BP803T · B.Pharm Semester VIII · Theory Notes

Industrial Pharmacy and Facility Design

Unit III — Facility Design: Non-Sterile Manufacturing (9 hours)

Unit III (9 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit III (9 hours).

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CHAPTER 4: Facility Design for Non-Sterile Manufacturing (Schedule M)

1. Learning Objectives

After studying this chapter, you should be able to:

1 Explain what Schedule M is and describe the general facility requirements for non-sterile manufacturing (location, layout, material/personnel flow, segregation, cross-contamination prevention).

2 Define potable water, purified water, and water for injection, and state where each is used.

3 Describe, in simple terms, how purified water is generated (RO, distillation, deionization) and outline water system design, operation, storage, distribution, and validation concepts.

4 Explain what clean steam is, why it is used, and how it is generated conceptually.

5 Describe the uses of compressed air and vacuum in manufacturing, and explain why oil-free air matters.

6 Define clean-in-place (CIP) and list its cycle steps, with a simple flowchart.

7 Explain effluent, ETP, and the significance of effluent testing, defining pH, BOD, and COD simply.

8 Describe layout design with process flow: unidirectional flow, dirty-to-clean progression, and a tablet facility example.

9 State cleaning and disinfection protocols and define Type A, Type B, and Type C cleaning.

10 Explain cleaning validation methods (swab, rinse, visual) and the concept of acceptance criteria ("as per approved protocol", no invented limits).

2. Definitions

Schedule M — The part of India's Drugs and Cosmetics Rules that lays down Good Manufacturing Practices (GMP): the minimum requirements for factory premises, equipment, and practices so that medicines are made with consistent quality. It applies to pharmaceutical manufacturing in India.

Non-sterile manufacturing — Making medicines that are not required to be completely free of microorganisms, such as tablets, capsules, syrups, and ointments (as opposed to sterile products like injections, which must be microbe-free).

Cross-contamination — Unwanted transfer of one product's material (drug, dust, microbes) into another product, which can harm patients. Facility design aims to prevent it.

Segregation — Keeping different things physically separate — different products, or clean and dirty areas — so they cannot mix.

Unidirectional flow — Movement of materials and people in one direction only (from "dirty" areas toward "clean" areas), without going backward, to reduce contamination risk.

Potable water — Water that is safe to drink; the basic starting water for a pharmaceutical plant.

Purified water (PW) — Potable water that has been further treated to remove chemicals and microbes; used for manufacturing non-sterile medicines and for final rinsing of equipment.

Water for injection (WFI) — Highly purified water used for making sterile (injectable) products and for final rinsing in sterile areas.

Clean steam — Steam made from purified water, free from boiler additives and contaminants; used where steam touches the product or product-contact surfaces.

CIP (clean-in-place) — Cleaning equipment without taking it apart, by circulating cleaning solutions through it in a fixed cycle.

Effluent — Wastewater leaving the factory, which may contain chemicals and must be treated before discharge.

ETP (effluent treatment plant) — The plant/facility that treats factory wastewater to make it safe for discharge.

Cleaning validation — Documented proof that a cleaning procedure consistently removes residues to an acceptable level.

3. Terminology Table

Term	Simple meaning
Schedule M	India's GMP rules for drug manufacturing premises and practices
GMP	Good Manufacturing Practices — quality rules for making medicines
Cross-contamination	Unwanted mixing of one product into another
Segregation	Physical separation of products/areas
Unidirectional flow	One-way movement: dirty → clean, no going back
Potable water	Safe drinking water; starting point
Purified water	Treated water for non-sterile manufacture
Water for injection (WFI)	Ultra-pure water for sterile products
RO (reverse osmosis)	Water purification by forcing water through a fine membrane
Distillation	Purifying water by boiling and condensing the vapour
Deionization	Removing dissolved salts (ions) from water using resins
Clean steam	Contaminant-free steam from purified water
Compressed air	Pressurised air used to run machines and processes
Vacuum	Low-pressure condition used for drying, filtration, transfer
CIP	Cleaning equipment in place without dismantling

Term	Simple meaning
Effluent / ETP	Factory wastewater / the plant that treats it
pH	How acidic or alkaline a liquid is
BOD	Biochemical oxygen demand — oxygen needed by microbes to break down waste
COD	Chemical oxygen demand — oxygen needed chemically to break down waste
Type A / B / C cleaning	Full changeover clean / batch-to-batch clean / rinse-only clean
Swab / rinse / visual	Cleaning-validation sampling: wiping a surface / testing rinse water / looking with eyes

4. Detailed Explanation (from Absolute Zero)

4.1 What is Schedule M? — general facility requirements

Technical concept: Schedule M of the Drugs and Cosmetics Rules, India, prescribes GMP requirements for manufacturing premises.

Simple explanation: Just as a restaurant kitchen must follow hygiene rules, a medicine factory must follow GMP rules. In India these rules are written in "Schedule M". They say how the factory building, rooms, air, water, equipment, and people-movement must be arranged so medicines are safe and consistent. (Section numbers and clause details change with revisions — always refer to the latest edition of the Rules; this chapter gives the concepts, not clause numbers.)

