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Visible Particle Control in Biologics and Advanced Therapy Products: Challenges, Case Studies, and Evolving Expectations

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Visible Particle Control of Parenterals - Conducted by Visual Inspection

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- **Visual inspection (VI)** is a critical component of the parenterals' quality system:
  - Detect **visible defects** and **particulate contamination**
  - Important process control tool

- It involves a systematic, documented evaluation of each inspected container **under controlled conditions, using trained and qualified human inspectors and/or validated automated systems**, to ensure compliance with GMP and relevant regulatory requirements (e.g., USP <790>, Ph. Eur. 2.9.20), product quality and patient safety.

Visual Inspection - one tool, different uses (ALL PARENTERALS)

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1. **100 % VI** is a critical (last) step of the manufacturing process - **removal of defective units from the good part of a batch.**
    a. Typically performed (or overseen) by the quality unit. Can be delegated to the manufacturing unit.
    b. Data from VI provide important process control
2. **Acceptable Quality Limit (AQL)** is in place to **provide assurance that VI operates correctly (100% visual inspection process was effective).**
    a. Confirm that the batch meets the specification for particles and can be released - the last step of the particle control system.
    b. Typically performed by the quality unit
3. **Visible Particle Test in QC** can be carried out as:
    a. A release test that requires sampling and destructive testing (e.g. Difficult-to-inspect products/ DIPs)
    b. Stability testing (clinical and commercial)
    Note: a. and b. are very different!
4. **Visible Particle Testing in Development (R&D)**

Different Contexts of VI - Challenges

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- **Different purposes (e.g. contamination control vs stability assessments)**
  - Different **acceptance criteria** (and some definitions)
  - Different **consequences**
    - Likely different clinical safety profiles (e.g. proteinaceous particles vs a cellulose fiber)
- Different groups may perform VI
  - Harmonization of training & qualification is essential

USP <1790>

7.7 Training and Qualification of Human Inspectors

Before training, potential inspectors should be tested for visual acuity (*69*) and color perception. Near-vision performance should be the equivalent of 6/6 m (20/20 ft), but not conducted at this distance, and with no impairment of color vision. Both the Snellen and Jaeger charts are useful for verifying visual acuity; they test far and near vision, respectively. The use of corrective lenses to achieve the desired visual acuity is permitted. Training should include a phased approach with a specified number of training hours expected for each segment. Initially, train the potential inspectors with defect photographs or a video library and clear, written descriptions. Utilize subject matter experts to mentor and provide hands-on training with defect standards for the specified method. Reinforce mental or silent counting and follow the paced sequence to achieve consistent inspection timing. Stress the importance of strict adherence to the inspection process (procedure, sequence, and timing). Inspector fatigue may be addressed in the qualification process by testing under worst-case conditions (e.g., at the end of a typical inspection shift).

Train all inspectors (QC, QA, and production) with common procedures used for 100% inspection and AQL inspection. All inspection practices should be standardized and consistently executed by all inspection groups.

Qualification should be performed for each product type and package that the inspector will encounter. A bracketed or matrix approach can be used to simplify qualification of products with similar physical or visual characteristics such as container type and size, dosage form, product viscosity, color, and others (product families or groups). It is common to initially train and qualify personnel on clear solutions in clear containers (if produced at the facility) and then expand their expertise to the inspection of more difficult dosage forms or presentations.

Pharmacopoeial Requirements for Visual Inspection: Inspection Conditions and Acceptance Criteria

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	USP <790>	EP 2.9.20	JP 6.06	ChP 0904
Illumination Intensity (lux)	2,000 – 3,750	2,000 – 3,750	2,000 – 3,750 *8,000 – 10,000 (plastic)*	1000-1500 lx *(colourless)* 2000-3000 lx *(coloured, brown glass or plastic)* approx. 4000 lx *(suspensions)*
Inspection Duration (sec)	10 (5 black, 5 white)	10 (5 black, 5 white)	10 (5 black, 5 white)	20 (10 black, 10 white)
Backgrounds	black and white	black and white	black and white	black and white
Acceptance Criteria	*"essentially free from visible particulates"* ANSI/ASQ Z1.4 AQL=0.65%	*"clear and practically particle-free"*	"free of readily detectable foreign insoluble matter"	*No obviously visible foreign matters (metal, glass, fibers, etc.) >2mm* *No protein particles >1mm* *No precipitate or turbidity* *No clusters of particles which are difficult to count (e.g. protein)*

What does “practically free” mean?

