# GPAT Pharmaceutics

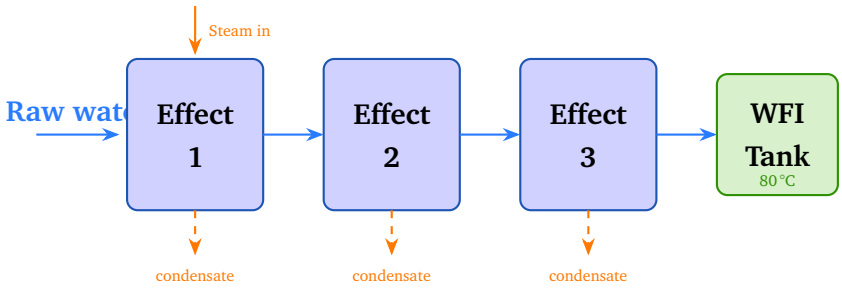
## Sample Paper – 8

**Duration: 36 Minutes** **Maximum Marks: 100**

### Instructions

- This paper contains **25** Multiple Choice Questions (Single Correct Answer), modelled on the Pharmaceutics portion of **GPAT** entrance.
- Each correct answer carries **+4 marks**. There is **a penalty of −1 mark** for each incorrect answer. Unattempted questions carry no marks.
- Only **one** option is correct per question.
- Syllabus: **GPAT Pharmaceutics — Sterile Products, Parenteral Preparations, Microbiology, Pharmaceutical QC/QA.**
- Personal calculators, mobile phones, and electronic gadgets are strictly prohibited. A simple on-screen calculator is provided in the CBT interface; rough sheets are supplied at the centre.

**Q1.** The schematic below depicts a three-effect distillation system for producing Water for Injection (WFI).




Which USP specification for Water for Injection (WFI) is **CORRECTLY** stated?

(A) TOC $\leq 1000$ ppb and conductivity $\leq 2.1\ \mu$S/cm at 25 °C

(B) EP WFI may only be produced by distillation; membrane-based processes remain prohibited under all current pharmacopoeial editions

(C) Bacterial endotoxins limit is $\leq 0.50$ EU/mL with a microbial count limit of $\leq 10$ CFU per 100 mL

(D) Conductivity $\leq 1.3\,\mu$S/cm at 25 °C, TOC $\leq 500$ ppb, and bacterial endotoxins $\leq 0.25$ EU/mL, with no organisms detected in 100 mL (membrane filtration)

**Q2.** A new intravenous drug product is dosed at a maximum rate of **20 mg/kg/hour**. Using the USP endotoxin threshold $K = 5.0$ EU/kg/hour for intravenous products and the formula:

$$\text{ELC} = \frac{K}{M}$$

where $M$ is the maximum dose per kg per hour, calculate the Endotoxin Limit Concentration (ELC) expressed per milligram of drug.

(A) 0.25 EU/mg

(B) 0.50 EU/mg

(C) 5.0 EU/mg

(D) 0.10 EU/mg

**Q3.** Endotoxins (lipopolysaccharides from gram-negative bacteria) are heat-stable and are NOT destroyed by standard moist-heat sterilisation at 121 °C. A pharmaceutical manufacturer needs to depyrogenate glass vials to achieve a $\geq 3$ **log** (1000-fold) reduction in endotoxin load. Which temperature/time combination achieves validated dry-heat depyrogenation at this level?

(A) 160 °C for 2 hours (standard dry-heat sterilisation of oils)

(B) 250 °C for 30 minutes (validated depyrogenation condition)

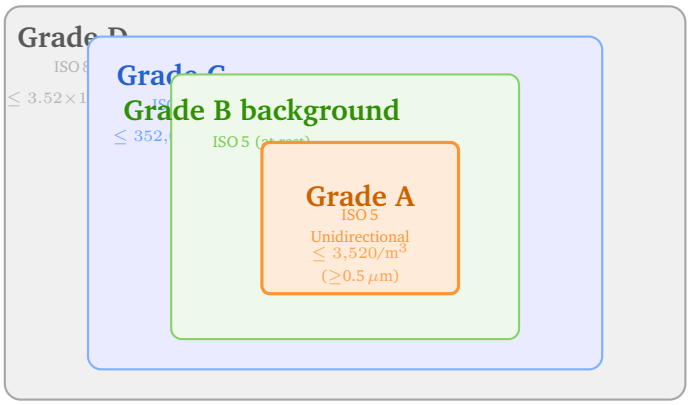
(C) 180 °C for 30 minutes (intermediate dry-heat sterilisation)

(D) 121 °C for 15 minutes (terminal moist-heat sterilisation)

**Q4.** Gamma radiation sterilisation using a cobalt-60 source is a terminal sterilisation method for heat-sensitive products. Which of the following parameters is the **MOST CRITICAL** for achieving a Sterility Assurance Level (SAL) of $10^{-6}$ in a radiation sterilisation process?

(A) The temperature of the irradiation chamber must be maintained below 25 °C to prevent thermal damage
(B) The wavelength of gamma radiation from cobalt-60, which must be confirmed as 1.25 nm before each batch
(C) The minimum absorbed dose of radiation (at least 25 kGy), verified by validated dosimetry throughout the product load
(D) The total exposure time to the cobalt-60 source, which must be exactly 4 hours for all product types

**Q5.** The nested diagram below represents the EU GMP cleanroom zoning used in aseptic manufacturing.




According to EU GMP guidelines, which cleanroom grade corresponds to the **critical zone** used for aseptic processing where product, open containers, and closures are directly exposed to the environment?

(A) Grade B — used as the immediate background for Grade A aseptic zones
(B) Grade C — used for less critical stages such as solution preparation
(C) Grade D — used for support activities such as gowning and material transfer
(D) Grade A — critical zone with ISO 5 unidirectional airflow at the point of fill/close exposure

**Q6.** During aseptic filling of injectable vials, the critical zone (Grade A / ISO 5) must be maintained by unidirectional (laminar) airflow passing through HEPA filters (99.97% efficiency at 0.3 $\mu$m). What is the **required**

**airflow velocity** specification for a Grade A unidirectional airflow zone during operation?

(A) 0.45 m/s ($\pm$20%) — the EU GMP and FDA guidance specification for unidirectional airflow in critical aseptic zones
(B) 0.10 m/s — the minimum velocity at which HEPA-filtered air maintains particle sweep in ISO 7 and ISO 8 areas
(C) 1.0 m/s — specified for turbulent airflow systems in Grade B background rooms
(D) 0.80 m/s ($\pm$10%) — the standard for Grade B corridors adjacent to filling suites

**Q7.** Blow-Fill-Seal (BFS) technology for parenteral manufacturing involves extruding a thermoplastic parison, blowing it into a mould, filling with drug solution, and sealing — all within a single automated sequence in a Grade A environment. What is the **PRIMARY regulatory advantage** of BFS over conventional glass vial filling?

(A) BFS containers are more optically transparent than glass, facilitating 100% automated visual inspection with greater sensitivity
(B) BFS eliminates the need for separate container washing, sterilisation, and depyrogenation steps and dramatically reduces human intervention, lowering the risk of microbial and particulate contamination
(C) BFS uses glass primary containers that are stronger and more chemically inert than conventional tubing-glass vials
(D) BFS technology allows room-temperature sterilisation of heat-sensitive drugs without any exposure to ethylene oxide or ionising radiation

**Q8.** A lyophilised antibiotic product for paediatric patients is reconstituted with Bacteriostatic Water for Injection (BWFI) containing 0.9% benzyl alcohol as antimicrobial preservative. Why is BWFI **CONTRAINDICATED** for reconstitution in neonates (infants $\leq$28 days)?

(A) Benzyl alcohol accelerates protein denaturation and aggregation in

lyophilised biologic formulations, rendering them ineffective at any concentration

(B) Benzyl alcohol lowers the reconstituted solution pH below 4.0, causing precipitation of the drug in neonatal intravenous lines

(C) Neonates have immature hepatic enzyme capacity (insufficient alcohol dehydrogenase and glycine conjugation) to metabolise benzyl alcohol, leading to toxic accumulation of benzoic acid and benzyl alcohol, causing the "Gasping Syndrome" (metabolic acidosis, CNS depression, gasping respirations)

(D) Benzyl alcohol is a proven teratogen; its parenteral use in the first month of life causes irreversible neural tube defects and developmental abnormalities

**Q9.** Physical-chemical incompatibility between co-administered parenterals is a patient safety concern. Which of the following combinations is **MOST likely to result in visible precipitation** when mixed together in an IV infusion bag?

