. This contact time is validated.

**STORAGE BETWEEN USE**

Equipment must be stored dry and protected. GMP rules require that stored equipment must have an "expiry date" or maximum storage time before it needs to undergo re-cleaning.

Most companies have a simple rule: all equipment is inspected thoroughly before use, and any
equipment that exceeds its maximum storage hold time is re-cleaned before use.

**Equipment cleaning status tag**

The status of equipment should be apparent at all times, including during storage.

For example, this status tag on a vessel indicates:

- whether the equipment is clean or requires cleaning
- when the equipment was cleaned or is to be cleaned
- the previous product in the vessel
- when the equipment is due to be re-cleaned

After it is cleaned, the equipment should be stored with a protective cover to prevent contamination on storage.

Regardless of its cleaning status, equipment should always be examined before use to verify that it is clean and suitable for use.
Use of water in equipment sanitation

Water is often used in the cleaning and sanitation of equipment. Therefore, you should know that:

- Water is a good breeding place for micro-organisms.
- Bacteria can double in 15 minutes in water.
- Many water bacteria are harmful and cause consumer sickness or product spoilage.
- To protect the next product from microbial contamination, equipment must be stored dry.
- The final rinse of equipment must be in either purified water or water for injection, so that the surfaces are not re-contaminated after the cleaning cycle is complete.

Cleaning agents and equipment

Cleaning agents and equipment need to be carefully evaluated before they can be used in a manufacturing facility. The choice of cleaning and sanitizing agents is a decision made by QA/QC, so it should be ensured that only QA/QC-approved cleaning agents and equipment be used.

Because of this, GMP rules state that cleaning procedures must indicate the nominated strengths of cleaning agents, and that cleaning agents cannot be changed without approval.

The selection of a cleaning or sanitizing agent is dependent upon:

- the previous product type, for example, a cream or powder
- compatibility with equipment to be cleaned
- ease and safety of use
- ease of removal of residues
required contact times on equipment

the targeted microbial population

Disinfectants must be used in strict accordance with instructions. They should never be topped up, used, or stored without labels and expiry dates.

### GOOD TO KNOW - DISINFECTANTS

Disinfectants are tested for their bactericidal activity against four standard cultures of micro-organisms, namely:

- Pseudomonas aeruginosa
- Pr. Vulgaris
- E. coli
- Staphylococcus aureus

The disinfectant is tested at the manufacturer's recommended dilution as stated on the product label. The disinfectant dilution is passed or failed according to the extent of growth shown by the challenge bacteria. This is the reason it is very important to make dilutions correctly during use.

A common practice in the industry is to rotate between different sanitizing agents on a regular basis (for example, monthly). The intent of this is to prevent the possible build up of organisms with resistance to the sanitizing agent being used.

### GOOD TO KNOW - POTENTIAL RESIDUES

Some potential residues can include:

- cleaning agents
denatured product

- denatured excipients
- heat-denatured residues (with biological products)
- endotoxins or pyrogens

**Cleaning equipment**

Cleaning equipment or materials that shed particles, raise dust, produce aerosols or otherwise generate contamination should be avoided where possible. These include compressed air, bristle brushes, fibre-shedding cloths and certain designs of floor-scrubbing machines.

Vacuum or wet cleaning methods are preferred. Vacuum cleaners or polishers should be fitted with fine dust filters.

<table>
<thead>
<tr>
<th>CLEANING EQUIPMENT</th>
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<tbody>
<tr>
<td><strong>Steel Wool:</strong></td>
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<tr>
<td>This is not a good item to use because steel wool sheds fibres and is very abrasive. It can cause fine surface scratches (even in stainless steel) which provides an ideal home from micro-organisms.</td>
</tr>
</tbody>
</table>

| **Nylon Scourer:** |
| Not a good item to use because scourers shed fibres and are very abrasive. They can create line surface scratches which makes cleaning more difficult. |

| **Wooden Brush:** |
| This is not a good item to use because wood is hard to dry, and the bristles are hard to clean and may break |
Brushes provide good habitats for microbes because they’re likely to be dirty and wet.

