Worldwide Regulatory Requirements and Standards for Inspection of Sterile Drugs – Visual Inspection

Andrea Simonetti
Convel Srl, Italy

Intro and Background

- Global direction
- 100% Visual inspection is a mandatory practice for injectable manufacturers to guarantee both quality and patient safety
- Sterile pharmaceutical and biological drug products are to be inspected prior to labeling to ensure that
  - The drug product be free of visible particulate matter
  - The drug product container meets predetermined specifications for container/closure integrity; in particular the container is to be free of defects that could lead to a breach in sterility

Particulate Matter…Visible / Non Visible

Particulate Matter Definitions

- Extrinsic (from outside the process, uncontrolled)
  - Environmental Contaminants
    - insect parts, hair, fibers, paint, rust
- Intrinsic (from within the process, unplanned)
  - Processing Equipment, Primary Package
    - qualified product contact materials (e.g. stainless steel, glass, rubber, silicone oil)
- Inherent (part of the formulation, controlled and expected)
  - Protein agglomerates

RISK

© 2016 John G. Shabushnig

Particulate Size Ranges

<100 nm	100 - 1,000 nm	1 - 100 µm	>100 µm
Nanometer	Sub-micron	Sub-visible	Visible
• SEC (Size Exclusion Chromatography) • FFF (Field Flow Fractionation) • SDS-Page Gels • AUC (Analytical Ultra-Centrifugation)		• Light Obscuration • Microscopy • Flow Microscopy • Coulter Counter	• Manual / Human • Semi-Automated • Automated

Narhi, et al. J Pharm Sci, 2012

© 2014 John G. Shabushnig

Visual Defects: Examples from a Defect Catalog

FLACONE CONFORME
Compliant vial

Il flacone conforme presenta cake o polvere bianca
(Compliant vial presents white cake or powder)
Dosaggio conforme/ *Compliant fill volume*

1 di 20

VISUAL INSPECTION DEFECTS CHECK LIST

N	Descrizione	Criticità	Tipo	Foto
1	Presenza di prodotto tra tappo e collo *Product between stopper and neck*	M	Prodotto *Product*	X
2	Flacone senza tappo/ *Vial without stopper*	C	Chiusura *Closure*	
3	Flacone senza ghiera/ *Vial without crimp cap (no overseal)*	C	Chiusura *Closure*	
4	Flacone con vetro sporco esternamente/ *Vial with external dirty glass*	M	Contenitore *Container*	X
5	Flacone con difetto evidente di ghiera/*Vial with evident defect of cap :*	C	Chiusura *Closure*	X
5a	Presenza di depressioni , ammaccature/ *(Presence of depression , Crushed seal)*			
5b	Presenza di tagli, strappi / *presence of Puncture, tear*			
5c	presenza di numerose grinze/*presence of significant wrinkles*			
6	Flacone con difetto di ghiera *Vial with defect of cap*	M	Chiusura *Closure*	X
6a	Visibilmente rigata, incisa / *Significant scratched, deep etching*			
6b	Presenza di eccesso evidente di alluminio/ *presence of evident excess of aluminum*			
7	Flacone con difetto lieve di ghiera *Vial with slight defect of cap*	m	Chiusura *Closure*	X
7a	Lievemente ammaccata/ *slight dented*			
7b	Lievemente rigata/ *slight scratched*			
7c	Presenza di leggero eccesso di alluminio/ *presence of slight excess of aluminum*			
7d	Presenza di una traccia nera sulla base della ghiera/ *banded crimp*			
8	Flacone con ghiera non sigillante *Vial with not sealing crimp cap*	C	Chiusura *Closure*	X
9	Flacone senza flip-off/ *Vial without flip-off*	C	Chiusura *Closure*	X
10	Difetto di flip-off/ *Flip-off defect*	M	Chiusura *Closure*	X
11	Colore di flip off non conforme* / *Flip-off colour not comply* * La ghiera conforme ha il disco in plastica di colore verde e la flangia in alluminio di colore grigio/*Compliant seal has green plastic flip off green and aluminum flange (silver color)*	C	Chiusura *Closure*	X