General facility requirements (concepts):

- **Location:** The factory should be in a suitable environment — away from open drains, heavy pollution, or anything that could contaminate products.
- **Layout:** Rooms must be logically arranged in the order of manufacturing steps, with enough space so that work flows smoothly and mix-ups are avoided.
- **Material and personnel flow:** Raw materials, finished goods, and people should move in a planned, one-way pattern. People and materials should not cross paths unnecessarily — separate entries, corridors, and change rooms help.
- **Segregation:** Different products — especially those needing special care (for example, products that are highly potent or sensitising) — must be made in segregated areas so they cannot contaminate each other.
- **Cross-contamination prevention:** Achieved through segregation, unidirectional flow, dedicated or properly cleaned equipment, controlled air movement (air flowing from clean to less-clean areas), and validated cleaning.

Segregation in practice — simple examples:

- A tablet for blood pressure and a tablet for diabetes are made in the same building but never in the same room at the same time without a full Type A changeover clean between them.

- Highly potent or sensitising products (for example, certain hormones or allergy-triggering drugs) are made in *dedicated, segregated* areas with their own air handling, so traces can never reach other products.
- Rejected or quarantined materials are kept in locked, clearly labelled areas — physically apart from released stock — so a mix-up is impossible, not just unlikely.

Key takeaway: Segregation means designing *impossibility of mixing* into the building — separate rooms, separate air, locked quarantine — not just good intentions.

Key takeaway: Schedule M = India's GMP rule book for factory design: right location, logical layout, one-way flow, segregation, and barriers against cross-contamination.

4.2 Water — types, generation, and the purification system

Technical concept: Water is the most used raw material in pharma. Different grades are used for different purposes; the purification system must be designed, operated, stored, distributed, and validated.

Simple explanation: Not all water is equal. Drinking water is fine for you, but a medicine factory needs cleaner grades, because impurities in water end up *inside the medicine*.

Types of water:

Type	What it is	Where used
Potable water	Safe drinking water, meeting drinking-water standards	Feed water to purification systems; general factory use
Purified water (PW)	Potable water further treated to reduce chemicals and microbes	Making tablets, capsules, syrups; final rinse of non-sterile equipment
Water for injection (WFI)	Even more highly purified; must also be free of bacterial endotoxins (fever-causing fragments of dead bacteria)	Making injections and other sterile products; final rinse in sterile areas

Generation methods (concepts, simply described):

- **Reverse osmosis (RO):** Water is pushed under pressure through a very fine membrane; dissolved salts, microbes, and particles are held back, and cleaner water passes through. Like a super-fine sieve for dissolved impurities.
- **Distillation:** Water is boiled into steam and the steam is condensed back to water; most impurities do not evaporate, so they are left behind. The oldest and most reliable method.
- **Deionization (DI):** Water passes through special resins that grab dissolved salts (ions) and release harmless hydrogen/hydroxyl ions — effectively removing the salts.

A real plant usually combines these (for example: RO followed by deionization, or distillation for WFI), as per its approved design.

Water system — design, operation, storage, distribution, validation:

- **Design:** The system is designed so water flows continuously (no dead legs — stagnant corners where microbes grow), using smooth, cleanable piping that can be sanitised.

- **Operation:** Run continuously with circulation; temperature or sanitisation controls keep microbial growth down.
- **Storage:** Stored in closed tanks designed to prevent contamination (vent filters, spray balls for cleaning).
- **Distribution:** A loop pipeline delivers water to each use-point; the loop returns unused water to the tank so it keeps moving.
- **Validation:** Documented proof, done in phases, that the system consistently delivers water meeting the approved specifications of the relevant pharmacopoeia (latest edition). Sampling is done at many points over time before the system is approved for routine use.

Industry standards for water (cautious): Water quality is governed by pharmacopoeias (such as the Indian Pharmacopoeia) and applicable IS/ISO standards — always follow the latest edition and confirm current requirements; this chapter does not state numerical limits because they are revised periodically.

Key takeaway: Match the water grade to the job (potable → purified → WFI), generate it by RO/distillation/deionization, keep it moving in a sanitary loop, and validate that it consistently meets pharmacopoeial quality.

4.3 Steam and clean steam

Simple explanation: Ordinary boiler steam can carry rust, boiler chemicals, and impurities — fine for heating a building, but not for touching medicines. **Clean steam** is steam generated from *purified water* (not raw boiler water), so it is free of boiler additives and contaminants. It is used where steam directly contacts the product or product-contact surfaces — for example, sterilising equipment or humidifying clean areas. Conceptually, a clean-steam generator boils purified water in a dedicated, cleanable unit and distributes the steam through stainless-steel piping.

Key takeaway: If steam touches the product or its contact surfaces, it must be clean steam made from purified water.

4.4 Compressed air, vacuum

Compressed air — grades and uses: Compressed air powers machines (tablet presses, filling lines), blows containers clean, and moves powders. Because it can touch products, its quality matters:

- It should be **oil-free** — ordinary compressors can leak lubricating oil into the air, and oil in a medicine is a contaminant. Oil-free compressors or proper oil-removal filters are used.
- It should be dry and filtered to remove particles, moisture, and microbes where it contacts products.