(A) Morphine sulfate injection + 0.9% sodium chloride injection

(B) Potassium chloride concentrate + Dextrose 5% in Water (D5W)

(C) Regular insulin injection + 0.9% sodium chloride injection

(D) Calcium gluconate injection + Sodium bicarbonate injection

**Q10.** Benzalkonium chloride (BAC) is the most widely used quaternary ammonium preservative in multi-dose ophthalmic preparations. It exerts its antimicrobial effect by disrupting bacterial cell membranes. What is the **standard (typical) concentration** of BAC used as a preservative in commercially available ophthalmic drops?

(A) 0.01% (w/v) — the standard concentration providing adequate antimicrobial efficacy while minimising corneal epithelial toxicity

(B) 0.1% (w/v) — used in ophthalmic preparations requiring enhanced broad-spectrum activity against fungi

(C) 0.001% (w/v) — the minimum inhibitory concentration for BAC against *Pseudomonas aeruginosa* in ophthalmic systems

(D) 1.0% (w/v) — standard concentration used in ophthalmic irrigating solutions during surgical procedures

**Q11.** The Sterility Assurance Level (SAL) of $10^{-6}$ for terminal sterilisation means the probability of a non-sterile unit is one in one million. Which statement **CORRECTLY** describes what must be achieved by the sterilisation process to attain SAL $10^{-6}$?

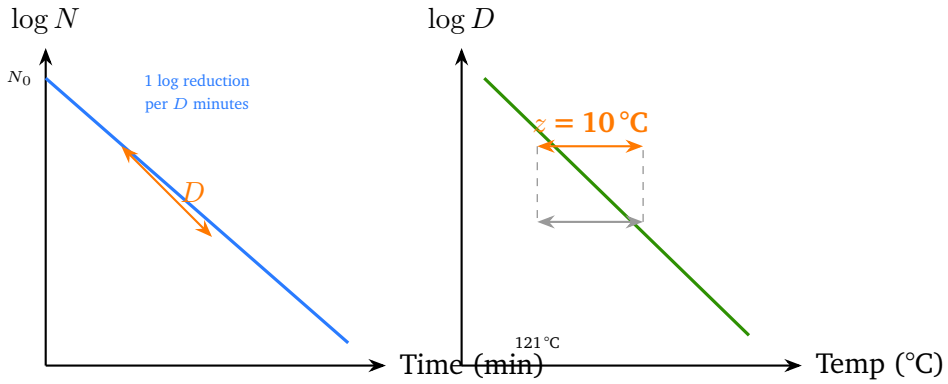
(A) The D-value of the sterilising agent must be at least 1.0 minute regardless of initial bioburden levels

(B) The total log reduction of viable organisms achieved by the process must exceed $(\log N_0 + 6)$, reducing the probability of a survivor to $\leq 10^{-6}$ relative to the pre-sterilisation bioburden $N_0$

(C) Every individual container must pass USP $\langle 71 \rangle$ direct sterility testing before batch release is authorised

(D) The $F_0$ value must always equal exactly 12 minutes irrespective of the initial bioburden or D-value of the bioburden organisms

**Q12.** The survivor curve and thermal destruction curve for a biological indicator (BI) for steam sterilisation are shown below.




**(a) Survivor curve** **(b) Thermal destruction**

A biological indicator for steam sterilisation contains $10^6$ spores of *Geobacillus stearothermophilus* with $D_{121} = 1.5$ minutes and $z = 10\,°C$. What $F_0$ value is required to achieve SAL $10^{-6}$?

(A) 9 minutes — based on 6 log reductions $\times$ $D_{121} = 1.5$ min

(B) 12 minutes — based on 8 log reductions as an overkill safety margin

(C) 18 minutes — based on reducing $N_0 = 10^6$ to SAL $10^{-6}$ requires 12 log reductions: $F_0 = 12 \times 1.5 = 18$ min

(D) 6 minutes — based on 4 log reductions using $D_{121}$

**Q13.** A formulator wishes to perform a USP ⟨71⟩ sterility test on a beta-lactam antibiotic solution using the **direct inoculation** method. Which additional procedural requirement is **ESSENTIAL** to prevent a false-negative result caused by residual antimicrobial activity?

(A) Replace the standard fluid thioglycollate medium with a selective chromogenic agar specific for the target beta-lactam-resistant organisms

(B) Include an additional incubation temperature of 4 °C to detect psychrophilic contaminants that might survive the antibiotic

(C) Neutralise the antibiotic solution with dilute sodium hydroxide immediately before inoculating the culture medium

(D) Incorporate a specific neutralising agent (e.g., penicillinase for beta-lactams, or sufficient dilution) to inactivate residual antimicrobial activity in the test medium before organism recovery

**Q14.** A batch of oral tablets (non-sterile solid dosage form) is being tested for microbiological quality according to USP ⟨2021⟩ (Microbial Examination of Non-Sterile Products). What is the **TAMC (Total Aerobic Microbial Count) limit** specified for this category of product?

(A) $\leq 10^3$ CFU/g — the USP ⟨2021⟩ limit for oral solid dosage forms (Category 2)

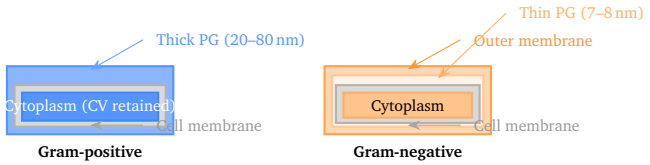
(B) $\leq 10^2$ CFU/g — the limit applied to aqueous oral liquid preparations (Category 3)

(C) $\leq 10^4$ CFU/g — the limit for topical non-sterile preparations not applied to mucous membranes

(D) $\leq 10^5$ CFU/g — the limit for herbal medicinal products that have been subjected to a hot-water extraction step

**Q15.** The diagram below shows a cross-section of a gram-positive and a gram-

negative bacterium at a stage during Gram staining.




In the Gram stain procedure, what is the **CORRECT function** of the iodine (Gram's iodine) step applied *after* the initial crystal violet staining?

(A) The iodine step decolourises gram-negative bacteria by extracting the crystal violet stain through the outer membrane

(B) Iodine acts as a **mordant**, forming a large insoluble crystal violet–iodine (CV–I) complex within all bacterial cells, intensifying the purple colour and making the stain more resistant to subsequent decolourisation

(C) Iodine is the counterstain that imparts the characteristic pink/red colour to gram-negative organisms after decolourisation

(D) Iodine directly intercalates into bacterial DNA, distinguishing gram-positive from gram-negative organisms based on differences in genomic GC content

**Q16.** During routine quality control testing, an analyst obtains an out-of-specification (OOS) result for assay of a tablet batch. A thorough Phase 1 laboratory investigation is conducted but **no assignable laboratory error** is identified. According to 21 CFR 211.192 and FDA OOS guidance, what is the **REQUIRED next step**?

(A) The failing result must be immediately reported to the relevant regulatory authority (e.g., FDA) before any further investigation is undertaken

(B) The entire batch is automatically quarantined and re-manufactured without additional investigation or testing of the original batch

(C) A Phase 2 extended investigation must be initiated, including a full manufacturing record review, reserve sample testing by an independent analyst, and an evaluation of related batches and stability samples

(D) The OOS result may be invalidated solely on the basis of Phase 1 findings, and no further action or documentation is required

**Q17.** ICH Q10 describes a Pharmaceutical Quality System (PQS) that supports product development and commercial manufacturing. It identifies four key enablers and four elements of the PQS. According to ICH Q10, which element is **PRIMARILY responsible** for ensuring that non-conformances and quality failures during commercial manufacturing are systematically investigated to determine root cause and are resolved to prevent recurrence?