2 di 20

VISUAL INSPECTION DEFECTS CHECK LIST

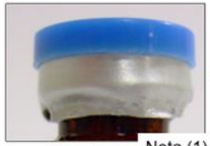
N	Descrizione	Criticità	Tipo	Foto
12	Tappi con inclusioni o macchie (Punti neri o colorati) *Stopper with inclusion or stains (black or coloured point)*	M	Chiusura *Closure*	X
13	Tappi danneggiato *Damaged stopper*	C	Chiusura *Closure*	
14	Flacone con prodotto parzialmente fuso/ *Vial with partially melted product*	C	Prodotto *Product*	
15	Flacone con prodotto totalmente fuso/ *Vial with totally melted product*	C	Prodotto *Product*	
16	Flacone con prodotto liquido/ *Vial with liquid product*	C	Prodotto *Product*	
17	Prodotto liofilizzato di colore non conforme* *Lyophilized product color not comply"* * Il colore conforme del cake è bianco-biancastro *"The compliant cake color is white to off white*	C	Prodotto *Product*	
18	Flacone con riempimento non conforme: sottodosato *Vial with not compliant filling volume: underdosed*	C	Prodotto *Product*	
19	Flacone con riempimento non conforme: sovradosato *Vial with not compliant filling volume: overdosed*	C	Prodotto *Product*	
20	Flacone con corpi estranei/*Vial with foreign particles :*	C	Prodotto *Product*	X
20a	Vetri/*glass*			
20b	Metallo/*metallic*			
20c	Particelle/*particles*			
20d	Fibre/*fiber*			
21	Flacone rotto/ incrinato *Broken/ craked vial*	C	Contenitore *Container*	X
22	Flacone vuoto *Empty vial*	C	Prodotto *Product*	
23	Flacone con imperfezioni lievi sul vetro (graffio) *Vial with slight impefection on the glass (scratch)*	m	Contenitore *Container*	X
24	Flacone con imperfezioni evidenti sul vetro (bolle, punti colorati, onde) *Vial with evident imperfection on the glass (bubbles, colored dots, waves, wrinkles or rifing)*	M	Contenitore *Container*	X

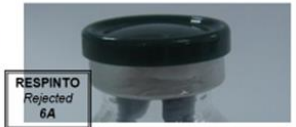
3 di 20

Visual Defects: Examples from a Defect Catalog

Tipo di difetto/ *Defect type*
Flacone con difetto di ghiera (ghiera visibilmente rigata, incisa, con evidente eccesso di alluminio)
Vial with defect of cap (significant scratched, deep etching, with evident excess of aluminum)

Categoria del difetto/ *Group category:*	M *(Major)*
Riferimento su scheda di sperlatura/ *Ref.*	N. 6 (6a, 6b,)





CRITERI DI ACCETTAZIONE/*Acceptance criteria*

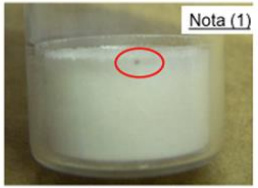
Accettare/ *Accept*
I flaconi che NON presentano difetto evidente di ghiera (ghiera visibilmente rigata, incisa, con evidente eccesso di alluminio)
Vial with NO defect of cap (significant scratched, deep etching, with evident excess of aluminum)

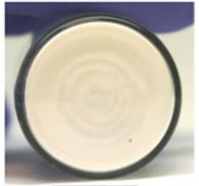
Respingere/ *Reject*
I flaconi che presentano difetto di ghiera (ghiera visibilmente rigata, incisa, con evidente eccesso di alluminio)
Vial with evident defect of cap (significant scratched, deep etching, with evident excess of aluminum)

7 di 20

Tipo di difetto/ *Defect type*
Flacone con corpi estranei (vetri, particelle, fibre, metallo)
Vial with foreign particles (glass, particles, fiber, metallic particles)

Categoria del difetto/ *Group category:*	C *(Critical)*
Riferimento su scheda di sperlatura/ *Ref.*	N. 20 (20a, 20b, 20c, 20d)





CRITERI DI ACCETTAZIONE/*Acceptance criteria*

Accettare/ *Accept*
I flaconi che NON presentano corpi estranei (vetri, particelle, fibre, metallo)
Vial without foreign particles (glass, particles, fiber , metallic particles)

Respingere/ *Reject*
I flaconi che presentano corpi estranei (vetri, particelle, fibre, metallo)
Vial with foreign particles (glass, particles, fiber, metallic particles)

