Mastering AVI

part 1: Introduction to regulatory landscape of visual inspection

- USP 1, USP 788 and 1788, USP 790 and 1790
- PhEur e.g. 2.9.20
- JP e.g. 6.06
- Annex 1
- Similarities and differences in compendial methods
- 100% inspection and AQL testing
- Definitions and practical examples of inherent, intrinsic and extrinsic particles
- Examples of regulatory citations 483s
- Recall recaps

PDA Parenteral Drug Association

Instructor Lead: Romain Veillon / Fernand Koert / Sébastien Koch

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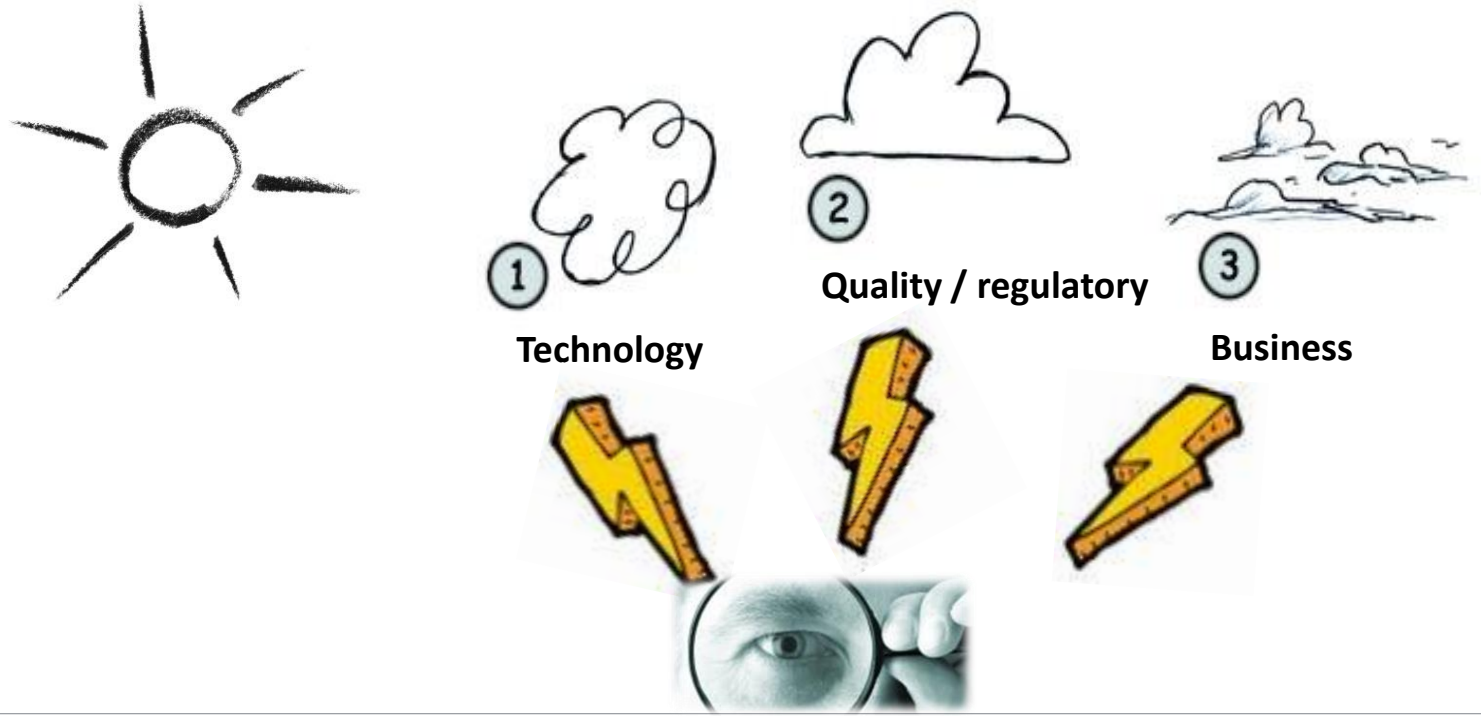
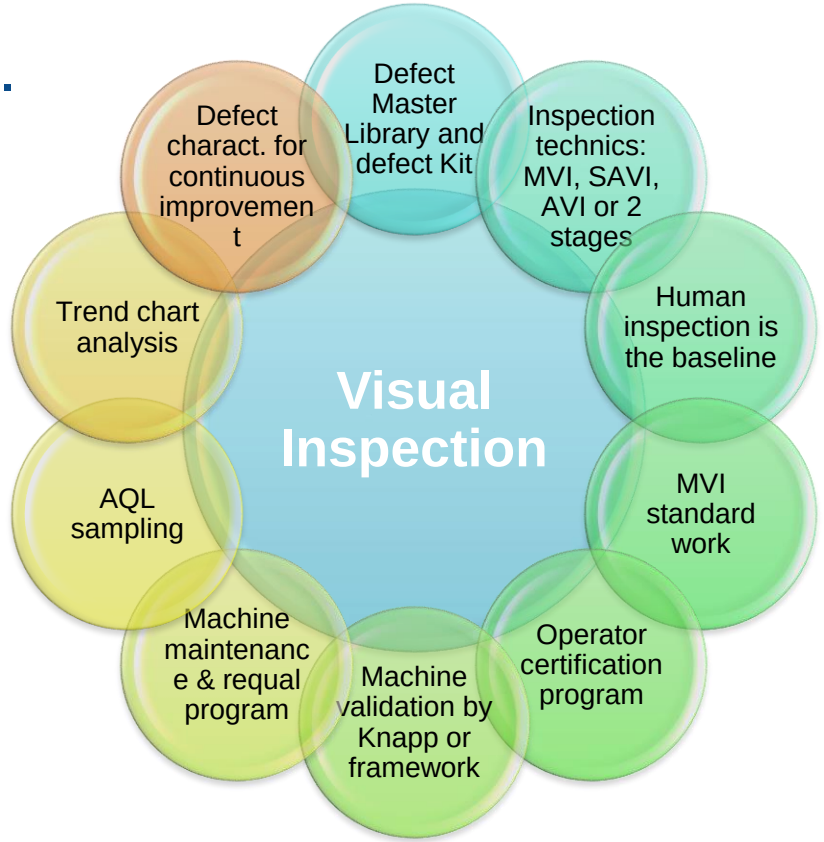
Introduction to regulatory landscape of visual inspection