(A) Management Review — senior management's periodic evaluation of the PQS to ensure its continuing suitability and effectiveness
(B) Change Management — the systematic approach to proposing, evaluating, and implementing changes to processes, equipment, and specifications
(C) Process Performance and Product Quality Monitoring — the ongoing collection and analysis of manufacturing data to detect trends and variability
(D) Corrective and Preventive Action (CAPA) System — the structured process for identifying, investigating, and resolving non-conformances through root-cause analysis and implementing measures to prevent recurrence

**Q18.** A pharmaceutical QA manager is reviewing the company's CAPA (Corrective and Preventive Action) register. Two distinct types of actions are recorded. Which statement **BEST distinguishes** a corrective action from a preventive action?

(A) A **corrective action** eliminates the root cause of a confirmed, existing non-conformance (reactive); a **preventive action** eliminates the potential cause of a non-conformance that has not yet occurred (proactive)
(B) Corrective actions prevent future problems; preventive actions correct current defects — the terms are used interchangeably in most

pharmaceutical QMS systems

(C) Corrective actions are implemented immediately by production personnel without formal documentation, whereas preventive actions require prior regulatory approval

(D) Both corrective and preventive actions apply exclusively to manufacturing process changes and do not extend to analytical laboratory non-conformances

**Q19.** Depyrogenation of glass vials by dry heat at 250 °C is a critical aseptic manufacturing step. Regulatory guidelines and pharmacopoeial standards require validation of this process using a spiked endotoxin challenge. What is the **minimum validated endotoxin reduction** that must be demonstrated for a depyrogenation process to be considered adequate?

(A) $\geq 1$ log (10-fold) reduction in endotoxin challenge

(B) $\geq 3$ log (1000-fold) reduction in endotoxin challenge

(C) $\geq 6$ log ($10^6$-fold) reduction in endotoxin challenge, analogous to microbial SAL for sterilisation

(D) $\geq 2$ log (100-fold) reduction in endotoxin challenge

**Q20.** Pharmaceutical-grade rubber stoppers for injectable vials must meet strict requirements for chemical compatibility, low extractables/leachables (E&L), and resealability. Which rubber stopper formulation is **MOST COMMONLY RECOMMENDED** for biological and biotechnology injectable products, particularly those containing proteins or monoclonal antibodies?

(A) Natural rubber (NR) stoppers, preferred for their superior elasticity and low cost relative to synthetic alternatives

(B) Chlorobutyl rubber, specifically chosen for its exceptionally low water vapour transmission rate, protecting lyophilised biologicals from moisture

(C) Bromobutyl rubber, favoured for its low extractables profile, excellent chemical compatibility with protein-based formulations, and

good resealability

(D) Polydimethylsiloxane (silicone) rubber, because it is completely chemically inert and has no known interactions with any protein or small molecule drug

**Q21.** In the quality control of parenteral preparations, osmolality is the pharmacopoeially preferred measurement for tonicity because it is more accurate than calculated osmolarity, especially in complex solutions. Which analytical method is used to **DIRECTLY MEASURE** osmolality (not calculate osmolarity)?

(A) Refractometry, based on measurement of the change in refractive index of the parenteral solution at a defined wavelength

(B) Titrimetry (acid-base), measuring the total concentration of dissolved solids by equivalence-point stoichiometry

(C) Spectrophotometry, measuring the combined UV absorbance of all osmotically active solute species at 280 nm

(D) Freezing-point depression osmometry, exploiting the colligative property $\Delta T_f = 1.86\,^{\circ}\text{C} \cdot \text{kg/mol} \times b_{\text{osm}}$ to directly measure solution osmolality from the observed freezing-point depression

**Q22.** USP $\langle 788 \rangle$ (Particulate Matter in Injections) specifies limits for subvisible particles in injectable preparations, measured by light obscuration or microscopy. For a **large-volume parenteral (LVP)** preparation of $\geq$ 100 mL volume, what is the maximum allowable particle count for particles $\geq 10\,\mu$m by light obscuration?

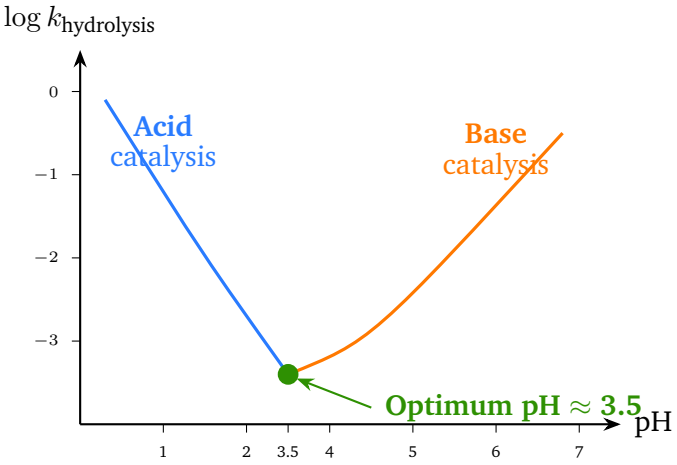
(A) $\leq 25$ particles/mL for particles $\geq 10\,\mu$m AND $\leq 3$ particles/mL for particles $\geq 25\,\mu$m

(B) $\leq 6{,}000$ particles per container for particles $\geq 10\,\mu$m AND $\leq 600$ per container for particles $\geq 25\,\mu$m

(C) $\leq 50$ particles/mL for particles $\geq 10\,\mu$m (less stringent limit applied to LVPs containing added electrolytes)

(D) $\leq 100$ particles/mL for particles $\geq 5\,\mu$m (the threshold for visible particle detection in the LVP particle size range)

**Q23.** The pH-stability profile below shows the degradation rate constant ($\log k$) versus pH for an ester-containing injectable drug undergoing hydrolysis.




In the pH-stability study of this ester injectable drug, the degradation rate constant is minimised at pH 3.5. What is the **pharmaceutical significance** of this "optimum pH"?

(A) At pH 3.5 the drug degrades maximally; acid and base catalysis are both absent, but spontaneous (pH-independent) hydrolysis reaches its peak

(B) pH 3.5 is the target formulation pH because the degradation rate is at its *minimum* there, maximising chemical stability and extending the shelf life of the injectable product

(C) At pH 3.5 the ester drug is completely un-ionised, which prevents hydrolytic attack by both hydronium ions and hydroxide ions through all mechanisms

(D) The optimum pH represents the point of maximum drug bioavailability; above and below pH 3.5 the drug is ionised and absorption through the injection site decreases

**Q24.** Mannitol (MW = 182 g/mol, non-electrolyte, van't Hoff factor $i = 1$) is used as an isotonicity agent in ophthalmic and parenteral preparations. Isotonicity is defined as an osmolality equivalent to 0.9% NaCl ≈ 308 mOsmol/kg. Using the relationship:

$$\text{Osmolality (mOsmol/L)} = \frac{c\,(\text{g/L})}{\text{MW (g/mol)}} \times i \times 1000$$

which concentration of mannitol produces an **isotonic** ophthalmic solution (osmolality $\approx$ 297–308 mOsmol/L)?

(A) 1.0% (w/v) mannitol $\rightarrow \approx$55 mOsmol/L (markedly hypotonic)
(B) 2.5% (w/v) mannitol $\rightarrow \approx$137 mOsmol/L (hypotonic)
(C) 5.4% (w/v) mannitol $\rightarrow \approx$297 mOsmol/L (isotonic)
(D) 10.0% (w/v) mannitol $\rightarrow \approx$549 mOsmol/L (markedly hypertonic)

**Q25.** For terminally sterilised injectable products, the "overkill approach" to moist-heat sterilisation is designed to provide a large safety margin independent of the routine bioburden. Parametric release (release of product on the basis of process data without end-product sterility testing) requires demonstrated and documented cycle validation. What **minimum** $F_0$ **value** is typically required to justify parametric release under the overkill sterilisation approach?