14 di 20

Tipo di difetto/ *Defect type*
Flacone con imperfezioni evidenti sul vetro (bolle, punti colorati, onde)
Vial with evident impefection on the glass (bubbles, colored dots, waves, wrinkles or rifling)

Categoria del difetto/ *Group category:*	M *(Major)*
Riferimento su scheda di sperlatura/ *Ref.*	N. 24

CRITERI DI ACCETTAZIONE/*Acceptance criteria*

Accettare/ *Accept*
I flaconi che NON presentano imperfezioni evidenti sul vetro (bolle, punti colorati, onde)
Vial with NO evident impefection on the glass (bubbles, colored dots , waves wrinkles or rifling)

Respingere/ *Reject*
I flaconi che presentano imperfezioni evidenti sul vetro (bolle, punti colorati, onde)
Vial with evident impefection on the glass (bubbles, colored dots, waves, wrinkles or rifling)

17 di 17

Intro and Background (Cont'd)

- Regulatory Requirements and Standards

  I. Europe: Annex 1, Pharmacopoeia 9.0

  II. US: USP <1>, <788>, <790>, <1790>

  III. Japan: JP XVII

  IV. China: CPh 2010

- FDA Enforcement Actions

  I. 483, Warning Letters, Recalls

Regulatory Standards – Europe

- EU GMP: Annex 1 – Manufacture of Sterile Medicinal Products / WHO: Annex 6 – GMP for sterile pharmaceutical products
  - *"Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects"*
  - *"When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background"*
  - *"Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection"*

Regulatory Standards – Europe

Revised Annex 1 – Sections Related to Visual Inspection

- ✓ *QRM principles should be used for determination of defect classification and criticality. Factors to consider include, but are not limited, to the potential impact to the patient of the defect and the route of administration.*
- ✓ *Where automated methods of inspection are used, the process should be validated to detect known defects with sensitivity equal to or better than manual inspection methods and the performance of the equipment checked prior to start up and at regular intervals.*
- ✓ *A defect library should be generated and maintained which captures all known defects. The defect library can be used as a training tool for production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling of acceptable containers as it indicates a failure of the original inspection process.*

Regulatory Standards – Europe

- EP 2.9.19 – Particulate Contamination: Sub-Visible Particles
  - *"Particulate contamination of injections and infusions consists of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions"*
  - *"For the determination of particulate contamination 2 procedures, Method 1 (Light Obscuration Particle Count Test) and Method 2 (Microscopic Particle Count Test), are specified hereinafter. When examining injections and infusions for sub-visible particles, Method 1 is preferably applied. However, it may be necessary to test some preparations by the light obscuration particle count test followed by the microscopic particle count test to reach a conclusion on conformance to the requirements.*

Regulatory Standards – US

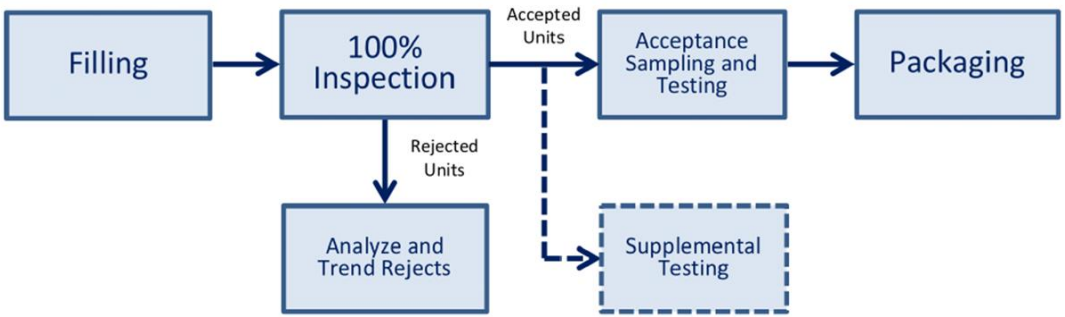
- USP <1> Injections – Foreign and Particulate Matter
  - *"Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter in its contents"*
  - *The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is* ***essentially free from visible particulates****"*
  - *"Every container that shows evidence of visible particulates shall be rejected"*
- USP <788> Particulate matter in injections
  - *"Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, is* ***essentially free from particulate matter*** *that can be observed on visual inspection"*