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- ***“Practically free from visible particles”***: when inspected under suitable conditions, no visible particles are observed, recognizing that occasional, infrequent particles may occur due to the limitations of manufacturing process & visual inspection.
  - It **does not mean zero particles**
  - It does mean particles must be **rare, infrequent, and well controlled**
- **Passing an appropriately justified AQL** is necessary evidence that a batch is “practically free from visible particles,” but regulators expect it **to be supported by 100% inspection, validated detection capability**, and **stable trend data**.
- Definitions may differ, depending on the context - e.g. 100% VI vs. stability

Particle Classification

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Important regional differences:

Classification	US FDA Guidance	USP <1790>	EP 5.17.2
Inherent	…innate **product characteristic**	…part of **clinical profile** and **appearance specification**	**X**
Intrinsic	… derived from the **manufacturing equipment**, **product formulation**, or container system	…from **within the process** (product-contact materials)	…related to the **formulation**
Extrinsic	…originate from the **manufacturing environment** and are **foreign** to the **manufacturing process**	…**foreign** to the **manufacturing process**	…**derived from the environment, equipment, primary packaging or personnel**

Usage *(referring to USP terminology)*:

Inherent	E.g. proteinaceous, cell clumps, etc. **Can occur.**	May be OK *(needs justification)*
Intrinsic	E.g. metal, glass, rubber, etc. **Rare occurrences – to be expected.**	Major defect. To be removed (100% VI). Process control tool.
Extrinsic	E.g. hair, insects, etc. **Likely GMP breach or a process failure.**	**Critical**

What does “visible” mean?

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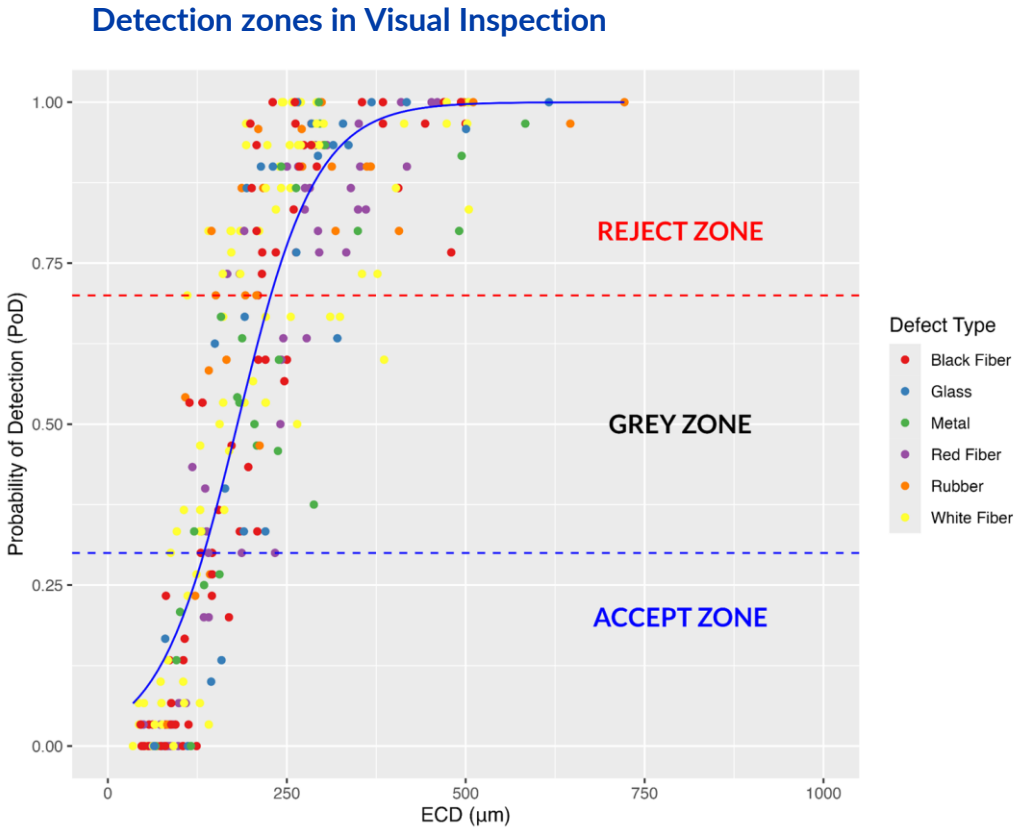
- Visual Inspection is a **probabilistic process** (element of chance), hence - **a statistical definition**.
- Statistical assessment tools required, hence challenges with e.g. **qualification acc. criteria**, **performance comparisons** etc.
- JZ Knapp - studied **defect probability of detection** (**PoD**) and defined VI detection zones via multiple inspection rounds (30-50x)
- Thes statistical definitions are the basis for qualification of inspectors