(A) $F_0 \geq 3$ minutes — sufficient for a 2-log reduction of *G. stearothermophilus* starting from a low bioburden
(B) $F_0 \geq 6$ minutes — required when the pre-sterilisation bioburden is confirmed to be $\leq 1$ CFU per container
(C) $F_0 \geq 8$ minutes — the EU GMP minimum for all terminally sterilised aqueous injections regardless of sterilisation approach
(D) $F_0 \geq 12$ minutes — the widely accepted overkill standard providing $\geq 8$ log reduction of *G. stearothermophilus* ($D_{121} = 1.5$ min), sufficient to justify parametric release

## Detailed Solutions

### Q1.

**Solution**

**Concept — Water for Injection (WFI) Specifications:** USP ⟨1231⟩ and the USP monograph for Water for Injection specify four key quality parameters: (1) conductivity $\leq 1.3\,\mu$S/cm at 25 °C, (2) Total Organic Carbon (TOC) $\leq 500$ ppb, (3) bacterial endotoxins $\leq 0.25$ EU/mL, and (4) no organisms detected in 100 mL by membrane filtration. WFI may be produced by distillation or by validated combinations of reverse osmosis and ultrafiltration (USP). The European Pharmacopoeia (EP) historically required distillation only, but has been amended to permit membrane-based processes provided they are validated.

**Why each option is correct or wrong:**

- Option A: TOC limit of 1000 ppb and conductivity 2.1 $\mu$S/cm are incorrect; the USP limits are $\leq$500 ppb and $\leq$1.3 $\mu$S/cm respectively.
- Option B: EP has been amended (EP 10th edition) to allow validated membrane-based (RO+UF) production of WFI; distillation-only is no longer the sole permitted method.
- Option C: The endotoxin limit is $\leq 0.25$ EU/mL (not 0.50 EU/mL), and the microbial limit is no organisms detected (not $\leq$10 CFU/100 mL).
- Option D: Conductivity $\leq 1.3\,\mu$S/cm at 25 °C, TOC $\leq 500$ ppb, endotoxins $\leq 0.25$ EU/mL, and no organisms detected in 100 mL. **Correct.**

**Final Answer:** USP WFI: conductivity $\leq$1.3 $\mu$S/cm; TOC $\leq$500 ppb; endotoxins $\leq$0.25 EU/mL $\Rightarrow$ $\boxed{\text{D}}$

**Answer: (D)** Go Back to Q1

### Q2.

**Solution**

**Concept — Endotoxin Limit Concentration (ELC) Calculation:** The Endotoxin Limit Concentration is calculated from:

$$\text{ELC} = \frac{K}{M}$$

where $K$ is the threshold pyrogenic dose for the route (5.0 EU/kg/h for IV products) and $M$ is the maximum dose per kilogram per hour. The result is expressed in EU per unit of dose (EU/mg, EU/mL, etc.).

**Step 1 — Identify the values:** $K = 5.0$ EU/kg/h (IV route); $M = 20$ mg/kg/h.

**Step 2 — Calculate ELC:**

$$\text{ELC} = \frac{5.0\,\text{EU/kg/h}}{20\,\text{mg/kg/h}} = 0.25\,\text{EU/mg}$$

**Step 3 — Verify LAL sensitivity:** The LAL sensitivity $\lambda$ used must be $\leq$ ELC/2 = 0.125 EU/mL. A standard reagent with $\lambda = 0.125$ EU/mL meets this requirement.

**Why other options are wrong:**

- Option A: 0.25 EU/mg is correct as derived above. **Correct.**
- Option B: 0.50 EU/mg would result from using $M = 10$ mg/kg/h; the stated dose is 20 mg/kg/h.
- Option C: 5.0 EU/mg equals $K$ itself, ignoring the dose denominator.
- Option D: 0.10 EU/mg would require $M = 50$ mg/kg/h.

**Final Answer:** ELC = 5.0/20 = 0.25 EU/mg $\Rightarrow$ A

**Answer: (A)** Go Back to Q2

## Q3.

### Solution

**Concept — Dry-Heat Depyrogenation vs Sterilisation:** Endotoxins (lipopolysaccharides, LPS) are extraordinarily heat-stable — they are not destroyed by standard moist-heat sterilisation at 121 °C or even by dry heat at 160–180 °C. Depyrogenation (destruction of endotoxins to achieve $\geq 3$ log reduction) requires temperatures of $\geq$**250 °C**. The standard validated condition is 250 °C for 30 minutes (or 300 °C for shorter tunnels). Moist heat cannot achieve depyrogenation.

**Step 1 — Recall depyrogenation threshold:** Dry heat $\geq 250$ °C is required to achieve $\geq 3$ log (1000-fold) reduction in endotoxin. Below this temperature (e.g., 160–180 °C), dry-heat sterilisation of micro-organisms is achieved but endotoxins survive intact.

**Step 2 — Match to the pharmacopoeial condition:** 250 °C / 30 min is the validated depyrogenation condition used for glass vials, metal trays, and equipment in aseptic manufacturing.

**Why other options are wrong:**

- Option A: 160 °C/2 h sterilises spores/vegetative organisms but does NOT

depyrogenate glass; endotoxins survive.

- Option B: 250 °C/30 min achieves validated ≥3 log endotoxin reduction. **Correct.**
- Option C: 180 °C/30 min can dry-heat sterilise but is insufficient for depyrogenation.
- Option D: 121 °C/15 min (autoclave) achieves moist-heat sterilisation (SAL $10^{-6}$) but is completely ineffective against endotoxins.

**Final Answer:** Depyrogenation requires ≥250 °C/30 min dry heat ⇒ B

**Answer: (B)** Go Back to Q3

## Q4.

### Solution

**Concept — Gamma Radiation Sterilisation Parameters:** Gamma irradiation using cobalt-60 ($\overline{E} = 1.25$ MeV) is a terminal sterilisation method validated by radiation dosimetry. The critical process parameter is the **minimum absorbed dose**, expressed in kilograys (kGy). A minimum dose of 25 kGy at the minimum-dose location in the validated product load has been established as achieving SAL $10^{-6}$ for most pharmaceutical products. Dosimetry (dose mapping) must be performed to verify that every point in the load receives ≥25 kGy. Temperature, time, and wavelength are not independently specified as critical parameters in radiation sterilisation.

**Step 1 — Identify the critical parameter:** Unlike moist-heat sterilisation (where temperature and time together define $F_0$), radiation sterilisation is governed by absorbed dose alone. Dose mapping with calibrated dosimeters throughout the product load is the regulatory requirement.

**Step 2 — Apply to the given options:** The minimum absorbed dose of ≥25 kGy (verified by validated dosimetry) is the parameter that must be controlled and documented to achieve SAL $10^{-6}$.

**Why other options are wrong:**

- Option A: Temperature is not a specified critical parameter; gamma radiation can be applied at ambient temperature without a specified maximum.
- Option B: Gamma radiation energy is 1.25 MeV (not 1.25 nm wavelength); moreover, the energy of cobalt-60 is fixed and not a controlled variable.
- Option C: Minimum absorbed dose ≥25 kGy, verified by dosimetry, is the critical parameter for SAL $10^{-6}$. **Correct.**

- Option D: Exposure time is a derived consequence of dose rate (which depends on source activity); it is not independently specified as a critical parameter.

**Final Answer:** Minimum absorbed dose $\geq$25 kGy verified by validated dosimetry $\Rightarrow$ C

**Answer: (C)** Go Back to Q4

## Q5.

### Solution

**Concept — EU GMP Cleanroom Grades and ISO Classification:** EU GMP Annex 1 defines four grades (A–D) for aseptic manufacturing environments:

- **Grade A** (ISO 5): Critical zone — unidirectional airflow, directly overlies open product, containers, and closures. Required at the point of fill. Particle limit: $\leq$3,520 particles/m$^3$ ($\geq$0.5 $\mu$m).
- **Grade B** (ISO 5): Background room for Grade A; used for preparation and filling of sterile preparations where Grade A activities take place.
- **Grade C** (ISO 7): For less critical stages, e.g., preparation of solutions for subsequent sterile filtration.
- **Grade D** (ISO 8): For handling of closed containers; support areas.

**Step 1 — Identify the critical aseptic zone:** The critical zone (where product is exposed) must be maintained at Grade A (ISO 5) with unidirectional airflow at 0.45 m/s ($\pm$20%). The nested diagram shows Grade A as the innermost box.