Vacuum — uses in manufacturing: Vacuum (pressure lower than the atmosphere) is used for:

- Drying (vacuum dryers remove moisture at lower temperatures),
- Filtration (pulling liquid through filters),
- Transferring powders/liquids without contamination,
- De-aeration (removing trapped air from liquids/ointments).

Key takeaway: Compressed air must be clean, dry, and oil-free where it contacts products; vacuum is a workhorse for drying, filtration, and transfer.

4.5 CIP — clean-in-place

Definition: CIP means cleaning equipment *without dismantling it* — cleaning solutions are circulated through tanks, pipes, and machines in a fixed, automated cycle.

Cycle steps (in order):

1. **Pre-rinse** with water — removes loose, easily dissolved residues.
2. **Detergent wash** — alkaline or acidic detergent solution circulated to dissolve and lift stubborn residues.
3. **Post-rinse** with water (often purified water) — washes away detergent and loosened dirt.
4. **Sanitise** — a sanitising agent (or hot water/steam) reduces microbes to an acceptable level.
5. **Final rinse** (where needed) — with purified water, to leave surfaces clean and residue-free.

Flowchart:

```
PRE-RINSE (water) → DETERGENT WASH → POST-RINSE (water)
       → SANITISE → FINAL RINSE (purified water) → READY FOR USE
```

Key takeaway: CIP = rinse → wash → rinse → sanitise → (final rinse), all without opening the equipment — consistent, documented, and reproducible.

4.6 Effluent testing — facility design and significance

What effluent is: Wastewater leaving the factory — from washing equipment, toilets, canteens, and processes. It can carry drug residues, chemicals, and microbes.

ETP concept: An effluent treatment plant treats this wastewater in stages so the discharged water is safe and meets the pollution-control requirements in force. The stages, simply described:

1. **Screening:** Big solids (rags, particles) are filtered out.
2. **Equalisation/settling:** Wastewater is collected in a tank where flow evens out and heavy solids settle down.
3. **Biological/chemical treatment:** Microbes digest the dissolved organic waste (biological), or chemicals neutralise/break down pollutants (chemical) — like a stomach digesting food.
4. **Clarification and disinfection:** Remaining solids are separated and microbes reduced, giving clear treated water ready for testing and discharge.

Why testing matters: Untreated pharma effluent can harm rivers, soil, and public health, and can spread drug residues into the environment. Regulators require factories to test treated effluent before discharge.

Key parameters (defined simply; no discharge limits stated — follow current norms):

- **pH** — how acidic or alkaline the water is (scale 0–14; 7 is neutral).

- **BOD (biochemical oxygen demand)** — the oxygen that microorganisms need to break down the waste in the water; high BOD means heavily polluted water.
- **COD (chemical oxygen demand)** — the oxygen needed *chemically* to break down the waste; a broader measure of pollution load.

Significance: Regular effluent testing proves the ETP works, keeps the factory legally compliant, and protects the environment and nearby communities.

> **Key takeaway:** Test what you discharge — pH, BOD, COD and other parameters as per current norms — because the factory is responsible for its wastewater.

4.7 Layout design with process flow

Unidirectional flow concept: Materials and people move in one direction — from receiving (dirty) through manufacturing (cleaner) to packing/dispatch (cleanest) — never flowing backward into a dirtier zone. This is the single most powerful design tool against mix-ups and cross-contamination.

Dirty-to-clean progression: Zones are graded: black/grey (dirty: goods receiving, washing) → cleaner manufacturing areas → cleanest (packing of finished product). Air pressure and gowning increase along the same direction.

Example layout description — tablet facility (conceptual):

```
GOODS RECEIVING → RAW MATERIAL STORE → DISPENSING → GRANULATION
    → COMPRESSION → COATING → BLISTER PACKING → FINISHED GOODS STORE → DISPATCH
```

- Separate entry for personnel with change rooms; separate corridors for materials vs people where possible.
- Washing area placed so dirty equipment never passes through clean manufacturing zones.
- QC laboratory nearby but with its own entry; rejects/quarantine areas clearly marked and locked.
- Each arrow moves forward only — no backtracking.

> **Key takeaway:** Design the building as a one-way street from dirty to clean, with the rooms in manufacturing order.

4.8 Cleaning and disinfection protocols; Types A, B, C; cleaning validation

Cleaning vs disinfection: Cleaning *removes* dirt and residues (with water/detergent); disinfection *kills/reduces* microbes (with a disinfectant). Both are needed; cleaning always comes first, because dirt shields microbes from disinfectants.

Types of cleaning:

Type	When done	What it involves
Type A (full/changeover clean)	When changing from one product to a *different* product	Complete dismantling where needed, thorough cleaning of all product-contact parts, disinfection — the deepest clean

Type	When done	What it involves
Type B (batch-to-batch clean)	Between batches of the *same* product	Cleaning of product-contact surfaces without full dismantling
Type C (rinse/wipe clean)	Minor/routine, e.g., at shift end or for non-contact parts	Rinsing or wiping; lightest level

Cleaning validation — methods:

- **Swab sampling:** A sterile swab is wiped over a defined area of the equipment surface, then analysed for residues — checks *specific spots* directly.
- **Rinse sampling:** The final rinse water is collected and analysed — checks the *whole* surface indirectly through what washed off.
- **Visual inspection:** Trained eyes (sometimes with good lighting) check that surfaces look clean — simple, but only the first check, never the only one.