**Nylon Brush:**
This is a good choice because nylon brushes are easier to keep clean and dry and the bristles are soft and non-abrasive.

**Non Fibre Shedding Wipe:**
This is a good choice because they will not shed fibres and non-abrasive. Usually they are used only once so they are very hygienic as well.

**Wooden Mop:**
Not a good item to use because wood can splinter and is hard to dry. Wood provides a good habitat for microbes because it is likely to get dirty and wet. String mop heads also shed fibres so they are best avoided.

**Wet Dirty Rag:**
Not a good item to use because it is wet and dirty. No doubt it contains thousands of micro-organisms.

**Steel Handled Squeegee Mop:**
A clean squeegee on a squeeze mop with a plastic or metal handle is an effective cleaning item.
Part IV: Cleaning Records

One of the most stated rules in GMP is "You cannot test quality into products. You must build it in at each step in the entire process." This statement is especially true with regard to effective cleaning and prevention of cross-contamination in products. No amount of laboratory testing can substitute for prevention. The cleaning records, if completed correctly, should verify that each item of equipment in contact with product was cleaned:

- using validated written procedures
- by trained employees
- prior to use and stored correctly as per its status tag

There must be evidence, via inspection and monitoring records, that the equipment was clean and free from contaminants when processing commenced. It also must be recorded what previous product was processed in the equipment prior to the current batch.

What do the GMP rules say?

US FDA CFR 211

Subpart J-Records and Reports
Sec. 211.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall
date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

**International GMPs**

**Ch. 5 Production**
Processing operations: intermediate and bulk products

5.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.

**Overview**

Cleaning records are critical in a manufacturing operation. They are needed to:

- provide evidence that equipment has been cleaned and checked before use
- demonstrate that cleaning was done in accordance with SOPs
- provide traceability and help in problem solving should a product prove to be contaminated

This is why equipment must have status tags stating "**Clean**" or "**To be cleaned**". The GMP rule is to never use equipment unless it has a "**Clean**" status label attached, and has been inspected as clean.

**Status tags and cleaning logs**

Status tags are essential for communicating to all operators the cleaning status of equipment and rooms. This is especially important when different shifts are sharing equipment.

The images on the right are examples of a status tag and an equipment cleaning record. Each requires the date of cleaning, the name of the previous product and the name of the person who did the cleaning. The status tag clearly shows the cleaning status.
Simple cleaning logs are also essential to ensure that each cleaning task is performed correctly. The logs may detail:

- the area or piece of equipment being cleaned
- the cleaning equipment that is to be used
- the frequency of cleaning
- the responsibilities for the cleaning

**GOOD TO KNOW - IMPORTANCE OF CLEANING LOGS**

Cleaning logs also allow for personnel signing that the cleaning has been performed, and perhaps in some cases, verifying that the cleaning was adequate.

The most important requirement of FDA 21 CFR 211.182 Equipment cleaning and use log is that each item of common use equipment must have an individual log that shows batch traceable cleaning history that is independent of the batch record.

**How clean is clean?**

A commonly-asked question is "How clean is clean?"
The answer is not straightforward. Company SOPs will specify the definition of clean, and appropriate acceptance criteria or limits. Generally, "how clean is clean" depends on a number of factors, including:

- the method of cleaning
- the nature and use of the equipment being cleaned
- the type of products being manufactured (e.g. injectable products, creams)
SOME CRITERIA FOR CLEANLINESS CAN BE

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visually clean</td>
<td>Visual inspection should always be used irrespective of other methods employed. Visual inspection should occur both post-cleaning and again before next use of the equipment.</td>
</tr>
<tr>
<td>&lt;0.1% detected</td>
<td>This limit is sometimes used as a default limit because it is less than 1/1000 of the previous active chemical in the next batch.</td>
</tr>
<tr>
<td>Certain per million detected</td>
<td>This limit is similar to the &lt;0.1% limit. A general guide for this limit is not more than 10ppm carryover to the next product.</td>
</tr>
<tr>
<td>No product detected</td>
<td>Sometimes this limit is used when the allowable carryover of residue is higher than the limits of the analytical method being applied.</td>
</tr>
<tr>
<td>No microbial activity detected</td>
<td>This limit is applied to microbial residues post-sanitation. While there is no specific limit required in regulations, the limit chosen should reflect that product risk. For example, for sterile products the limit is nil, while for tablets it may be higher.</td>
</tr>
</tbody>
</table>