Regulatory Focus - Recurring Themes

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- Most frequently recurring themes related to VI, featured in **US FDA Warning Letters** and **Form 483** observations:
  - **VI Training & Qualification, e.g.:**
    - *"failed to provide robust training…",*
    - *"failed to comprehensively document training and qualification…",*
    - *"failed to establish training and qualification conditions which align with routine 100% inspection conditions…"*
    - *"failed to address inspection fatigue during qualification…",*
    - *"failed to periodically re-qualify visual inspection operators"*
  - **Contamination control - investigation handling and follow-up; monitoring & trending, e.g.:**
    - *"failed to investigate limit exceedances and atypical particulate matter thoroughly…",*
    - *"failed to initiate a timely investigation to determine root causes…",*
    - *"failed to adequately investigate both extrinsic and intrinsic particulate contamination issues…",*
    - *"your investigations into these product quality defects were inadequate and failed to spur appropriate corrective and preventive actions…"*
- **EU GMP Annex 1** places strong emphasis on a holistic **Contamination Control Strategy (CCS)**

Qualification of Human Inspectors and AVI Systems

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VI operators and automated visual inspection (AVI) systems must be formally **trained, qualified, and periodically requalified** to demonstrate **adequate defect detection capability**.

- Demonstrate adequate **probability of detection (PoD)** using **representative defect standards/ test sets**, confirming reliable detection at defined defect thresholds.
- **VI Test sets** are used to establish, verify, and maintain inspection performance for both human inspectors and AVI systems throughout the inspection lifecycle.

Qualification Test Sets – THE Foundation of VI Qualification

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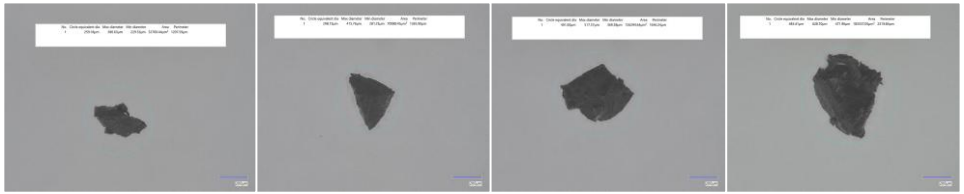
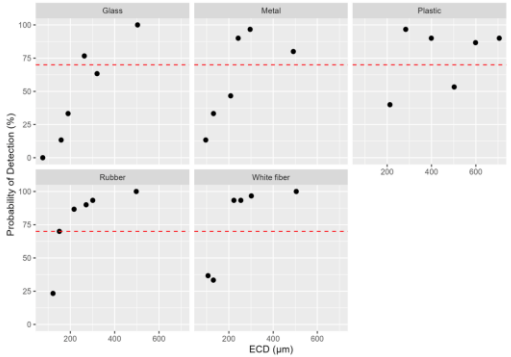
- Qualification is established by **challenging inspectors and AVI systems** with **representative** defect standards (**VI test sets**) to determine PoD at **defined particle sizes** and defect types.
- Single particles are **intentionally seeded** into containers **across gradient of sizes**, including defects near the threshold of reliable detection (reject zone, ~70% PoD).





