PDA Missouri Valley Chapter
Difficult to Inspect Injectable Drug Products
A Case Study

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Presentation Agenda

- A Story From the Past
- Alert / Action
- USP <790>, USP <1790>
- Agency Expectations
- Case Study
- Batch Disposition of DIP
- Key References

2010: A Knock at the Door…

- It's April, 2010, and as Head of Quality at a firm producing sterile parenteral proudcts, I am hosting an FDA Pre Approval Inspection

- After introductions the Lead Inspector asks for … *"a list of all batches manufactured over the last 2 years. I would like to see the visual inspection results for each batch, specifically for visible particulates. Also please indicate whether or not the batch has been released for human use…"*

Essentially Speaking

- *FDA - Looks like you released some batches that contained particles*
- *Me – No, we of course only released the units that didn't have particles. We rejected the ones that did.*
- *FDA - But how do you know for certain that the one's you released didn't also have particles?*
- *Me - We can't say for certain that the acceptable units are entirely free of particles. We take a statistically significant sample from the acceptable units and subject them to a reinspection by the Quality Unit and assess against an AQL standard to confirm that the inspection was effective and the batch is suitable for release.*
- *FDA - So basically you're releasing batches that could very well have some level of what you consider to be tolerable contamination?*
- *Me – We only release the batch if it is <u>essentially</u> free of particles.*
- *FDA - Essentially free or essentially adulterated!? What about your other tests? Do they have similar criteria? Is your pH result <u>essentially</u> within your spec of 6.7 – 7.0? Or your in-process assay results <u>essentially</u> between 97% - 103%?"*
- *Me – No, we are definitively, not essentially, achieving the specification….of 'essentially free'.*
- *FDA - We may have different ideas of what the word 'essentially' means…*

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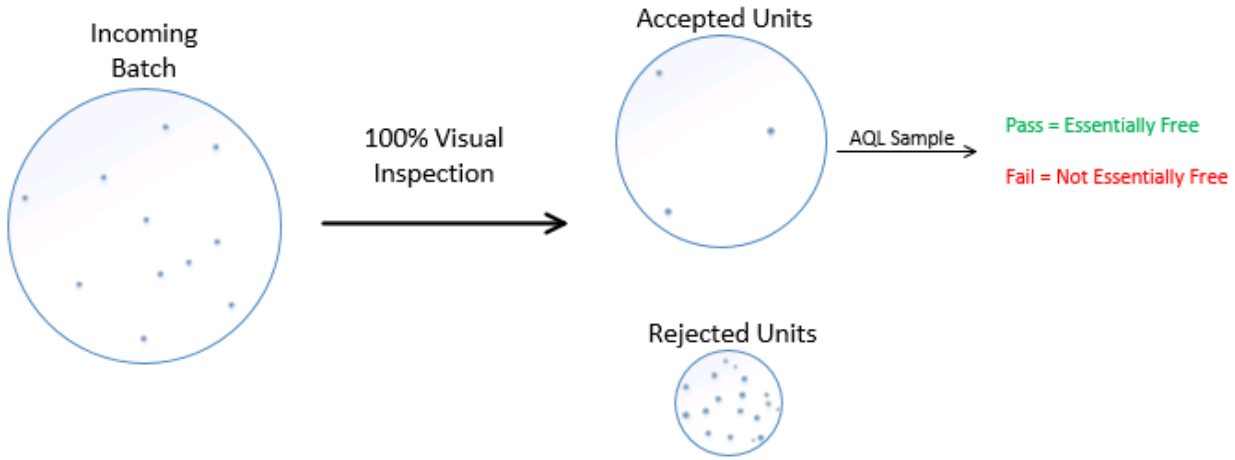
Alert / Action Limits and AQL