**Why other options are wrong:**

- Option A: Grade B is the background room *surrounding* Grade A; it is not the critical zone itself.
- Option B: Grade C is used for preparatory steps, not for critical aseptic filling where product is exposed.
- Option C: Grade D is the least stringent grade, used for general support activities and transfer corridors.
- Option D: Grade A (ISO 5 unidirectional) is the critical zone for aseptic processing. **Correct.**

**Final Answer:** Grade A (ISO 5 unidirectional) = critical zone for aseptic processing $\Rightarrow$ D

**Answer: (D)** Go Back to Q5

## Q6.

**Solution**

**Concept — Unidirectional Airflow Velocity Specification (Grade A):** Grade A (ISO 5) unidirectional airflow zones in aseptic manufacturing must meet specific airflow velocity requirements to ensure effective particle sweep-out and prevention of turbulence. Both EU GMP Annex 1 (2022 revision) and FDA aseptic processing guidance specify an airflow velocity of **0.45 m/s (±20%)** (i.e., 0.36–0.54 m/s) for critical zones. This applies to both horizontal and vertical unidirectional airflow systems. The HEPA filters must provide ≥99.97% efficiency at 0.3 $\mu$m particles.

**Step 1 — Recall the regulatory specification:** EU GMP Annex 1 (2022): Grade A unidirectional airflow velocity = 0.45 m/s (±20%) at the working position. Smoke visualisation studies confirm adequate sweep-out at this velocity.

**Why other options are wrong:**

- Option A: 0.45 m/s (±20%) is the correct EU GMP and FDA specification for Grade A unidirectional airflow. **Correct.**
- Option B: 0.10 m/s is far too slow for Grade A; at this velocity turbulent mixing would occur, compromising particle sweep-out.
- Option C: 1.0 m/s would be excessively turbulent and is not specified for any GMP grade; it could disturb exposed product.
- Option D: 0.80 m/s (±10%) has no pharmacopoeial or regulatory basis for any cleanroom grade.

**Final Answer:** Grade A unidirectional airflow = 0.45 m/s (±20%) ⇒ $\boxed{\text{A}}$

**Answer: (A)** Go Back to Q6

## Q7.

**Solution**

**Concept — Blow-Fill-Seal (BFS) Technology Regulatory Advantage:** BFS technology is an advanced aseptic filling system in which a thermoplastic container (LDPE, HDPE, or PP) is formed, filled, and sealed in one continuous automated sequence within a Grade A environment. The key regulatory advantage is the **elimination of separate container preparation steps**: conventional glass vial filling requires washing, depyrogenation (250 °C/30 min), sterilisation, and transfer — each step involving human handling and contamination risk. BFS eliminates all of these. Containers are formed from sterile virgin plastic resin extruded at >180 °C, and the integrated process minimises human intervention in the critical

aseptic zone.

**Why each option is correct or wrong:**

- Option A: BFS containers (LDPE/PP) are less optically clear than glass; visual inspection is typically performed by transmitted-light inspection systems that compensate for lower transparency.
- Option B: BFS eliminates separate container preparation (washing, depyrogenation, sterilisation, transfer) and maximally reduces human exposure in the aseptic zone. This is the primary regulatory/quality advantage. **Correct.**
- Option C: BFS uses *plastic* (not glass) primary containers, which have different chemical compatibility properties.
- Option D: BFS is a form-fill-seal process for heat-stable drugs; heat-sensitive proteins and biologicals typically require separate aseptic filling steps, often with cold-chain requirements.

**Final Answer:** BFS eliminates separate container prep and minimises human intervention $\Rightarrow$ B

**Answer: (B)** Go Back to Q7

## Q8.

### Solution

**Concept — Benzyl Alcohol Toxicity in Neonates (Gasping Syndrome):** Benzyl alcohol is an aromatic alcohol used as an antimicrobial preservative in Bacteriostatic Water for Injection (BWFI) at 0.9% (w/v). In adults and older children, benzyl alcohol is metabolised in the liver:

$$\text{Benzyl alcohol} \xrightarrow{\text{alcohol dehydrogenase}} \text{Benzaldehyde} \xrightarrow{\text{aldehyde dehydrogenase}} \text{Benzoic acid} \xrightarrow{\text{glycine conjugation}} \text{H}$$

Neonates have **immature hepatic enzyme systems** (insufficient alcohol dehydrogenase, aldehyde dehydrogenase, and glycine conjugation capacity), resulting in accumulation of benzoic acid and benzyl alcohol. Toxic accumulation (typically $>$100 mg/kg/day from multiple reconstitutions) causes "Gasping Syndrome": metabolic acidosis, CNS depression, cardiovascular collapse, and characteristic gasping respirations. The FDA issued a warning in 1982; BWFI is contraindicated in neonates.

**Why other options are wrong:**

- Option A: Benzyl alcohol at 0.9% may affect some protein stability, but protein denaturation is not the basis for the contraindication in neonates.

- Option B: Benzyl alcohol does not significantly alter reconstituted solution pH to cause precipitation; pH effects are not the toxicity mechanism.
- Option C: Immature hepatic metabolism leading to toxic accumulation and Gasping Syndrome is the correct pharmacological basis for the neonatal contraindication. **Correct.**
- Option D: Benzyl alcohol is not classified as a teratogen; neural tube defects are not associated with benzyl alcohol exposure in neonates.

**Final Answer:** Neonates lack adequate hepatic metabolism capacity → Gasping Syndrome ⇒ C

**Answer: (C)** Go Back to Q8

## Q9.

### Solution

**Concept — IV Fluid Physical-Chemical Incompatibility:** Calcium gluconate and sodium bicarbonate are a classic example of an incompatible parenteral combination. When mixed, free calcium ions ($Ca^{2+}$) from calcium gluconate react with bicarbonate/carbonate ions from sodium bicarbonate to form **calcium carbonate** ($CaCO_3$), an insoluble white precipitate:

$$Ca^{2+}_{(aq)} + 2\,HCO_3{}^{-}{}_{(aq)} \rightarrow CaCO_{3\,(s)} \downarrow + H_2O + CO_2$$

This precipitation is pH-dependent and concentration-dependent but can occur rapidly when these two solutions are mixed in an IV bag. Calcium-phosphate precipitation in total parenteral nutrition (TPN) is similarly dangerous. This incompatibility is particularly clinically significant and has caused patient deaths.

**Why other options are wrong:**

- Option A: Morphine sulfate + normal saline is a compatible combination; no precipitation occurs under standard conditions.
- Option B: KCl + D5W is routinely administered as a single solution; no precipitation occurs.
- Option C: Regular insulin + normal saline is standard clinical practice (insulin infusions); no precipitation or chemical incompatibility occurs.
- Option D: $Ca^{2+} + HCO_3^- \rightarrow CaCO_3 \downarrow$ (visible white precipitate, potentially life-threatening if administered). **Correct.**

**Final Answer:** Calcium gluconate + sodium bicarbonate → $CaCO_3$ precipitate ⇒ D

**Answer: (D)** Go Back to Q9

## Q10.

### Solution

**Concept — Benzalkonium Chloride (BAC) Concentration in Ophthalmic Drops:** Benzalkonium chloride (BAC), a quaternary ammonium compound, is the most commonly used preservative in multi-dose ophthalmic preparations. The standard concentration is **0.01% (w/v)** (equivalent to 0.1 mg/mL or 100 $\mu$g/mL). At this concentration, BAC provides adequate antimicrobial efficacy against the spectrum of organisms required by the Preservative Efficacy Test (Category 1, ophthalmic use). Higher concentrations (0.02–0.05%) may be used in some products but increase the risk of corneal epithelial cytotoxicity, especially with chronic multi-dose glaucoma medications. BAC is incompatible with anionic surfactants, nitrates, and certain active ingredients.

**Why other options are wrong:**

- Option A: 0.01% (w/v) is the standard concentration for ophthalmic preservative use. **Correct.**
- Option B: 0.1% (w/v) is 10 times the standard concentration and would cause significant corneal toxicity; it is not used as a preservative in ophthalmic drops.
- Option C: 0.001% is below the effective preservative concentration; it would not meet pharmacopoeial antimicrobial efficacy requirements.
- Option D: 1.0% BAC is a disinfectant/antiseptic concentration for skin and surface use; it is not used in ophthalmic preparations.