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- Repeated inspection of test sets is used to determine **PoD curves**, supporting **qualification, routine performance monitoring, and requalification** of both human inspectors and AVI systems.
- **VI test sets provide a common, standardized basis** for characterizing human visual inspection performance and transferring equivalent detection requirements to AVI systems.

Inherent Particles – Biologics and ATMPs

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Products	Inherent Particles	Considerations
Biologics *(Proteins / mAbs)*	Proteinaceous particles (aggregation, agglomeration)	- Explicit scientific justification required to authorize acceptance - Extensive physicochemical characterization (size, morphology, reversibility) - Clinical risk assessment based on route, dose, and patient population - Trending over shelf life and control of interfaces (container, silicone, agitation)
Cell Therapies	Cell clumps, cell debris, aggregates	- The product itself is particulate by design - Visual inspection focuses on abnormal morphology or unexpected agglomeration, not particle absence; Process control - Acceptance criteria driven by clinical risk and functionality
LNP-Based Products *(e.g., mRNA Vaccines)*	Lipid nanoparticles; lipid–lipid agglomerates	- Differentiation between intended nanoparticles and unintended visible agglomerates - Stability-driven growth or fusion must be characterized; Process control - Acceptance justified via size distribution, functionality, and clinical exposure
Viral Products *(Vaccines, Gene Therapies, Vectors)*	Viral particles, viral aggregates, proteinaceous particles	- Viral particles are the active product; aggregation may impact potency and safety - Visual inspection targets unexpected aggregates or foreign particulates - Risk assessment integrates infectivity, dose, and patient population

Biologics and ATMPs - Special Considerations & Challenges for VPs

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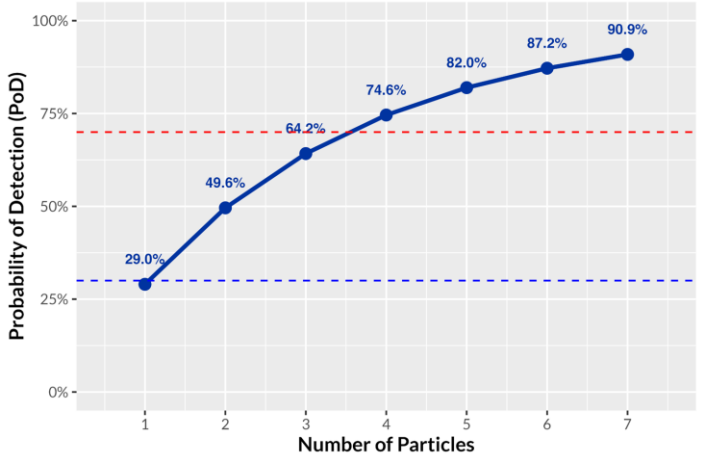
- **Occurrence of visible particles**
  - Process- or formulation- related
  - Stress during manufacturing, storage, distribution
  - Can manifest as an occasional particle or many
- **Acceptance criteria**
  - 100% VI vs Stability Testing - is “practically free” sufficient?
  - Nuance between early (detect any) vs. commercial (qualify to distinguish types and levels)
- **Detection**
  - Small, irregular, RI similar to solution, low contrast
  - Often multiple particles
  - Can be reversible, fragile
- **BUT for Qualification of VI operators** we need:
  - **Stable** standards
  - **Well characterized**
  - **Representative** - match particle behavior
  - **To be seeded** in different containers and @ **different sizes**



If PoD for a single particle is **0.29 =>**
$PoD_n = 1 - (0.71)^n$

Inherent Particles - How to Quantify VI Operators & AVI systems?