- The # of particle defects found in your batch during the 100% inspection is, technically, not a direct reflection of batch quality since the particle defects are removed from the batch as part of the 100% inspection and thus not included in the batch (acceptable units) being released.
- However, because inspection is probabilistic in nature (known to not be 100% effective) we may have concern if the particle load coming into inspection is “too high” since it brings into question whether or not the 100% inspection was effective enough at removing these defects.
- Alert / Action Limits
  - Tells us if the incoming particle load is ‘too high’ compared to the norm and thus requires additional 100% inspection and/or potentially something is atypical about this batch production
  - Derived from process history
  - What if no process history yet exists from which to derive these limits? Need to establish Preliminary Limits
- AQL
  - Measures the quality of the batch that passed the 100% visual inspection (i.e. the proposed ‘acceptable units’)
  - Direct measure of batch quality
- DIP’s For products that are difficult to inspect we need to take additional measures to have the confidence that the batch is “essentially free of particles”
  - Supplemental Destructive Testing

Preliminary Inspection Limits

- One of the biggest challenges when you're just starting out with a new product platform is "how do we know if the level of particle defects found during inspection is cause for concern?"

  - How to choose your preliminary alert/action limits?
  - After 30+ batches we submit for statistical analysis to derive meaningful alert/action limits
  - Scope of investigation if action limit triggered
    - Specifically assess potential factors that may have contributed to the particle contaminant to determine if the batch (i.e., the units deemed acceptable through the course of inspection) is at risk for being compromised.
    - Factors to consider include number of defects found throughout all inspections for this batch, defect type (i.e., inherent, intrinsic, extrinsic), defect criticality, overall state of environmental control, the results of non-destructive AQL inspection and supplemental destructive inspection.
      - *Note that according to the PDA 2014 Industry Survey of Visual Inspection practices (Parenteral Drug Association. PDA Survey: 2014 PDA Visual Inspection. PDA : Bethesda, Md,. 2015) typical reject rates for visual inspection defects are* $\leq$ *5%.*

Supplemental Destructive Testing

- Do we need to do it? Is our product really a DIP?
- Which method to utilize? Reconstitution, Filtration, Clarification, Transfer/Dilution, Sieve/Mesh, Rinse/Flush and Filtration, Panning
- Establish confidence that the method will not yield false positive → Run method on multiple blanks (i.e. 'good units')
- How to qualify operators?
- Establish acceptance criteria – at what point is it "game over"?? (i.e., batch rejected)
- From PDA's Technical Report 79:

> When followed for an AQL of 0.65% for particles, as specified in USP <790>, these plans generally result in a sample size of 20 or more with an accept number of zero for commercially sized batches (e.g., 3201–500,000 units). If several units in the sample show evidence of particles, that batch most likely will not meet accepted standards for being "essentially free" or "practically free" of visible particles. Since further inspection is unlikely to reduce the particle load, the batch will probably be rejected. When a single unit is found with a particle, additional units may be tested to better assess overall batch quality. Sufficient additional units should be tested to reach a sample size where an accept number of 1 is found for an AQL of 0.65%. Simply resampling an additional 20 units from the batch is not recommended because of the relatively low sensitivity (high unacceptable quality limit) of these plans due to the small sample size. Alternative sampling plans are permitted if they provide comparable or

USP<790> From all of us,,, THANK YOU!

As per AQL which <790> has specified!

- Defines 'essentially free' – when you inspect in this specified manner **and the batch has no more particles than specified**, then it can be considered essentially free
- Difficult to Inspect products shall include supplemental destructive testing in addition to the normal 100% inspection procedure *along with an effective program for monitoring and control of particulate matter*
- Wash and Dry the unit prior to inspection
- Minimum intensity of 2000 – 3750 lux
- The "unit"…not "units"… Should be gently swirled and inspected for approx 5 seconds under each background.
- Sampling - ANSI/ASQ Z1.4 (or ISO 2859-1). General Inspection Level II, single sampling plans for normal inspection with an AQL of 0.65%.
- Product in Distribution

USP <1790> describes effective program

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USP<1790> The Icing on the Cake…

- While USP<790> tells us *what* to do insofar as the inspection procedure, USP<1790> tells us in great detail both *what* to do at the program level as it relates to monitoring, control and life cycle management as well as tells us *how* to do it