10 Golden rules for VI…..



Compendias

- USP<1>
- USP<788> particle definition
- USP<790>and <1790>
- PhEur e.g. 2.9.20 vis
- JP e.g. 6.06
- Annex 1: new draft for comment dec 17
- Similarities and differences in compendial methods
- 100% inspection and AQL testing
- Definitions and practical examples of inherent, intrinsic and extrinsic particles

Compendias

- USP<1790> Effective Aug. 2017

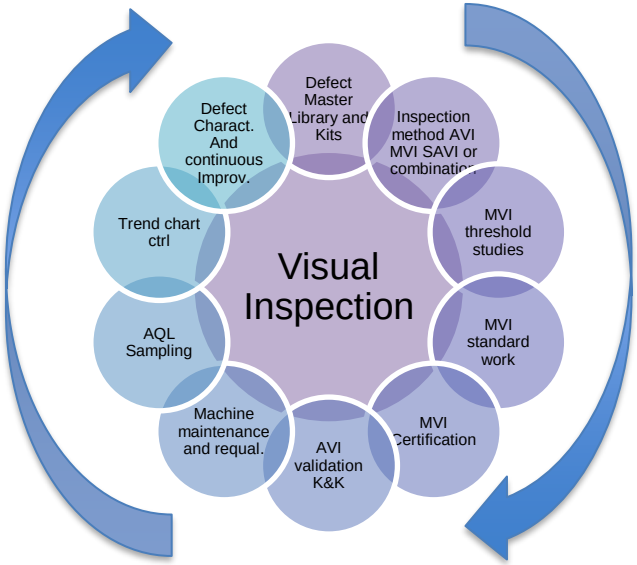
Adobe Acrobat Document

- New Annex 1 draft 2017

Adobe Acrobat Document

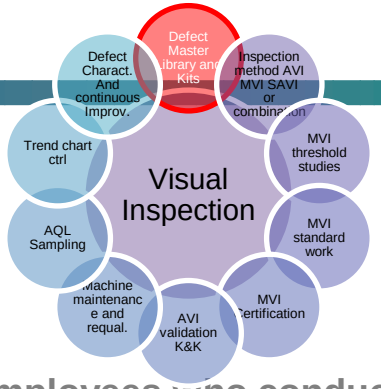
Inspection trends with Recent FD 483s

Inspection trends and market recall for Visual Inspection



Note: the findings statements reported after are excerpts of a list released under the Freedom of Information Act and published by the FDA on FDA website. Those findings are anonymized.

Defect kits



2009

« There is **no standardized kit of defects for the training** of employees who conduct visual inspection of the vials components “

2013

“Your operator's visual inspection of Lyophilized drug product qualification program **does not include examples of glass particulate in vials for training purposes**.”

2014

“The defect sets utilized for qualification of inspection **do not have defects that are representative of defects found in routine inspection**, **retention examination, and complaints**”

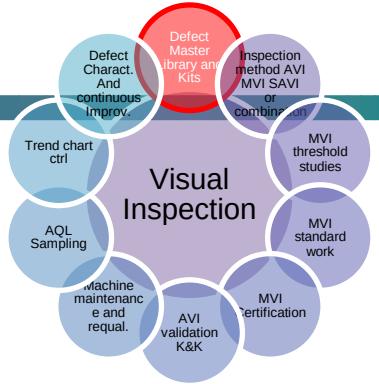
2018

“There are no documented procedures or reference for the creation of the visual inspectors qualification kits. ….. There are no established specifications for the size of the particle included with the kits”

USP<1790>

- 7.1 Standards
- 7.2 Preparing Defect Standards
- 7.3 Particle Types

Test sets



2016

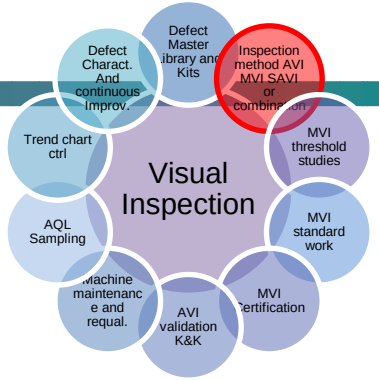
« Qualification of visual inspectors and validation and verification of the **….inspection system are not based on well-characterized test sets. No written procedure has been established to ensure test sets** for visual inspection include particles in the visible size range similar to production rejects other than a …..micron glass particle.
No record documenting the creation of test sets used for qualification of visual inspectors was provided….”

2017

“Defects that typically occur during production **are not characterized in sufficient detail** to allow for consistent creation or selection of defects to include in test sets used for qualification of inspectors. Additionally, during creation of defect test sets, **defects in the test sets are not well-characterized to ensure they are representative of typical production defects. For example, there is no information on particle size, particle material type (for light and dark particles), crack size, and crack location.”**

USP<1790>
- 7.1 Standards
- 7.2 Preparing Defect Standards
- 7.3 Particle Types

Multiple stage inspection



2015

« Lots of finished drug product that fail the initial automated visual inspection limit on the system can then be re-inspected using the semi-automated manual system .**There are no establish limits for the re-inspection of lots of product that fail the initial inspection that are then re-inspected..**”

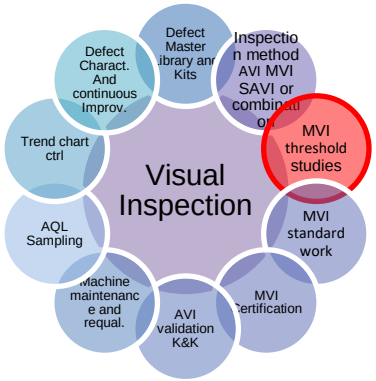
2018

“You have not adequately assessed **spinning parameters, such as rotation per minute (RPMs) of your semi-automated inspection** equipment which affect the capability of your visual inspection process.”