Acceptance criteria (concept): Limits are set in the approved cleaning-validation protocol (for example, "no visible residue" plus analytical limits derived per the approved procedure) — this chapter states no numerical values; always use the criteria in the approved protocol and confirm current requirements.

Key takeaway: Clean first, then disinfect; match cleaning depth to the situation (A/B/C); prove it works with swab, rinse, and visual checks against approved criteria.

4.9 Supporting design elements — HVAC, change rooms, lighting, drainage

Technical concept: Beyond rooms and utilities, several building systems protect product quality.

Simple explanation:

- **HVAC (heating, ventilation, air conditioning):** The factory's "lungs". It supplies filtered air, controls temperature and humidity, and creates **pressure cascades** — cleaner rooms kept at slightly higher air pressure than dirtier ones, so air always flows from clean to dirty, carrying dust and microbes *away* from the product. Filters trap particles; the most critical areas use the finest filters.
- **Change rooms:** People are the biggest contamination source. Staff enter through change rooms where they remove street clothes and wear clean factory garments, in stages (especially before cleaner areas). Separate change rooms for men and women, with hand-washing, are standard.
- **Lighting:** Bright, even lighting so operators can see what they are doing — and spot mix-ups or dirt. Lights are covered/shatterproof so broken glass cannot fall into products.
- **Drainage:** Floors slope gently to trapped drains so wash water flows away; drains are covered and trapped (water seal) so odours, pests, and microbes cannot come back up. Drains must never allow back-flow into clean areas.

Key takeaway: Air, people, light, and drains are all designed — clean air pushed the right way, people gowned in stages, bright safe lighting, and one-way drainage.

4.10 Effluent testing facility — design aspects

Technical concept: Beyond the ETP itself, the factory needs a proper setup for *testing* effluent.

Simple explanation: Testing is only trustworthy if samples are taken and analysed properly. Design aspects include:

- **Sampling points:** Fixed, labelled points — at the ETP inlet (raw effluent), after each major treatment stage, and at the final outlet — so results can be compared stage by stage.
- **Sampling method:** Composite samples (collected over time) represent the day's discharge better than a single grab sample.
- **Testing laboratory:** An on-site or contracted lab with calibrated instruments for pH, BOD, COD, and other parameters as per current norms; analysts trained in the methods.
- **Records:** Every result logged with date, time, sampling point, and analyst name — forming the evidence of compliance shown to inspectors.

Key takeaway: Design testing in, not on — fixed sampling points, proper methods, calibrated lab, complete records.

4.11 Facility documentation — drawings, URS, and design qualification

Technical concept: A facility is built from documents before it is built from bricks.

Simple explanation: Before construction, the design exists on paper and must be checked:

- **Layout drawings:** Floor plans showing every room, door, corridor, airlock, and flow arrow — the visual version of the unidirectional-flow concept. Any change during construction is marked on the drawings so the final "as-built" drawings match reality.
- **URS (User Requirement Specification):** A written list of what the users (production, QA, engineering) need the facility and utilities to do — for example, "the purified-water loop shall supply X use-points with continuous circulation". It is the starting point against which the design is checked.
- **DQ (Design Qualification) for the facility:** The same DQ idea from Chapter 3, applied to the building and utilities — documented proof that the *design* meets the URS and GMP requirements before a single brick is laid. Catching a design error on paper costs almost nothing; catching it after construction costs a fortune.

Airlocks and pass boxes (supporting concepts): An **airlock** is a small room with two doors (never both open at once) between areas of different cleanliness — people or materials pass through it, and the airlock buffers the pressure difference. A **pass box** is a small hatch in the wall for moving materials between rooms without opening the main doors. Both protect the pressure cascade and reduce contamination.

Key takeaway: Design on paper first (drawings + URS), qualify the design (DQ), and use airlocks and pass boxes to protect clean zones.

4.12 Commissioning and handover

Simple explanation: After construction comes **commissioning** — testing every system (water loop, HVAC, steam, air, drains, CIP) to prove it works as designed, followed by qualification (IQ/OQ/PQ, as in Chapter 3). Only then is the facility **handed over** from the builders to the manufacturing team, with all documents: as-built drawings, equipment manuals, qualification reports, and SOPs. A facility without its documents is

like a car without keys — you cannot legally or safely run it.

> **Key takeaway:** Build → commission → qualify → hand over with complete documents — then manufacture.

4.13 Worst-case thinking in cleaning validation

Technical concept: You cannot validate cleaning for every product on every machine separately — instead, you validate the hardest case.

Simple explanation: A factory makes many products. Validating cleaning after *each* one would take forever. Instead, scientists pick the **worst case** — the product that is hardest to clean (sticky, low-solubility, or potent) on the hardest-to-clean equipment — and validate cleaning for that combination. The logic: if the cleaning procedure removes the toughest residue, it will handle the easier ones too. Related ideas:

- **Bracketing:** Grouping similar products/equipment and validating the extremes (strongest/weakest, largest/smallest), so the middle is covered by logic.
- **Grouping by risk:** Products are grouped by how hard they are to clean and how harmful their residues are; validation focuses on the riskiest group.