**Final Answer:** Standard BAC concentration in ophthalmic drops = 0.01% (w/v) $\Rightarrow$ A

**Answer: (A)** Go Back to Q10

## Q11.

**Solution**

**Concept — Sterility Assurance Level and Log Reduction Requirement:** SAL $10^{-6}$ is a probabilistic concept: no more than one unit in one million is non-sterile after sterilisation. It is NOT achieved by testing (USP $\langle 71 \rangle$ has insufficient sensitivity to confirm SAL $10^{-6}$). Instead, it is *validated* through process design and bioburden reduction data.

**Mathematical basis:** If the pre-sterilisation bioburden is $N_0$ organisms per container, the process must deliver a log reduction of at least $(\log N_0 + 6)$:

$$\log(\text{survivors}) = \log N_0 - \frac{F_0}{D} \leq -6 \quad \Rightarrow \quad \frac{F_0}{D} \geq \log N_0 + 6$$

For example, if $N_0 = 10$ ($\log N_0 = 1$), then $\log$ reduction required $\geq 7$.

**Why other options are wrong:**

- Option A: The D-value of the sterilising agent must be considered relative to bioburden and SAL; a minimum D-value of 1.0 min alone is not the SAL criterion.
- Option B: Total log reduction $\geq (\log N_0 + 6)$ is the correct criterion for achieving SAL $10^{-6}$. **Correct.**
- Option C: End-product sterility testing (USP $\langle 71 \rangle$) cannot confirm SAL $10^{-6}$; parametric release is based on validated process data.
- Option D: $F_0 = 12$ min is a specific overkill target, not a universal requirement independent of bioburden and D-value.

**Final Answer:** Log reduction $\geq (\log N_0 + 6)$ is required to achieve SAL $10^{-6} \Rightarrow$ B

**Answer: (B)** Go Back to Q11

## Q12.

**Solution**

**Concept — $F_0$ Calculation from D-value and Initial Spore Count:** The $F_0$ value required to achieve a target SAL is calculated as:

$$F_0 = D_{121} \times (\log N_0 - \log N_{\text{final}})$$

where $\log N_{\text{final}}$ is the log of the target SAL.

**Step 1 — Identify the parameters:** $D_{121} = 1.5$ min; $N_0 = 10^6$; target SAL $= 10^{-6}$.

**Step 2 — Calculate the required log reduction:**

$$\text{Log reduction} = \log(10^{6}) - \log(10^{-6}) = 6 - (-6) = 12 \,\text{log cycles}$$

**Step 3 — Calculate $F_0$:**

$$F_0 = 1.5\,\text{min} \times 12 = 18\,\text{min}$$

**Why other options are wrong:**

- Option A: $9\,\text{min} = 1.5 \times 6$ accounts for only the 6-log reduction from $N_0 = 10^6$ to $N = 1$, not to SAL $10^{-6}$ (which goes 6 logs further below a single organism).
- Option B: $12\,\text{min} = 1.5 \times 8$ corresponds to 8 log reductions but is based on the overkill criterion, not this specific calculation.
- Option C: $18\,\text{min} = 1.5 \times 12$ correctly accounts for the full 12 log reductions from $10^6$ to $10^{-6}$. **Correct.**
- Option D: $6\,\text{min} = 1.5 \times 4$ accounts for only 4 log reductions, leaving survivors far above SAL $10^{-6}$.

**Final Answer:** $F_0 = D_{121} \times 12 = 1.5 \times 12 = 18\,\text{min} \Rightarrow$ C

**Answer: (C)** Go Back to Q12

## Q13.

**Solution**

**Concept — USP ⟨71⟩ Sterility Test: Antibiotic Neutralisation:** USP ⟨71⟩ specifies that when testing antimicrobial products by direct inoculation, any residual antimicrobial activity in the test solution must be **neutralised or eliminated** to prevent false-negative results. Without neutralisation, the drug's antimicrobial action would kill or inhibit any incidental microbial contaminants in the test medium, giving a false appearance of sterility.

**Neutralisation methods for common antibiotics:**

- Beta-lactams: penicillinase enzyme (beta-lactamase) cleaves the beta-lactam ring, inactivating the antibiotic
- Aminoglycosides, polymyxins: dilution to below MIC
- General principle: the suitability test (growth promotion) must demonstrate that the neutraliser works in the presence of the test article

**Why other options are wrong:**

- Option A: Chromogenic selective agar is not used in USP ⟨71⟩ sterility testing; standard media (FTM and SCDM) are specified.
- Option B: An additional incubation at 4 °C is not required by USP ⟨71⟩; standard incubation is 20–25 °C and 30–35 °C.
- Option C: Neutralisation with NaOH is incorrect; NaOH does not inactivate beta-lactam antibiotics and would alter pH adversely.
- Option D: Addition of a specific neutralising agent (e.g., penicillinase for beta-lactams) to eliminate residual antimicrobial activity is the correct and required step. **Correct.**

**Final Answer:** A specific neutralising agent (e.g., penicillinase) must be used to inactivate residual antimicrobial activity $\Rightarrow$ $\boxed{\text{D}}$

**Answer: (D)** Go Back to Q13

## Q14.

### Solution

**Concept — USP ⟨2021⟩ TAMC Limit for Oral Solid Dosage Forms:** USP ⟨2021⟩ (and EP 5.1.4) classify non-sterile products into categories based on route of administration. Category 2 covers non-aqueous preparations for oral use and oral solid dosage forms (tablets, capsules, powders):

- **TAMC**: $\leq 10^3$ CFU/g (total aerobic microbial count)
- **TYMC**: $\leq 10^2$ CFU/g (total yeast and mould count)
- Absence of *Escherichia coli* per 1 g

Category 3 (aqueous oral liquids): TAMC $\leq 10^2$ CFU/mL (more stringent because aqueous environment supports microbial growth).

**Why other options are wrong:**

- Option A: $\leq 10^3$ CFU/g is the correct TAMC limit for oral solid dosage forms (Category 2). **Correct.**
- Option B: $\leq 10^2$ CFU/g is the TAMC limit for aqueous oral liquid preparations (Category 3), not tablets.
- Option C: $\leq 10^4$ CFU/g is not a standard pharmacopoeial limit for any oral dosage form category; it may apply to some herbal products.
- Option D: $\leq 10^5$ CFU/g applies to herbal medicinal products subjected to hot-water extraction, not conventional oral tablets.

**Final Answer:** TAMC for oral solid dosage forms (Category 2) = $\leq 10^3$ CFU/g $\Rightarrow$ A

**Answer: (A)** Go Back to Q14

## Q15.

### Solution

**Concept — Gram Stain Mechanism: Role of Iodine (Mordant):** The four steps of the Gram stain and their functions:

(a) **Crystal violet** (primary stain): All bacteria stain purple/violet.

(b) **Gram's iodine** (mordant): Iodine forms a large, insoluble crystal violet–iodine (CV–I) complex (MW ≈900 Da) within the cell wall. This complex is *too large to diffuse out easily* from the thick peptidoglycan layer of gram-positive cells. The mordant intensifies the stain and anchors it within the cell.

(c) **Decolouriser** (ethanol/acetone): Lipid solvent extracts the outer membrane of gram-negative cells, creating large pores in the thin peptidoglycan; CV–I washes out. In gram-positive cells, dehydration closes pores in the thick peptidoglycan, trapping CV–I (cells remain purple).

(d) **Safranin** (counterstain): Gram-negative cells (now colourless) absorb safranin and appear pink/red. Gram-positive cells (already purple) appear unaffected.

**Why other options are wrong:**

- Option A: Decolourisation of gram-negative bacteria is performed by the ethanol/acetone step (Step 3), not the iodine step.
- Option B: Iodine acts as a mordant, forming the CV–I complex that makes the stain more difficult to remove. **Correct.**
- Option C: Safranin (not iodine) is the counterstain that gives gram-negative cells their pink colour.
- Option D: Iodine does not interact with bacterial DNA; it complexes with CV within the cell wall matrix.

**Final Answer:** Iodine = mordant forming insoluble CV–I complex, anchoring purple stain in gram-positive cells $\Rightarrow$ B

**Answer: (B)** Go Back to Q15

## Q16.

**Solution**

**Concept — OOS Investigation Two-Phase Process (21 CFR 211.192):** The FDA guidance on investigation of OOS results (2006) requires a structured two-phase investigation:

**Phase 1 — Laboratory Investigation:** The analytical laboratory investigates possible assignable causes of the OOS result (instrument malfunction, calculation errors, sampling errors, analyst technique). If a documented assignable cause is found, the result may be invalidated and a single retest performed. If **no assignable laboratory cause is found**, the result stands and a Phase 2 investigation is mandatory.