USP<1790>

- **3. TYPICAL INSPECTION PROCESS FLOW**
- **3.3 Remediation and Alternative Practices- two stage inspection**
- **6.2 Semi-Automated Visual Inspection**

MVI Baseline performance studies



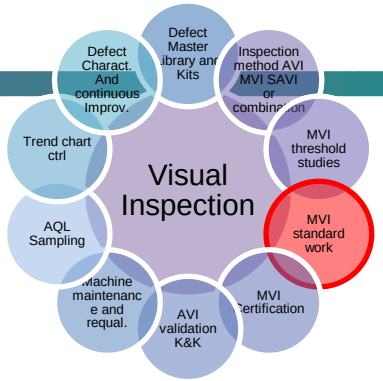
2017

"The probability of detection of particulates used in the defect test sets for manual visual inspection has not been determined to qualify these defects for use in the test set."

USP<1790>

- 7.4 Rejection Probability Determination
- 7.6 Types of Test Sets – Threshold studies

Standard work MVI



2011

« The visual inspection certification program is not adequate : ….., no rotation of the unit required during the visual inspection..”

2016

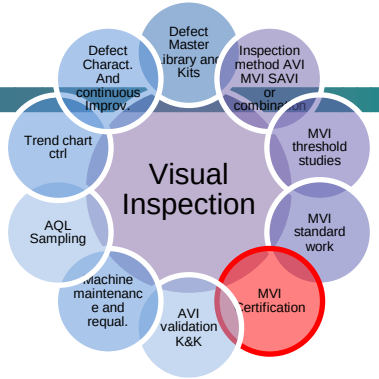
“During the visual examination, I observed that the operator's visual inspection process was inconsistent in the amount of inspection time she spent on drug product units.”

“SOP … does not instruct the visual inspector to gently swirl and invert the container during visual inspection”

USP<1790>

- 6.1 Manual Visual Inspection – critical process parameters in MVI

Certification conditions



2011

"procedures and current practices for the certification of the operators conducting visual inspection were found not representative of current production conditions »

2012

« ..The qualification does not entail reviewing and identifying defects under the same conditions that during manufacturing operations "

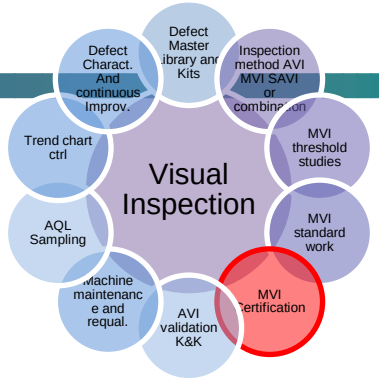
2016

"The certification exercise does not simulate conditions observed during routine product inspection operations ……..Therefore, the current certification/re-certification procedure does not challenge the capability of the operators to recognize and separate all types of defective vials during the maximum individual inspection interval "

USP<1790>

- 7.7 Training and qualification of human inspectors

Certification conditions



2017

“Routine visual inspection occurs on-line with operators ….. During the qualification the operators work offline …”

2018

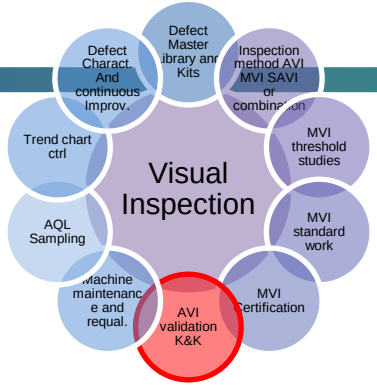
“however these photographs are unclear and inadequate to identify glass particles in vials. Without an adequate qualification vial, your firm cannot ensure your operators can observe this defect during I00% visual inspection.

…. your firm does not have a procedure to address an employee who repeatedly failed to identify a specific defects during all operator qualification runs”

USP<1790>

- 7.7 Training and qualification of human inspectors

AVI Validation



2014

"….**Data was not available** at the time of the inspection to demonstrate that the ….. **has been qualified as equal to or better** than the ….. inspection..."

2017

« ….. There is no documentation of Process Qualification study of the … **machines capabilities to detect vials heel crack defects**."