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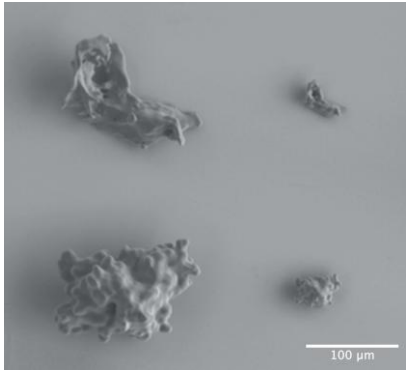
- **Pioneering work from Dean Ripple's group from NIST:**
  - Developed and evaluated polymer-based protein-like particle standards (e.g., ETFE, photolithographic particles)
- Technical challenge - **matching inherent particle behaviour…**
- **New technology to answer:**

  3D printed protein-like particles



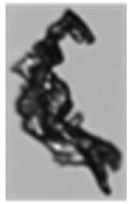
Amara I, et al.. J Pharm Sci. 2024;113(8):2394-2404.

Partiris setting standards

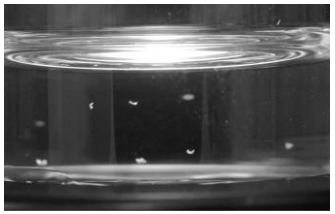
Proteinaceous particle

PS bead std.

SU8 particle (NIST)



Partiris 3D printed particle



- **Advantages:**
  - **Representative** (look and behavior), **stable**, **tunable** (size, shape, behavior)

Routine Qualification vs. Challenge Standards

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It is important that routine qualification relies on stable, well-characterized surrogate defect standards.

- **Use robust surrogate particles for qualification:**
  - Well-characterized & available in size gradients
  - Relevant - mimic well the visual appearance and behavior of inherent particles
  - Stable

Actual inherent particles can be used as supplemental training aids to confirm relevance.

- Use inherent particulate material for supplemental / fit-for-product studies:
  - development studies (what does “real” look like in this matrix/container?)
  - investigations (does the method detect this morphology?)
  - periodic confirmatory work and re-training (not daily handling)

Visible Particle Characterization - an essential tool for investigation and prevention

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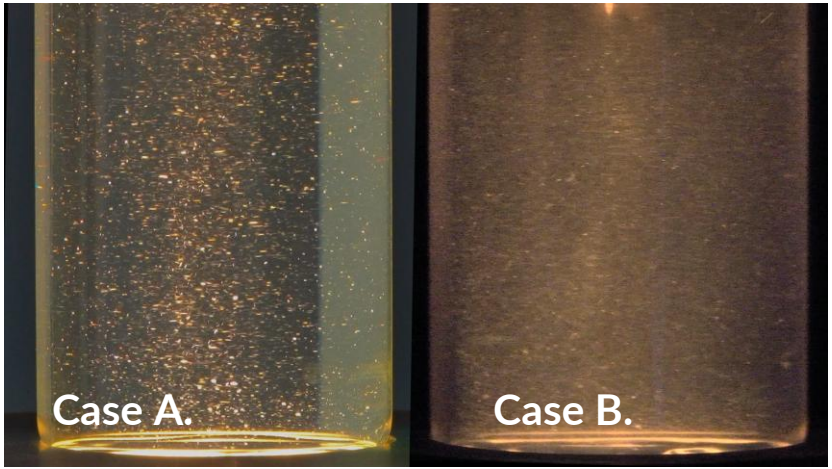
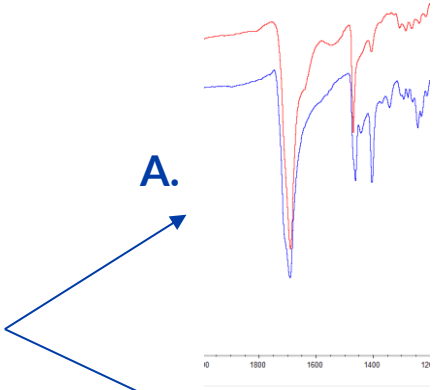


FFA particles (Polysorbate degradation), proteinaceous, or both?