> **Key takeaway:** Validate the hardest-to-clean case — success there covers the easier cases by scientific logic, not by luck.

5. Classifications

5.1 Water grades (summary)

Grade	Purity level	Typical use
Potable water	Drinking-water quality	Feed to purification; general use
Purified water	Low chemicals and microbes	Non-sterile manufacture; final rinse (non-sterile)
Water for injection	Highest; endotoxin-free	Sterile manufacture; final rinse (sterile areas)

5.2 Utility systems in a non-sterile plant

Utility	Purpose	Quality note
Purified water	Ingredient, rinsing	Pharmacopoeial grade; validated loop
Clean steam	Sterilising contact surfaces, humidification	From purified water; no boiler additives
Compressed air	Machine power, blow-cleaning, transfers	Oil-free, dry, filtered
Vacuum	Drying, filtration, transfer, de-aeration	As per equipment design
HVAC (air handling)	Clean air, pressure cascades	Designed to prevent cross-contamination

5.3 Cleaning types vs situations

Situation	Cleaning type
Product changeover (different product)	Type A — full clean
Next batch, same product	Type B — batch-to-batch clean
End of shift / non-contact surfaces	Type C — rinse/wipe

6. Mechanisms / Process Flows

6.1 Water purification train (conceptual, step by step)

```
POTABLE WATER → PRE-TREATMENT (filtration, softening)
    → REVERSE OSMOSIS → (DEIONIZATION or second RO)
    → STORAGE TANK → DISTRIBUTION LOOP → USE-POINTS
                            ↑ (return loop — water keeps circulating)
```

For WFI, distillation is the classic final step (as per the pharmacopoeia's accepted methods — confirm the latest edition).

6.2 CIP cycle (step by step)

1 Drain and pre-rinse with water (removes loose soil).

2 Circulate detergent solution at the approved temperature and time.

3 Rinse with water until detergent is removed.

4 Sanitise (chemical sanitiser or hot water/steam) for the approved contact time.

5 Final rinse with purified water; drain/dry; equipment released for use.

6 Document every step (time, temperature, concentrations as per the approved procedure).

6.3 Effluent treatment concept (step by step)

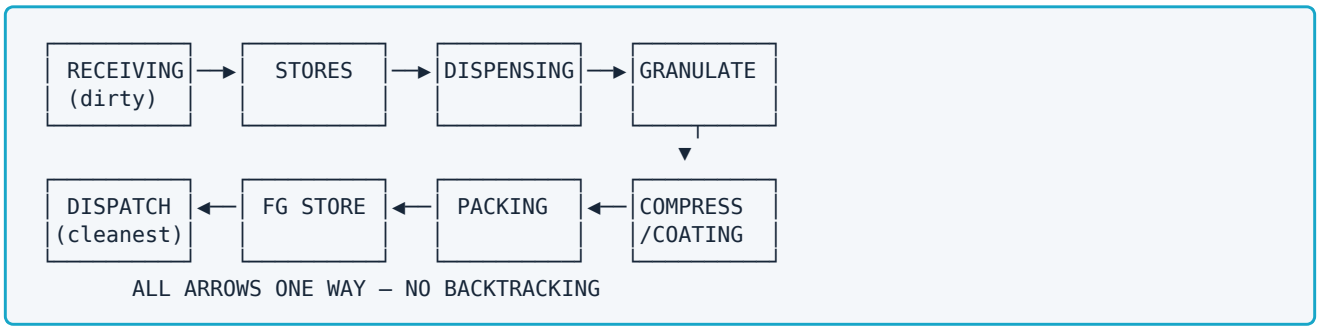
```
FACTORY WASTEWATER → SCREENING (removes solids) → SETTLING/EQUALISATION
    → BIOLOGICAL/CHEMICAL TREATMENT → CLARIFICATION → TESTING (pH, BOD, COD…)
    → DISCHARGE (only if meeting current norms) or reuse
```

6.4 Cleaning validation workflow

```
APPROVED PROTOCOL (with acceptance criteria) → SOIL EQUIPMENT (worst case)
  → CLEAN per procedure → SAMPLE (swab + rinse + visual)
  → ANALYSE → COMPARE with criteria → REPORT → APPROVE / RE-CLEAN
```

7. Text Diagrams / Flowcharts

Tablet facility one-way flow:



Pressure cascade concept:

```
CLEANEST ROOM (highest pressure) → CLEANER → GREY → DIRTY (lowest)
       Air always flows from clean toward dirty — never reverse.
```

8. Infographic Concepts

1. **"The water ladder"** — three rungs: potable (bottom), purified (middle), WFI (top), each with its use; impurities falling off at each step (RO membrane, distillation flask icons).
2. **"The loop that never sleeps"** — a circular pipeline with arrows showing continuous circulation, labelled "no dead legs", with sampling taps marked.
3. **"One-way street factory"** — a floor plan with a single bold arrow from RECEIVING to DISPATCH passing through each department; a red "no entry" sign on any backward arrow.
4. **"CIP in five drops"** — five water-drop icons: rinse, wash, rinse, sanitise, final rinse.
5. **"A/B/C cleaning traffic light"** — red = Type A (full stop, full clean), yellow = Type B (caution, batch-to-batch), green = Type C (go, routine rinse).