- High level outline of USP<1790> Methods for Particle Defect Identification – typical inspection flows (100% inspection, AQL, Tightened AQL)
  - Particle Prevention
  - Determining Process Capability
  - Patient risk factors → *see also "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products." Parenteral Drug Association.* Bukofzer, S., Ayres, J., Chavez, A., Devera, M., Miller, J., Ross, D., Shabushnig, J., Vargo, S., Watson, H., and Watson, R., PDA J Pharm Sci and Technol 69, 123-139 (2015)
  - Life Cycle Management – Trending, Equipment Maintenance, Operator/Equipment requalification, Risk Assessment, lessons from ongoing stability studies, establish defect library
  - Qualification and Validation of Inspection Processes – Test kits, Operator training and qualification

Your VI Program is being audited: *What are they looking for?*

- Adherence to USP <790>
- Are you testing into compliance? – inordinate # of inspections and/or sample testing to meet acceptance criteria
- Alert / Action limits – what are they and are they meaningful? When action limit is triggered are representative particles being submitted for analytical testing for the purposes of particle identification to aid in trending and root cause analysis?
- AQL limits - are they appropriate? How are defect types characterized (i.e., critical, major, minor)
- Operators – how are they trained and qualified? Are operators fatigued prior to qualification? Criteria for disqualification. Consistency in technique.
- Test Kits – how representative is the test kit(s) of the product(s)? Type, size and morphology of particles. Ratio of particle defects to good units. Kit certification. Is the kit actually challenging your operators?
- Process Capability – how sensitive / effective is your inspection procedure?
- Life Cycle components of the program – building defect library, periodic trending, reevaluation of process limits, learnings captured to enhance particle prevention
- Batch acceptance criteria
- Risk Assessment - prevention of particle contamination in the first place so as to minimize the overall reliance on visual inspection to identify and cull out defects.
- Effective controls to ensure rejects remain physically segregated from acceptable units.
- Product complaints

Case Study - The Assignment

- Build a GMP visual inspection program from scratch at a new facility manufacturing new sterile injectable products that are difficult to visibly inspect for particles (i.e. DIP).

- ***NOTE: For the purposes of this presentation, only the monitoring and control of particle defects will be discussed (i.e., physical defect monitoring and control, while essential to any effective visual inspection program, is not the focus of this presentation).***

Profile

- New Facility / New Product → no prior process/product history or experience to help gauge meaningful alert / action limits.
- DIP → Somewhat opaque nano dispersion filled into clear 2R and 10R vial presentations at different API concentrations
- Small batch sizes → 3,500 – 10,000 units
- Patient Population → Large population consisting mostly of adults 25 – 60 years old.
- Unstable → special considerations needed for using actual drug product material for particle test kits used for operator qualification
- Route of Administration → Intravenous; not filtered upon administration

Step 1: Form Project Team

- Project Manager – tracks equipment procurement and qualification, and exploratory studies. Establishes cross functional alignment with program development strategy and consensus as to development findings and appropriate next steps.
- Technical Operations representatives – tacit knowledge of cleanroom operations/controls, manufacturing material/personnel flows. Manufacturing SME's with ability to perform prospective risk assessment
- Quality Assurance - it is essential that those in QA whose role it is to help determine final batch disposition, are thoroughly trained in order to make informed decisions relating to the quality of the batch; to understand the limitations of test data, the difference between how the batch performs against the in process alert/action limits vs the AQL limits, etc.
- Key Consultants / Advisors
    - Experienced Visual Inspector(s) - training, test kit confirmation, Exploratory Studies, Process Capability determination. He/She acts as "calibrated/qualified" data generator.
    - Statistician (I've had great experience with Jason Orloff) – identify and apply appropriate control chart(s) to determine a) if operating under an overall state of control, b) effectiveness of visual inspection procedure, c) derive meaningful alert and action limits