USP<1790>

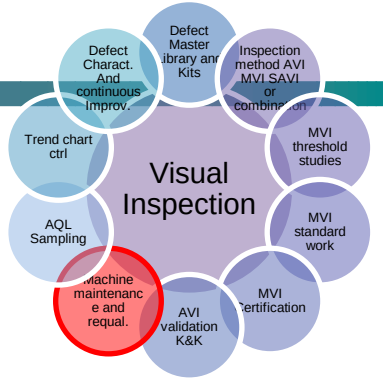
9. Conclusion –

……Where machine methods are used, the equipment must be validated to demonstrate equivalent or better performance when compared to manual inspection.

6.3 Automated Visual Inspection

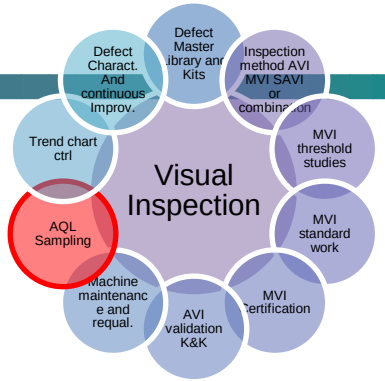
……Significant effort is required to program these systems and to test their performance against a range of known defects,

Machine Maintenance / Daily test



2014
"Vials could be heard hitting against each other during the addition... This practice potentially subjects post visually inspected vials to damage. "
2015
« **The light intensity of each unit is not verified during routine preventive maintenance** and is not verified prior to use. …….
The functionality test used to determine the reject function of the equipment is required before and after 100% visual inspection.
The functionality test results for each equipment is not clearly documented as to the test results. …. „
2015
"The …. equipment are used to perform 100% visual inspection of lyophilized vials, …... For example,…. **The light intensity of each unit is not verified during routine preventive maintenance** and is not verified prior to use. "

AQL QUALITY OVERSIGHT



2011

“There is no direct QA oversight of the operators performing the visual inspections. Operators are only observed during their certification process, but not on a routine basis.”

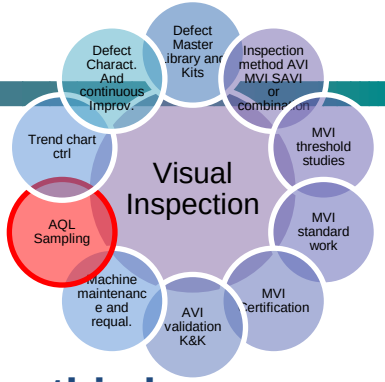
2015

« Quality oversight over visual inspection is deficient. For example,

a. AQL inspections are conducted by personnel that also perform the 100% visual inspection

b. From September 2013 to September 2015, **QA oversight over the 100% visual inspection operations has occurred six times**.”

- Inspection trends for VI with some recent FD 483s



Action after AQL failed

2015

« **There was no tightened 100% inspection performed for this lot even though the initial AQL failed for a Major defect.** “

2015

“There are no established limits for the number of times any single lot can be re-inspected. Additionally, there are no tightened limits established for the re-inspection”

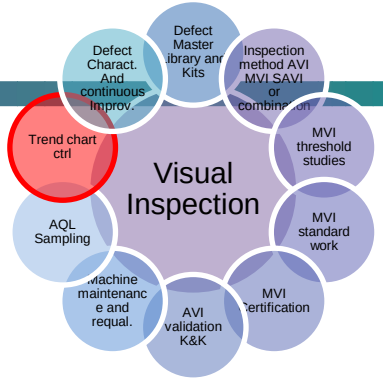
2016

“reported a particle identified in a vial during an AQL inspection. There was no documentation on the identity of the particle and whether it was inherent or foreign (black debris, fiber, glass fragments, etc.).”