9. Summary Tables

Master summary — Chapter 4

Topic	One-line essence
Schedule M	India's GMP rules for manufacturing premises and practices
Layout principles	Logical order, one-way flow, segregation, no cross-contamination
Potable / PW / WFI	Drinking water → treated process water → endotoxin-free sterile water
Generation	RO (membrane), distillation (boil–condense), deionization (resins)
Water system	Designed sanitary loop; stored, distributed, validated; pharmacopoeial quality
Clean steam	Steam from purified water; for product-contact uses
Compressed air	Oil-free, dry, filtered where it contacts product

Topic	One-line essence
Vacuum	Drying, filtration, transfer, de-aeration
CIP	rinse → detergent wash → rinse → sanitise → final rinse, without dismantling
Effluent/ETP	Treat wastewater; test pH, BOD, COD as per current norms
Layout	Dirty → clean one-way progression; tablet line example
Cleaning types	A = changeover full clean; B = same-product batch clean; C = routine rinse/wipe
Cleaning validation	Swab, rinse, visual vs approved acceptance criteria
HVAC / pressure cascade	Filtered air; clean rooms at higher pressure so air flows clean → dirty
Effluent testing facility	Fixed sampling points, proper lab, calibrated instruments, complete records

10. Worked Examples and Calculations

Example 1 — Illustrative water-system sizing (numbers invented for teaching)

This is an "illustrative example" — real sizing follows the approved design procedure.

A small tablet plant estimates its purified-water needs:

Step 1 — List uses per day: granulation 200 L + equipment final rinse 150 L + miscellaneous 50 L = 400 L/day. Step 2 — Add a safety margin (illustrative 25%): 400 × 1.25 = 500 L/day. Step 3 — Storage tank sized for about one day's need plus margin: choose an illustrative 600-L tank (rounded up to a standard size). Step 4 — Distribution loop designed so water circulates continuously with no dead legs; use-points get valves with return to the loop. Step 5 — Validation: sample each use-point over the qualification period and confirm water meets the pharmacopoeial specification (latest edition) before routine use.

Lesson: Size from real demand + margin, keep water moving, and validate before use.

Example 2 — Illustrative cleaning-validation sampling plan (conceptual)

Numbers invented for teaching ("illustrative example").

After a Type A clean of a tablet press:

Step 1 — Identify worst-case spots: die table corners, feed frame — places hardest to clean. Step 2 — Swab a defined area at each spot; collect final rinse water sample; do a visual check under good light. Step 3 — Analyse swabs/rinse for residues; compare results with the acceptance criteria in the approved protocol. Step 4 — All criteria met + visually clean → cleaning validated for this product/equipment combination. Any failure → investigate, re-clean, re-sample.

Lesson: Sample the hardest-to-clean spots — if they pass, the easy spots are safe.

Example 3 — Illustrative CIP cycle time estimate (numbers invented for teaching)

This is an "illustrative example" — real cycles follow the approved CIP procedure.

A mixing tank's CIP cycle is planned:

Step 1 — List steps with illustrative times: pre-rinse 5 min → detergent wash 20 min → post-rinse 10 min → sanitise 15 min → final rinse 10 min → drain/dry 5 min. Step 2 — Total: 5+20+10+15+10+5 = 65 minutes per cycle. Step 3 — The plant runs 3 product batches per day needing CIP between different products: 3 × 65 min ≈ 3.25 hours of cleaning time daily — this must fit into the production schedule. Step 4 — Water use is estimated per step (illustrative 100 L/min flow × minutes) to size the purified-water demand, feeding back into the water-system design (Example 1).

Lesson: Cleaning takes real time and water — plan it into production schedules and utility sizing, or it becomes the bottleneck.

11. Analogies

1. **The one-way street:** A pharma layout is like a one-way street — traffic (materials, people) flows forward from dirty to clean; U-turns (backtracking) cause accidents (contamination).
2. **The water ladder:** Water grades are like school classes — potable is primary school, purified water is high school, WFI is college; each higher class needs to pass tougher exams (quality tests).
3. **CIP as a washing machine:** CIP is like a washing machine for factory equipment — you don't dismantle the machine; you run a fixed cycle: rinse, wash, rinse, sanitise.
4. **BOD as hunger:** BOD is like measuring how "hungry" the waste is for oxygen — very polluted water has waste that hungrily eats up oxygen, starving fish.
5. **Type A/B/C as house cleaning:** Type A is the deep Diwali cleaning (everything out, every corner); Type B is weekly cleaning (same house, regular tidy); Type C is a quick daily wipe-down.
6. **The airlock as an air-tight tiffin:** An airlock is like a tiffin with two lids — you open one lid, put food in, close it, then open the other. Smells (contamination) never escape both sides at once.
7. **URS as a shopping list:** Building a factory without a URS is like going to the market without a list — you come home with the wrong things and forget what you needed.