The Project Scope

- Establish visual inspection procedure for the effective identification, removal and characterization of visible defects
- Establish visual inspection program for the effective monitoring and control of visible batch defects. To do so, the Project Team will need to determine / assess:
  - What type of product are we dealing with? Characterize the product(s) to the extent necessary to develop an effective particle control strategy via Exploratory Studies (i.e., understand feasibility of process optimization)
  - Threshold of Sensitivity and Manual Baseline: Determine threshold detection sensitivity in order to understand limitations of visual inspection (process capability) with this specific product and thus the overall risk that particle defects are not routinely identified and removed during inspection. Recommend controls to be implemented commensurate with the risks identified. Compare performance to compendial method via Manual Baseline Study.
  - Inspection Flows and Acceptance Criteria: Recommend inspection flows and controls for decision making (i.e. # of 100% reinspections permitted and under what circumstances, Alert/Action limits for initiating batch investigation, supplemental destructive testing requirements, if any, AQL limits and sampling strategy, and batch disposition).
  - Particle Prevention: Perform risk assessment for the prevention of particle defects in the first place.
  - Test Kits Generate particle defect test kit(s) to be used for various studies such as establishing threshold detection sensitivity, performing optimization studies supporting a modified inspection methodology as compared with compendial method, establishing manual baseline, operator qualification and requalification.
  - Procure and qualify inspection equipment: inspection booth, tools, lux meter, etc..
  - Operator training and qualification identify and create training materials and develop qualification methodology and acceptance criteria using knowledge gained from Exploratory Studies.
  - Develop Supplemental Destructive testing method and acceptance criteria
  - Author Program Summary document / Risk Assessment that summarizes the visual inspection program and life cycle management process (including future commitments and/or changes to the plan). Among other things, this document will provide justification to the program. For example, justifying the establishment of preliminary alert/action limits in lieu of production history that would otherwise provide for statistically meaningful limits. Considered a prospective risk assessment of entire program. The risk assessment that describes Particle Prevention will be one section in this umbrella document that covers the entire program.
  - Author visual inspection parent SOP and associated SOP's / forms

The Plan

- Develop test kits → Product Placebo
- Confirm particles and blanks (i.e. good units)

- Compendial method feasibility
- Threshold sensitivity approximation
- Optimization feasibility
- Manual baseline approximation
- Identify test set candidates (particles and 'good units') with consistent performance across operators
- Supplemental Destructive testing method identification / feasibility

- Manual Baseline and Threshold Sensitivity
- Operator Qual with Clear Test Kit (if applicable)
- Operator Qual with Product Placebo Test Kits
- Baseline particle contamination → Media Fills
- Supplemental Destructive testing qualification

- Approve parent visual inspection SOP
- Approve Risk Assessment / Program Summary

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that's not all…

Sprinkled In

- 100% Inspection - Determine Preliminary Alert/Action Limits
- AQL Limits for critical, major, minor defects
- Determine appropriate materials and sizes to represent in Test Kits
- How many test kits do we need?
- Train Quality Unit to perform AQL
- Operator Qual Acceptance/Failure criteria
- Statistical Analysis
- How many repeat 100% inspections?
- Defect Library – how to populate? Training?
- Determine Supplemental Testing Particle Limits
- Operator eye checks
- Operator Training Program
- Limits on total defects?
- Determine Appropriate Inspection Booth Model
- How to perform trending
- Particle Prevention Risk Assessment
- Test Engineering Runs