GOOD TO KNOW - ISSUES IN EQUIPMENT CLEANING VALIDATION

Other issues to consider when validating equipment cleaning include:

- using the active ingredient as a marker
- considering all components of the product (not just the active)
- ensuring that the analytical detection methods have been validated
Part V: Clean-in-Place (CIP) Systems

Overview

Many facilities use automated cleaning processes known as "Clean-in-Place" (CIP) systems. CIP systems rely on both chemical removal and physical agitation of the pipes, valves and tanks, rather than just physical removal of residues.

The success of CIP systems is determined in their design, installation and commissioning/validation. The design must ensure that there are no "dead legs" (areas where cleaning solution cannot penetrate) and must facilitate the complete rinsing of any residues. The CIP system may be "recirculating" or a "once-through" design. Both systems must be controlled and alarmed so that malfunctions are detected and the system is only considered to be clean after a totally successful cleaning cycle.

As with manual equipment cleaning, CIP systems must be validated to ensure that the previous product has been removed, there is no residual cleaning agent left after cleaning, and the microbial population has been reduced to a safe and acceptable level.
**SOME ADVANTAGES OF CIP SYSTEMS INCLUDE**

<table>
<thead>
<tr>
<th>Safety</th>
<th>CIP systems don’t expose the operator to hazardous cleaning situations or chemical exposure.</th>
</tr>
</thead>
</table>
| Cost-effectiveness | CIP systems are cost-effective, because of:  
|               | - efficient use of water and steam  
|               | - minimal amount of cleaning agent used  
|               | - minimal cleaning time                                                             |
| Less variability | With CIP systems, there is less variability in cleaning when compared with a manual cleaning systems. Because of this, CIP systems are validatable in many cases. |

**GOOD TO KNOW - TYPICAL CIP CLEANING SEQUENCE**

The steps below outline a typical CIP cleaning sequence:

- Pre-rinse and drain
- Detergent wash and drain
- Post rinse and drain
- Acid wash and drain
- Final rinse and drain

If the system also had a sanitizing step, suitable sanitizing agent would be introduced at Step 4.

**CIP system considerations**

The major factors when considering a CIP process include:
the time of exposure to cleaning solution

the type of cleaning agent selected

the strength of cleaning agent selected

the smoothness of the surfaces to be cleaned

the degree of turbulence in the pipes and the tank (ensuring there are no air pockets or dead legs)

the temperature of the cleaning solution

the nature of the contaminating compounds

ease of removal of cleaning solution residues
Summary

Cleaning and sanitation practices may compromise product quality by contamination with other products, cleaning agents, and micro-organisms. There are many factors which may affect the effectiveness of cleaning, for example;

- the type, strength, volume, and concentration of the cleaning agent
- the time needed for soaking, cleaning, and rinsing

Cleaning and sanitation is a technical function requiring diligence, competence, and an awareness of the effect that poor cleaning and sanitation can have on the quality of the final product. So:

- Wear the correct protective clothing when cleaning
- Use status tags to identify the cleaning status of equipment.
- Use only approved cleaning agents.
- Clean cleaning equipment regularly, inspect equipment after cleaning and again before reuse.
- Follow standard cleaning procedures exactly.
- Maintain records of cleaning.

Cleaning procedures have been written and validated to achieve the best possible results. If you notice anything abnormal report it to supervision.
TAKE THE TEST NOW

- Number of questions: 10
- No time limit
- Allow you save and finish at a later date
- Allow you to go back and change your answer
- Attempting each question is mandatory
- Pass mark at and above 70%
- Print results and certificates