12. Pharmacy Relevance

- Every tablet, capsule, and syrup a pharmacist dispenses was made in a Schedule M-compliant facility — the building itself is part of the medicine's quality.
- Pharmacists work as production officers (running granulation/compression lines), QA officers (layout qualification, cleaning validation), QC chemists (water testing, swab analysis), and EHS staff (effluent monitoring).
- Water testing and cleaning validation are classic entry-level responsibilities for B.Pharm graduates in industry — this chapter is directly interview-relevant.
- A poorly designed facility causes the recalls and quality failures pharmacists read about; good design prevents them.

13. India Context

Schedule M is Indian law — every drug factory in India, from a small SSI unit in an industrial estate to a large export-oriented plant, must comply with it. Indian plants that export to regulated markets additionally meet WHO GMP and other international expectations, but Schedule M is the baseline at home. Water scarcity in many Indian regions makes water-system design and effluent treatment especially important: factories are expected to treat and, where possible, reuse water responsibly. For students, "Schedule M", "purified water loop", "Type A/B/C cleaning", and "cleaning validation" are among the most frequently asked topics in production and QA job interviews in the Indian pharma industry.

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14. Key Points

- Schedule M = India's GMP requirements for manufacturing premises, equipment, and practices (latest edition governs; no clause numbers memorised here).
- Design principles: suitable location, logical layout, one-way material/personnel flow, segregation, cross-contamination prevention.
- Water grades: potable (feed) → purified water (non-sterile manufacture) → WFI (sterile manufacture).
- Generate PW by RO, deionization, distillation (combinations as per approved design); distribute in a continuously circulating sanitary loop; validate against the pharmacopoeia.
- Clean steam (from purified water) where steam contacts product/surfaces; compressed air oil-free, dry, filtered; vacuum for drying/filtration/transfer.
- CIP cycle: pre-rinse → detergent wash → rinse → sanitise → final rinse.
- Effluent must be treated (ETP) and tested — pH, BOD, COD and others as per current norms.
- Layout: dirty → clean one-way progression; tablet line: receiving → stores → dispensing → granulation → compression → coating → packing → FG store → dispatch.
- Cleaning: clean before disinfecting; Type A (changeover), Type B (same-product batch), Type C (routine).
- Cleaning validation: swab + rinse + visual against approved acceptance criteria.

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15. Common Confusions

1 **Potable vs purified vs WFI.** Potable = drinkable; purified = further treated for non-sterile manufacture; WFI = highest purity, endotoxin-free, for sterile products. They are not interchangeable.

2 **"Boiler steam = clean steam."** No — boiler steam contains boiler-water additives; clean steam is made from purified water in a dedicated generator.

3 **Cleaning vs disinfection vs sanitisation.** Cleaning removes dirt; disinfection/sanitisation reduces microbes. Cleaning must come first.

4 **Type A vs Type B.** A = different product (full changeover clean); B = same product, next batch (lighter clean). Mixing them up is a classic exam trap.

5 **Swab vs rinse sampling.** Swab checks a specific surface spot directly; rinse checks the whole system indirectly via the rinse water. Both are used together.

6 **"Validation proves the water is pure once."** No — validation proves the system *consistently* delivers quality water over time.

7 **Dead legs.** A dead leg is a stagnant pipe branch where water doesn't circulate — microbes love it. Good design eliminates them.

8 **"HVAC is just air conditioning."** Comfort cooling is only part of it — in pharma, HVAC also filters air and maintains pressure cascades that protect products.

9 **Effluent testing vs ETP operation.** The ETP *treats* the water; the testing facility *proves* the treatment worked. Both are needed — treatment without testing is unverified.

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16. Common Mistakes

- Memorising invented numerical limits for water or effluent — limits change; always cite "as per the latest pharmacopoeia/norms".
- Designing material flow that backtracks through clean areas.
- Using the same equipment for different products without a Type A clean and changeover procedure.
- Forgetting vent filters on water storage tanks (airborne contamination entry).
- Relying on visual inspection alone for cleaning validation.
- Skipping the sanitisation step in CIP ("rinsing is enough") — it is not.
- Discharging effluent without testing, or testing without a calibrated procedure.
- Storing purified water in an open or poorly vented tank — airborne microbes and dust enter, undoing the whole purification effort.
- Letting untrained contract workers enter clean areas without gowning discipline — people are the largest contamination source in any plant.

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17. Mnemonics

- **Water grades — "Please Pass Water":** **P**otable → **P**urified → **W**FI (increasing purity).
- **CIP steps — "Really Wash, Rinse, Sanitise":** **R**inse → **W**ash (detergent) → **R**inse → **S**anitise (+ final rinse).
- **Cleaning types — "ABC = All-change, Batch, Casual":** **A** = product change (all-out clean), **B** = next batch (same product), **C** = casual/routine wipe.
- **Validation sampling — "SRV":** **S**wab, **R**inse, **V**isual — "See Residues Vanish".
- **Layout — "One-Way, Dirty-to-Clean":** think of a river — it never flows uphill.