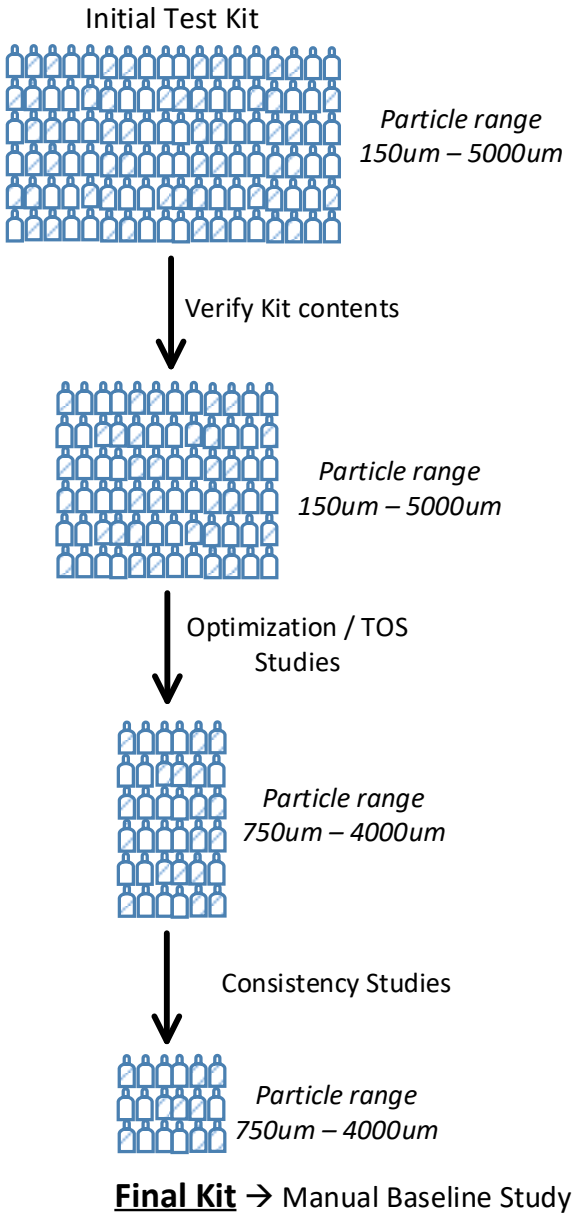
VI Process Development - Consider The Possible Outcomes

Performance	Routine 100% Inspection	Destructive Supplemental Testing Needed?	Formal Study Needed? i.e., Manual Baseline and TOS	Comments
Effective	Compendial	No	No	This must not be a DIP since Compendial method is effective
Effective	Custom	No	Yes	Conduct Manual Baseline Study
Semi Effective (e.g., suspension product with TOS of 1000um)	Custom	Yes	Yes	Conduct Manual Baseline Study and Threshold Sensitivity Study
Not Effective (i.e., can't find virtually any particles)	Compendial or Custom	Yes	Leaning towards "No"…	TOS is so poor that there may not be a lot of value in establishing how ineffective VI is through a formal study.

"TOS" → Threshold of Sensitivity

Effective Performance → can readily identify different particle types down to 200um

Test Kit Development



1. Kit Verification → experienced inspector(s) confirm the claims of the kit for both blanks (good units) and particle seeded units. Remove any unconfirmed.
2. Optimization / TOS Studies → run initial TOS study. See if performance can be improved by varying/introducing parameters. If further optimized, rerun TOS study.
3. Consistency Studies → using optimized inspection procedure conduct multiple runs to identify units with consistent performance. Remove poor performing units. Identify final particle set to establish approximate 1:10 ratio of particle seeded units to blanks
4. Create final kit and conduct Manual Baseline study to confirm optimized process is equal to or better than compendial method.