**Phase 2 — Full OOS Investigation:** Initiated when Phase 1 reveals no laboratory error. Includes: full manufacturing record review, reserve (retained) sample testing by an independent analyst, evaluation of related batches, and review of stability data. The Phase 2 outcome determines batch disposition (reject, release under deviation, or recall).

**Why other options are wrong:**

- Option A: Regulatory notification is not the immediate next step; internal Phase 2 investigation must be completed first.
- Option B: Automatic re-manufacture without investigation contradicts 21 CFR requirements for documented investigation.
- Option C: Phase 2 extended investigation (manufacturing review, reserve sample testing, independent analyst) is the required next step. **Correct.**
- Option D: An OOS result cannot be invalidated from Phase 1 findings alone if no assignable laboratory error was identified; Phase 2 is mandatory.

**Final Answer:** No Phase 1 assignable cause found $\rightarrow$ mandatory Phase 2 full OOS investigation $\Rightarrow$ $\boxed{\text{C}}$

**Answer: (C)** Go Back to Q16

## Q17.

**Solution**

**Concept — ICH Q10 Pharmaceutical Quality System: CAPA Element:** ICH Q10 identifies four elements of the Pharmaceutical Quality System (PQS):

(a) Process Performance and Product Quality Monitoring System
(b) **CAPA System** — addresses non-conformances through root-cause analysis and implements corrective and preventive actions
(c) Change Management System
(d) Management Review

The CAPA system is *specifically* responsible for systematically investigating root causes of quality failures, implementing corrective actions to resolve identified issues, and implementing preventive actions to stop future recurrence. It is the reactive/proactive quality improvement engine of the PQS.

**Why other options are wrong:**

- Option A: Management Review is the periodic senior-management evaluation of PQS effectiveness; it relies on CAPA data but does not perform investigations.
- Option B: Change Management governs planned changes to processes, equipment, and specifications; it is proactive and not primarily for investigating failures.
- Option C: Process Performance and Product Quality Monitoring detects trends and signals potential problems but does not investigate or resolve root causes.
- Option D: CAPA System is responsible for root-cause investigation and resolution of non-conformances during commercial manufacturing. **Correct.**

**Final Answer:** CAPA System = ICH Q10 element for root-cause investigation and resolution $\Rightarrow$ D

**Answer: (D)** Go Back to Q17

## Q18.

**Solution**

**Concept — Corrective Action vs Preventive Action (CAPA Definitions):** In pharmaceutical quality management systems (QMS), CAPA has two distinct and non-interchangeable components:

**Corrective Action (CA):** An action to *eliminate the root cause* of a detected (confirmed, existing) non-conformance or other undesirable situation. It is **reactive** — triggered by an event that has already occurred (OOS result, batch failure, audit finding). Example: a wrong calibration certificate caused an OOS result → corrective action = revise calibration procedure and retrain analysts.

**Preventive Action (PA):** An action to *eliminate the potential cause* of a non-conformance or other undesirable situation that has **not yet occurred**. It is **proactive** — triggered by risk assessment, trend analysis, or industry-wide signals. Example: trend data shows increasing particulate counts in an isolator → preventive action = replace HEPA filter before failure.

**Why other options are wrong:**

- Option A: Corrective action = reactive (existing non-conformance); preventive action = proactive (potential non-conformance). **Correct.**
- Option B: The terms are NOT interchangeable; they have distinct regulatory definitions under ICH Q10 and ISO 9001.
- Option C: Both types of actions require formal documentation and are subject to QMS control; neither requires prior regulatory approval for implementation.
- Option D: CAPA applies to all quality system functions including analytical laboratory, manufacturing, packaging, and distribution non-conformances.

**Final Answer:** CA = reactive (existing non-conformance); PA = proactive (potential non-conformance) ⇒ A

**Answer: (A)** Go Back to Q18

## Q19.

**Solution**

**Concept — Minimum Endotoxin Reduction for Depyrogenation Validation:** Endotoxin (LPS) destruction is validated by challenging the depyrogenation process with a known quantity of endotoxin (typically $\geq 1000$ EU per test piece) and measuring the residual endotoxin after treatment. The regulatory requirement for a valid depyrogenation process is a $\geq 3$ log **(1000-fold) reduction** in the endotoxin challenge. This is analogous to the SAL $10^{-6}$ concept for micro-organisms but is specified as 3-log reduction for endotoxins.

**Regulatory basis:**

- FDA Guideline on Sterile Drug Products (1987) and EU GMP Annex 1: validate depyrogenation to $\geq$3 log reduction.
- USP $\langle 1211 \rangle$ and Ph. Eur. 5.1.1: 250 °C/30 min achieves $\geq$3 log reduction as the standard condition.
- The initial endotoxin challenge must be $\geq 1000$ EU/item and the final level must be $\leq 1$ EU/item (i.e., $\leq 10^{-3}$ of initial).

**Why other options are wrong:**

- Option A: $\geq 1$ log reduction is insufficient; 10-fold reduction would leave 100 EU from a 1000 EU challenge, far above acceptable endotoxin limits.
- Option B: $\geq 3$ log (1000-fold) reduction is the minimum validated requirement for depyrogenation. **Correct.**
- Option C: $\geq 6$ log reduction is the SAL criterion for microbial sterilisation; it is not required (or achievable at 250 °C) for endotoxin depyrogenation.
- Option D: $\geq 2$ log (100-fold) reduction is below the regulatory minimum and does not demonstrate adequate depyrogenation.

**Final Answer:** Depyrogenation validation requires $\geq 3$ log (1000-fold) endotoxin reduction $\Rightarrow$ B

**Answer: (B)** Go Back to Q19

## Q20.

**Solution**

**Concept — Rubber Stopper Formulations for Injectable Products:** Rubber stoppers for parenteral vials must be compatible with the drug product and must not contribute toxic extractables or leachables. For biological/biotechnology products (proteins, monoclonal antibodies, vaccines), the stopper formulation is critical because proteins are sensitive to metal ions, antioxidants, and processing aids that can leach from rubber.

**Stopper types:**

- **Natural rubber (NR):** High extractables; allergenic (latex proteins); not recommended for modern injectable products.
- **Bromobutyl rubber:** Low extractables, excellent chemical compatibility, good resealability, low moisture permeability; preferred for biologicals and lyophilised products.
- **Chlorobutyl rubber:** Good extractables profile but slightly higher zinc and tin extractables than bromobutyl; used for aqueous parenterals.
- **Silicone-coated stoppers:** Reduce drug adsorption and enhance resealability; used as a supplement, not as the base elastomer formulation.

**Why other options are wrong:**

- Option A: Natural rubber is not recommended due to high extractables and potential latex allergenicity.
- Option B: Chlorobutyl rubber has a reasonable extractables profile but bromobutyl is preferred for biologicals.
- Option C: Bromobutyl rubber is the industry standard for biological injectables due to lowest extractables and best compatibility with protein formulations. **Correct.**
- Option D: Polydimethylsiloxane (silicone) is used as a coating on rubber stoppers, not as the primary elastomer body; a solid silicone stopper would have poor resealability.

**Final Answer:** Bromobutyl rubber = preferred stopper for biologicals due to low extractables $\Rightarrow$ C

**Answer: (C)** Go Back to Q20

## Q21.

**Solution**

**Concept — Osmolality Measurement by Freezing-Point Depression:** Osmolality (mOsm/kg water) is a *colligative property* of solutions — it depends only on the number of dissolved solute particles, not their chemical nature. Freezing-point depression is one of four colligative properties and is the basis for direct osmolality measurement:

$$\Delta T_f = K_f \times b_{\text{osm}} = 1.86\,^{\circ}\text{C} \cdot \text{kg/mol} \times b_{\text{osm}}\,(\text{Osm/kg})$$

A freezing-point osmometer measures the freezing point of the solution and calculates osmolality directly. Normal plasma osmolality of 285–295 mOsm/kg corresponds to a freezing-point depression of $\approx$0.53 °C below 0 °C.