2015

“there is **no requirement to tighten the inspection limits or increase the sample size** for the second AQL inspection”

Trending



2011

« There is no written SOP that include performing trend evaluation to determine the root cause that created the quality related attributes”

2013

“There is no tracking or trending of the number of xx vials initially rejected as “Particulate Fiber” ”

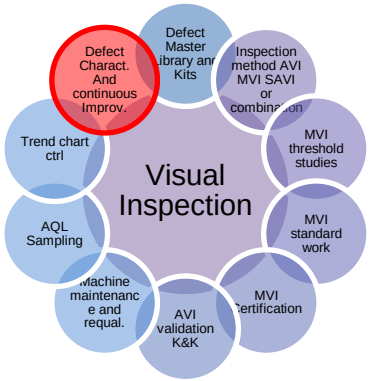
2016

“inspection system, does not have an overall alert/action limit for total rejections”

2018

“You do not monitor long term drift during your establishment / re-establishment of in-process limits.”

Continuous improvement



2015

« According to SOP …., the test set library shall be largely covered with regards to existing (i.e., known) defects. No less than eight deviations for cracks on vial bottoms occurred since approximately ….., for example, deviation …... This defect type has not been added to the test set library to date"

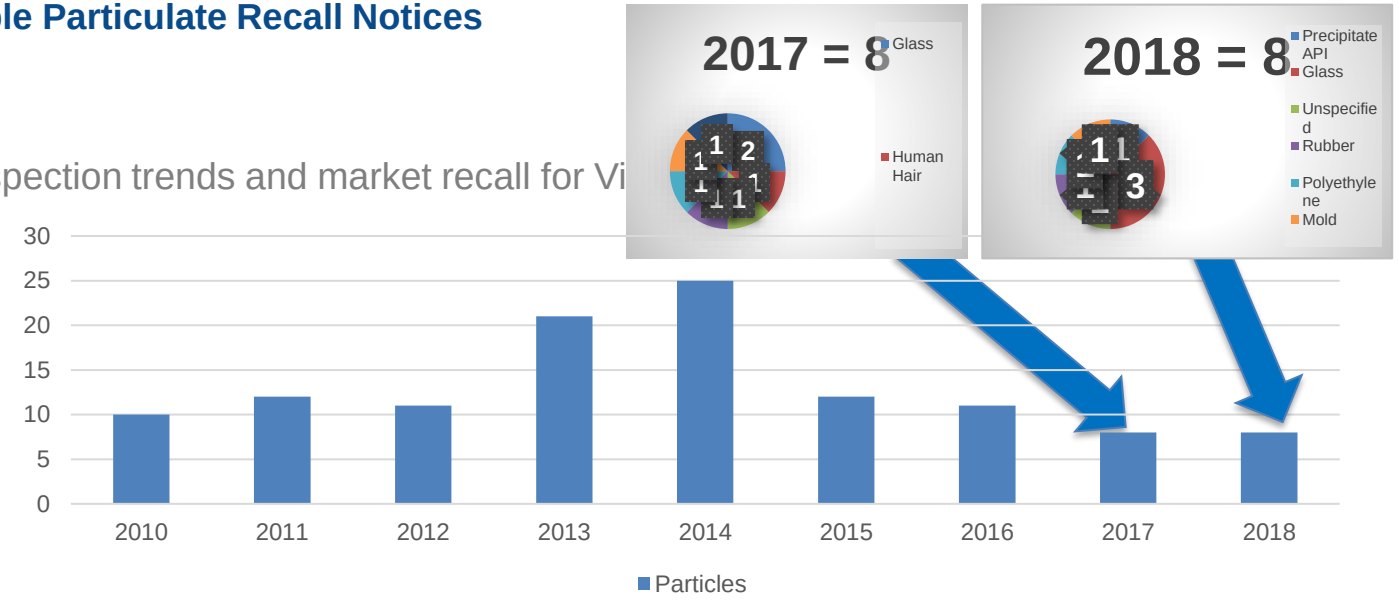
2015

"Particles size was not determined to facilitate assessment of the reliability of detection during visual inspection"

Market recall trends for Visual Inspection

VI Recall trends for US Market
Visible Particulate Recall Notices

- Inspection trends and market recall for Vi



Prepared by John Shabushnig, Insight Pharma Consulting from Recall Archive data on fda.gov

Many thanks to contributors
- John Shabushnig for FDA recall analysis

Thanks you for your attention
Contact: romain.veillon@gsk.com