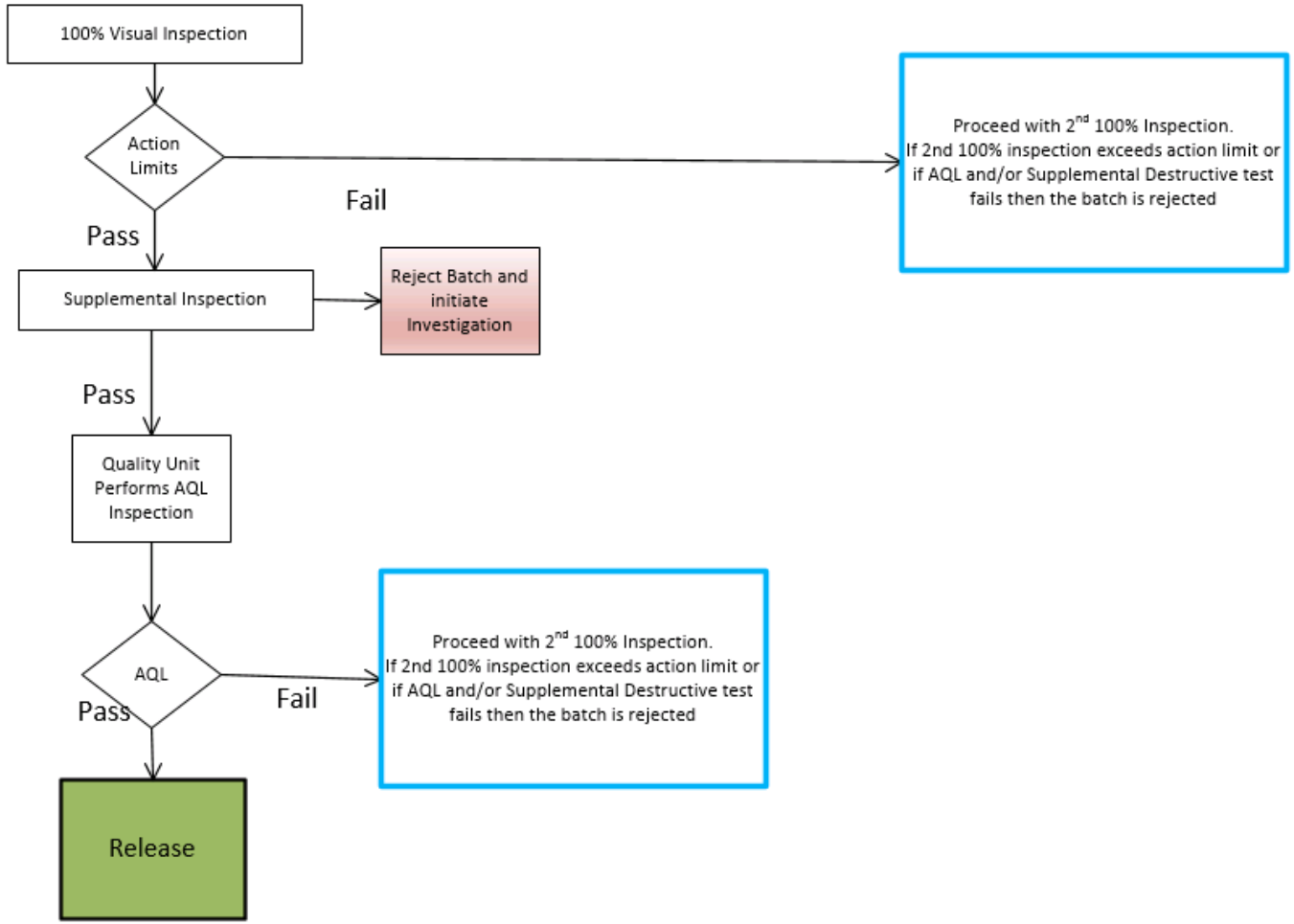
Order Test Kit

Particle Type	Particle Size (microns)
	Synthetic Placebo Test Kit
A	200, 350, 750, 1500, 3000, 5000
B	150, 200, 1000, 1500, 2000, 3000, 4500
C (*provided by customer*)	200, 750, 1200, 2000, 3000, 4000, 5000
D	200, 750, 1500, 2000, 2500, 3000, 4000
E type of Fiber	500, 1000, 1400, 2200, 4000, 5000
F type of Fiber	500, 1000, 1500, 2000, 3300, 4000, 5000
G	200, 1000, 1300, 2200, 3000, 4000
H	200, 1000, 1200, 2000, 3500, 4500
I (*provided by customer*)	200, 1200, 2000, 2500, 3000
J (*provided by customer*)	200, 500, 1000, 3000, 3500
K (*provided by customer*)	200, 750, 1350, 1700, 2500
TOTAL	**67 units**

Final Particle Kit for Our DIP

Particle Type	Particle Size (microns)
	Synthetic Placebo Test Kit
A	750, 1500, 3000
B	1500, 2000
C (*provided by customer*)	1200
D	1500
E type of Fiber	2200, 4000
F type of Fiber	2000, 3300
G	1300, 2200
H	1200, 2000
I (*provided by customer*)	3000
J (*provided by customer*)	1000, 3000
K (*provided by customer*)	1350, 1700
TOTAL	**20 units**

VI Process Routine
100% Inspection



Note: "Action Limits" are triggered for the 1st 100% Inspection when any particle is found (i.e. > zero) until such time that statistically prescribed alert/action limits can be assigned based on process history. If a 2nd 100% Inspection is performed, QA will review the total # and type of particles identified in conjunction with AQL and Supplemental Inspection results to determine acceptability of the batch.