**Why other options are wrong:**

- Option A: Refractometry measures refractive index, which is related to solute concentration but does not directly measure osmolality; it is not a pharmacopoeial method for osmolality.
- Option B: Titrimetry does not measure osmolality; it measures chemical equivalents, not colligative particle count.
- Option C: Spectrophotometry at 280 nm measures protein concentration (aromatic amino acids), not total osmolality.
- Option D: Freezing-point depression osmometry directly measures osmolality as a colligative property. **Correct.**

**Final Answer:** Freezing-point depression osmometry directly measures osmolality $\Rightarrow$ D

**Answer: (D)** Go Back to Q21

## Q22.

**Solution**

**Concept — USP ⟨788⟩ Particulate Matter Limits:** USP ⟨788⟩ sets limits for subvisible particles in injectable preparations, measured by light obscuration or microscopic methods. The limits differ between large-volume parenterals (LVP, $\geq$100 mL) and small-volume parenterals (SVP, $<$100 mL):

| Container | $\geq$10 $\mu$m | $\geq$25 $\mu$m |
|---|---|---|
| LVP ($\geq$100 mL) | $\leq$25 particles/mL | $\leq$3 particles/mL |
| SVP ($<$100 mL) | $\leq$6,000/container | $\leq$600/container |

**Why other options are wrong:**

- Option A: $\leq$25 particles/mL ($\geq$10 $\mu$m) and $\leq$3 particles/mL ($\geq$25 $\mu$m) are the correct LVP limits. **Correct.**
- Option B: $\leq$6,000 per container ($\geq$10 $\mu$m) and $\leq$600 per container ($\geq$25 $\mu$m) are the SVP limits for volumes $<$100 mL, not LVP limits.
- Option C: $\leq$50 particles/mL is twice the specified LVP limit and has no pharmacopoeial basis.
- Option D: $\leq$100 particles/mL at $\geq$5 $\mu$m is not a USP $\langle 788 \rangle$ limit; the specified sizes are 10 $\mu$m and 25 $\mu$m.

**Final Answer:** LVP limit = $\leq$25 particles/mL ($\geq$10 $\mu$m) by light obscuration $\Rightarrow$ A

**Answer: (A)** Go Back to Q22

## Q23.

### Solution

**Concept — pH-Stability Profile and Optimum Formulation pH:** Injectable drugs susceptible to hydrolysis (esters, amides, lactams) typically show a pH-dependent degradation rate constant $k$ that follows a U-shaped profile when plotted as $\log k$ versus pH:

- At **low pH**: specific acid catalysis dominates (rate increases as $[H^+]$ increases, i.e., as pH decreases).
- At **high pH**: specific base catalysis dominates (rate increases as $[OH^-]$ increases, i.e., as pH increases).
- At the **optimum pH** (minimum of the curve): the contributions of acid and base catalysis are both minimised, giving the slowest degradation rate.

Formulating the injectable drug at the optimum pH maximises chemical stability and extends shelf life. The buffer system selected must maintain this pH throughout the product's shelf life. For the ester drug in this question, pH 3.5 is the optimum.

**Why other options are wrong:**

- Option A: The minimum of the $\log k$ vs pH curve corresponds to the *slowest* (not fastest) degradation rate; the drug is most stable, not most unstable, at this pH.
- Option B: pH 3.5 is the formulation target because $k$ is minimised, maximising stability and shelf life. **Correct.**

- Option C: The optimum pH does not require the drug to be completely unionised; ionisation and catalytic hydrolysis are separate phenomena.
- Option D: Optimum pH refers to chemical stability of the formulated product, not bioavailability; injectable drugs bypass GI absorption entirely.

**Final Answer:** Optimum pH = formulation pH that minimises $k_{\text{hydrolysis}}$ and maximises shelf life $\Rightarrow$ B

**Answer: (B)** Go Back to Q23

## Q24.

**Solution**

**Concept — Isotonic Mannitol Concentration:** Using the provided osmolality formula:

$$\text{Osmolality (mOsmol/L)} = \frac{c\,(\text{g/L})}{\text{MW (g/mol)}} \times i \times 1000$$

**Step 1 — Calculate osmolality for each option:** Mannitol: MW = 182 g/mol, $i = 1$.

- 1.0% = 10 g/L: $\frac{10}{182} \times 1 \times 1000 = 54.9$ mOsmol/L (hypotonic)
- 2.5% = 25 g/L: $\frac{25}{182} \times 1 \times 1000 = 137.4$ mOsmol/L (hypotonic)
- **5.4% = 54 g/L:** $\frac{54}{182} \times 1 \times 1000 = 296.7$ mOsmol/L (isotonic, within 297–308 mOsmol/L range)
- 10.0% = 100 g/L: $\frac{100}{182} \times 1 \times 1000 = 549.5$ mOsmol/L (hypertonic)

**Step 2 — Identify the isotonic concentration:** 5.4% mannitol gives 297 mOsmol/L, which falls within the isotonic range (285–310 mOsmol/L) and is equivalent to approximately 0.9% NaCl for ophthalmic use.

**Why other options are wrong:**

- Option A: 1.0% mannitol is markedly hypotonic ($\sim$55 mOsmol/L).
- Option B: 2.5% mannitol is hypotonic ($\sim$137 mOsmol/L).
- Option C: 5.4% mannitol is isotonic ($\sim$297 mOsmol/L). **Correct.**
- Option D: 10.0% mannitol is markedly hypertonic ($\sim$550 mOsmol/L).

**Final Answer:** 5.4% mannitol $= 54/182 \times 1000 \approx 297$ mOsmol/L (isotonic) $\Rightarrow$ C

**Answer: (C)** Go Back to Q24

## Q25.

**Solution**

**Concept — Overkill $F_0$ for Parametric Release:** The "overkill" sterilisation approach is designed to achieve a very large safety margin independent of the measured pre-sterilisation bioburden. For moist-heat sterilisation, the reference organism is *Geobacillus stearothermophilus* with $D_{121} = 1.5\,\text{min}$ (most resistant spore former). The overkill standard requires:

$F_0 \geq 12\,\text{min}$ (equivalent to $12/1.5 = 8$ log reductions of $G.$ stearothermophilus at $121\,^\circ\text{C}$)

A process delivering $F_0 \geq 12\,\text{min}$ can justify **parametric release** (release based on documented process data without end-product sterility testing) when the validated cycle consistently achieves this $F_0$ at every point in the load. The overkill $F_0 = 12\,\text{min}$ means that even if the initial bioburden were $10^6$ organisms with $D_{121} = 1.5\,\text{min}$, the log reduction would be 8, giving SAL = $10^{-2}$; with typical bioburden of $\leq 10$ CFU/container and $D \leq 1.5\,\text{min}$, SAL $\leq 10^{-6}$ is achieved with large margin.

**Why other options are wrong:**

- Option A: $F_0 = 3\,\text{min}$ provides only 2 log reductions; this is grossly insufficient for parametric release.
- Option B: $F_0 = 6\,\text{min}$ provides 4 log reductions; still below the overkill standard and insufficient for parametric release.
- Option C: $F_0 = 8\,\text{min}$ (≈5.3 log reductions) is not the accepted overkill minimum; EU GMP Annex 1 does not specify 8 min as a universal minimum.
- Option D: $F_0 \geq 12\,\text{min}$ is the widely recognised overkill standard for parametric release, providing ≥8 log reductions of *G. stearothermophilus*. **Correct.**

**Final Answer:** Overkill approach for parametric release requires $F_0 \geq 12\,\text{min} \Rightarrow$ D

**Answer: (D)** Go Back to Q25

# Answer Key

| Q | Ans | Q | Ans | Q | Ans | Q | Ans | Q | Ans |
|---|---|---|---|---|---|---|---|---|---|
| 1 | D | 2 | A | 3 | B | 4 | C | 5 | D |
| 6 | A | 7 | B | 8 | C | 9 | D | 10 | A |
| 11 | B | 12 | C | 13 | D | 14 | A | 15 | B |
| 16 | C | 17 | D | 18 | A | 19 | B | 20 | C |
| 21 | D | 22 | A | 23 | B | 24 | C | 25 | D |