- Different consequences
- Different mitigation strategies

1. Particle Isolation

2. Particle ID (FTIR)



CCS: Prevention -> Detection & Control -> -> Monitoring -> Cont. Improvement

Summary & Conclusions

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- **Regulatory expectations** converge on a holistic strategy: contamination control, inspection capability, investigation quality, and clinical risk assessment must be aligned and defensible.
- **Visible Particle control strategy** relies on Visual Inspection - a probabilistic but critical GMP control, requiring scientifically sound qualification, monitoring, and lifecycle management.
- **Biologics and ATMPs** challenge traditional “particle-free” paradigms: inherent particles may be acceptable, but only when explicitly justified through characterization, risk assessment, and clinically relevant acceptance criteria.
- **Qualification of human inspectors and AVI systems** must rely on stable, well-characterized, and representative test sets, with innovative surrogate standards increasingly required to reflect inherent particle behavior.

“KEEP CALM, PARTICLES HAPPEN”

- Jamie Moore

expertise. insight. agility.

Thank you!

Inherent Particles – Biologics and ATMPs

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USP <1790>

"… an inherent particle type that varies with dosage form and ***includes solutions, suspensions, emulsions, and other drug delivery systems that are designed as particle assemblies (agglomerates, aggregates)****. …*

In biologics, ***protein particles are generally considered inherent and may be accepted when their presence is measured, characterized, and determined to be part of the clinical profile.*** *Aggregation or agglomeration of proteins associated with a change in preparation constituents or other causative agents like excessive siliconization should be minimized. The manufacturer may allow inherent particles if the product appearance specification allows their presence or if the product is an emulsion, suspension, or implant."*

Clinical Safety of Visible Particles

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Visible Particles (general):

- ***Ayres JD, PDA J Pharm Sci Technol, 2018, 72:489–503***
  -> Clinical risk from visible particles depends on particle attributes, source, patient population, and route of administration—not particle presence alone.
- ***Bukofzer S, Ayres JD, et al., PDA J Pharm Sci Technol, 2015, 69:123–139***
  -> A risk-based, medically grounded assessment is appropriate for visible particles; zero-defect expectations are unrealistic given probabilistic inspection.
- ***Ayres JD, PDA J Pharm Sci Technol, 2016, 70:579–590***
  -> Visible particle investigations must link particle identity and origin to patient risk to support scientifically sound disposition decisions.
- ***FDA, Guidance for Industry (Draft), 2021***
  -> FDA expects robust investigation, trending, and clinical risk consideration for visible particles—not solely inspection pass/fail outcomes.
- ***USP General Chapter <1790>, USP–NF, 2022***
  -> USP frames visible particle risk around particle size, material, dose, route, and patient vulnerability, acknowledging inspection limits and inherent particles.

Inherent visible particles:

- ***Narhi LO, et al., PDA J Pharm Sci Technol, 2022, 76:1–16***
  -> For biologics, proteinaceous visible particles may be inherent, requiring context-specific risk assessment rather than automatic rejection.
- ***Liu F, Hutchinson R, Curr Res Toxicol, 2024, 5:100105***
  -> Current practice supports differentiated safety assessment for intrinsic vs inherent particles, integrating toxicology, exposure, and clinical context.

Two levels of regulations

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1. **Legislation and regulations** (such as EU law or national medicines acts) are the **legal framework** to protect patients and consumers. E.g.:
    - **US FDA Food Drug and Cosmetic (FD&C) Act**:
        - 501(a)(1), 501(a)(2)(A), 501(a)(2)(B)
    - **21 CFR:**
        - 211.94 Drug Product Containers and Closures;
        - 211.165 Testing and Release for Distribution
        - 21 CFR §211.110(a) Sampling and testing of in-process materials and drug products
    - **EU GMP (Annex 1)**
2. **Technical guidance:**
    - **Pharmacopoeial guidance** (such as the European Pharmacopoeia, USP, etc.) provides **technical standards** for how the quality and purity of medicines should be assessed. E.g.:
        - USP General chapters with # <1000: mandatory (**USP<1>, USP<790>**)/ **EP 05.20, EP 2.9.20, EP 2031**
        - USP General chapters with # >1000: informational (**USP<1790>**)/ **EP 5.17.2**
    - Additional guidance, e.g. **US FDA Guidance for Industry** (Draft 12/2021), **US FDA Compliance Program Guidance Manual 7356.002A**