18. Exam Summary

Schedule M of India's Drugs and Cosmetics Rules lays down GMP requirements for manufacturing premises: suitable location, logical layout in manufacturing order, planned one-way material and personnel flow, segregation of different products/areas, and prevention of cross-contamination. Water is a critical utility: potable water (drinkable, feed water) → purified water (treated; for non-sterile manufacture and final rinsing) → water for injection (highest purity, endotoxin-free; for sterile products). Purified water is generated by reverse osmosis, deionization, and/or distillation, stored in sanitary tanks, distributed through a continuously circulating loop with no dead legs, and validated to consistently meet pharmacopoeial quality (latest edition; no invented limits). Clean steam — steam from purified water, free of boiler additives — is used where steam contacts products or contact surfaces. Compressed air must be oil-free, dry, and filtered where it contacts products; vacuum serves drying, filtration, transfer, and de-aeration. CIP (clean-in-place) cleans equipment without dismantling: pre-rinse → detergent wash → rinse → sanitise → final rinse. Factory wastewater (effluent) is treated in an ETP and tested before discharge; key parameters are pH (acidity/alkalinity), BOD (oxygen needed by microbes to break down waste), and COD (oxygen needed chemically) — limits as per current norms. Facility layout follows unidirectional dirty-to-clean flow; a tablet plant flows receiving → stores → dispensing → granulation → compression → coating → packing → finished-goods store → dispatch. Cleaning precedes disinfection; Type A = full changeover clean (different product), Type B = batch-to-batch (same product), Type C = routine rinse/wipe. Cleaning validation uses swab, rinse, and visual sampling against acceptance criteria in the approved protocol.

19. One-Minute Revision

Schedule M = India's GMP for factory design: right location, logical one-way layout, segregation, no cross-contamination. Water ladder: potable → purified (RO/DI/distillation, circulating loop, validated) → WFI. Clean steam from purified water; oil-free compressed air; vacuum for drying/filtration. CIP: rinse–wash–rinse–sanitise–rinse. Treat and test effluent (pH, BOD, COD). Layout flows dirty → clean, never backward. Cleaning types A (changeover), B (same product), C (routine); validate cleaning by swab, rinse, and visual checks. Design on paper first — drawings, URS, and DQ — then build, commission, qualify, and hand over.

20. MCQs

1 Schedule M of the Drugs and Cosmetics Rules prescribes:

a) Drug prices b) Good Manufacturing Practices for manufacturing premises and practices c) Pharmacy college syllabus d) Import duties on medicines

1 Unidirectional flow in a factory means:

a) Workers walk fast in one corridor b) Materials and personnel move one way, dirty → clean, without backtracking c) Air conditioning in one room only d) One product per factory

1 Purified water is:

a) Ordinary tap water b) Potable water further treated to reduce chemicals and microbes, used for non-sterile manufacture c) Water for making injections d) Boiler feed water

1 Water for injection (WFI) differs from purified water in that it:

a) Is cheaper to make b) Is of higher purity and must be free of bacterial endotoxins c) Is used for washing floors d) Contains added minerals

1 Reverse osmosis purifies water by:

a) Boiling and condensing b) Forcing water through a fine membrane that holds back impurities c) Adding chlorine d) Freezing and thawing

1 A "dead leg" in a water distribution system is:

a) A broken pipe b) A stagnant branch where water does not circulate, encouraging microbial growth c) A type of valve d) A water meter

1 Clean steam is:

a) Ordinary boiler steam b) Steam generated from purified water, free of boiler additives, for product-contact uses c) Steam used in the canteen d) Cold vapour from air conditioning

1 Compressed air used where it contacts products should be:

a) Oily and moist b) Oil-free, dry, and filtered c) Heated to boiling d) Mixed with nitrogen always

1 The correct CIP sequence is:

a) Sanitise → wash → rinse b) Pre-rinse → detergent wash → rinse → sanitise → final rinse c) Wash → sanitise → pre-rinse d) Final rinse → wash → rinse

1 BOD stands for:

a) Biochemical oxygen demand — oxygen microbes need to break down waste b) Basic oil density c) Batch output data d) Boiler operation date

1 Type A cleaning is done:

a) Between batches of the same product b) At product changeover, between different products — the deepest clean c) Only on Sundays d) For office furniture

1 In cleaning validation, swab sampling:

a) Tests the rinse water b) Directly wipes a defined equipment surface area to check for residues c) Is done with the eyes only d) Measures air quality

Answer key: 1-b, 2-b, 3-b, 4-b, 5-b, 6-b, 7-b, 8-b, 9-b, 10-a, 11-b, 12-b

21. Viva / Application Questions

1 What is Schedule M? Name three facility-design principles it requires.

2 A factory makes both tablets and syrups. How would you arrange material flow to prevent cross-contamination?

3 Distinguish potable water, purified water, and WFI with one use of each.

4 Why can't ordinary boiler steam be used for sterilising product-contact equipment? What is used instead?

5 Draw the CIP cycle from memory and explain the purpose of each step.

6 What is the significance of testing effluent? Define BOD and COD in simple words.

7 Explain Type A, B, and C cleaning with one example situation for each.

8 During cleaning validation of a mixer, which spots would you swab and why? What would you do if a swab fails?

22. References

- Drugs and Cosmetics Rules, India — Schedule M: Good Manufacturing Practices (refer to the latest edition).
- Indian Pharmacopoeia — monographs and general chapters on water quality (refer to the latest edition).
- WHO Technical Report Series — Good Manufacturing Practices: main principles (refer to the latest edition).
- Applicable IS/ISO standards for water and steam quality — general reference (confirm current editions before citing).