Note: The Supplemental Inspection is subjected to S4 special ANSI sampling plan with an AQL of 0.65%.

Prospective Risk Assessment and Program Summary

- Covers 3 main areas of risk management in order to understand overall risk of particle contamination in released batches
  - Product Profile including target patient population → severity of harm
  - Identification and removal of defects → probability of detection
  - Prevention of defect occurrence in the first place → probability of occurrence
- Serves as a mechanism for capturing future commitments per life cycle approach
- Defines the overall life cycle approach to establishing a VI program whereby procedural, engineering, and statistical controls (including interim controls prior to generating process history) are administered to support an effective program
- To be documented and approved prior to commencement of GMP production
- Prospective in nature; practices have not been implemented yet so, as part of life cycle management, risk assessment should be repeated once some process experience has been gained in order to risk assess procedures against actual practices.

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Risk Assessment / Program Summary Content

- Life Cycle Approach / Commitments → document those plans / commitments to the program that will ultimately allow you to use actual data to enhance the ability to monitor program performance and improve program effectiveness over time
  - Examples; Defect Library, Trending, inspecting media fills, reperform risk assessment in 1 years time, interim controls implemented until data available (e.g., ≥ 30 batches)

- Defect Prevention → process mapping of entire process; quality of raw materials, receipt of materials, component prep, filler design, filler set up, sterile filtration, filling operations, post fill operations

  - Identify controls for mitigating risk of defect occurrence. Risk based approach -> e.g., inherent increased risk (severity of harm) with extrinsic non sterile particles that could enter product downstream of the sterilizing grade filter.

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Risk Assessment / Program Summary Content - continued

- Ensuring an effective VI procedure and overall program

- Includes a description of all the elements that support your claim of having an effective visual inspection procedure.

  - Examples; Developed both Clear and Product Placebo test kits, alignment with USP<790>, operator training and qualification, Preliminary Action limits, describe formal studies performed to demonstrate process capability, max # of repeat inspections, supplemental destructive testing, acceptance testing

Batch Disposition - Considerations for claiming "essentially free of visible particle defects"

Holistic Approach – Cannot just point to results of 100% inspection and AQL. Need to demonstrate an overall state of control due to limitations in inspection capability:

- Trends - How results compare to historical
- EM non viable particulate airborne control in the room throughout the fill
- # and type of particles found during 100% inspection, Supplemental Destructive testing, and non destructive AQL
- # of re-inspections performed
- Nature of predominant particle found (I,e, forensic ID results, Intrinsic, Inherent, Extrinsic, probability of sterility assurance, consistency in findings amongst visual inspection operators involved in the inspection)
- Particle defects evenly dispersed throughout the batch or do they correlate to discrete events?
- Any non routine interventions performed during the manufacturing?
- Post use filter integrity results
- Inherent patient risk – intraocular or intrathecal administration (high risk)? Immunocompromised (high risk)?
- Threshold of sensitivity – how much can you rely on the 100% non destructive visual inspection?

Key References

- USP <790> Visible Particulates in Injections
- USP <1790 Visual Inspection of Injections
- PDA Technical Report 79, Particulate Matter Control in Difficult to Inspect Parenterals. Parenteral Drug Association.
- *PDA Survey: 2014 PDA Visual Inspection.* PDA : Bethesda, Md,. 2015
- Parenteral Drug Association. *PDA Survey: Particulate Matter in Difficult-to-Inspect Parenterals.* PDA: Bethesda, Md., 2016
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