Regulatory Standards – US

- USP <790> Visible Particulates in Injections
  - Inspection conditions defined and harmonized with EP / 2,000-3,750 lux /B&W backgrounds
  - 5 sec viewing against each background / No magnification
  - Alternative light sources (e.g. incandescent, LED) acceptable
- USP <790> Acceptance Criteria
  - Sampling at Batch Release
    - ✓ 100% inspection followed by acceptance sampling
    - ✓ ANSI/ASQ Z1.4-2003 or ISO 2859
    - ✓ AQL= 0.65%, UQL= 2.3-3.3% typical
    - ✓ Alternate plans with equivalent or better protection are acceptable
  - Product in Distribution
    - ✓ Sample + inspect 20 units: If no particles are observed, batch is considered essentially free of visible particulates
    - ✓ AQL= 0.26%, UQL= 10.9%

Regulatory Standards – US

- USP <1790> Visual Inspection of Injectable Products
  - Typical Process Flow



  - Typical AQL Values
    - ✓ Critical 0,010-0,10 %
    - ✓ Major 0,15-0,65 %
    - ✓ Minor 1,0-4,0 %

Regulatory Standards – Japan

- JP XVII Particulate Matter in Injections
  - 6.06 Foreign Insoluble Matter Test for Injections
  - 6.07 Insoluble Particulate Matter Test for Injections
- Recent facts:
  - JP 16: 6.06 reviewed by PMDA Pharmaceuticals and Medical Devices Agency
  - *"... inspect with the unaided eye at a position of light intensity of approximately 1,000 lx under an incandescent lamp: Injections or vehicles must be clear and free from readily detectable foreign insoluble matters"*
  - Inspection conditions harmonized with EP and those proposed in USP
  - Comparative testing of a range of illumination intensities (1,000 / 2,000 / 3,000 / 5,000 lux)

Worldwide Pharmacopoeias

FDA

Compendial Differences:

''Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles''

– Ph. Eur. - 520 - Parenteral Preparations

When inspected with the unaided eye, "Injections must be clear and free from readily detectable foreign insoluble matter."

– JP - 6.06 - Foreign Insoluble Matter Test for Injections

"The inspection process should….ensure that every lot of all parenteral preparations is essentially free of visible particulates."

– USP <1> - Injections

4

PDA

Pharmacopeial Requirements

	USP <790>	EP 2.9.20	JP 6.06
Illumination Intensity (lux)	2,000-3,750	2,000-3,750	2,000-3,750 lux (8,000-10,000)*
Inspection Time (sec)	10 sec	10 sec	10 sec
Background	Black/White	Black/White	Black/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"

* Illumination intensity for plastic containers

© 2016 John G. Shabushnig

5

Regulatory Standards – China

- Effective Oct 2010. Test for Visible Particle in Injections
  - Visible particles are defined as insoluble substances that present in injections or eye drops and can be observed under the required conditions by visual test. Their size or lengths are usually more than 50 µm.
  - Inspector's vision of distant and near distance should be 4.9 or more than 4.9 (vision after correction should be 5.0 or more than 5.0). Inspector is also not color blind
- Apparatus
  - An inspection station with a non-glare white and black background. A light source with a daylight lamp
- Procedure
  - The test is carried out in a dark room
  - The intensity of illumination should be 1,000-1,500 lx for colorless injections or eye drops. The intensity of illumination should be 2,000-3,000 lx for samples with colored glass, transparent plastic containers or colored solutions.
  - For suspensions for injections or eye drops the intensity of illumination should be 4,000 lx.

US FDA 483 Themes

- Must establish a maximum allowable reject rate
- Must control reinspection of product, including when appropriate, inspection conditions and number of re-inspections permitted
- Inspectors must be trained and training documented
- Inspectors must be periodically recertified
- Training and certification conditions must align with routine 100% inspection conditions
- Address inspection fatigue during qualification

US FDA 483 Themes

- After a Form 483 is issued and the inspector completes the Establishment Inspection Report, the agency may issue a Warning Letter.
- A Warning Letter indicates that higher FDA officials have reviewed the observations and that a serious violation may exist.
- This formal notification allows for voluntary and prompt correction action
- Form 483s and warning letters are public information:
  - https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

US FDA Recall

- Recalls are actions taken by a firm to remove a product from the market
- Recalls may be conducted
  - on a firm's own initiative
  - by FDA request
  - or by FDA order under statutory authority
- Type of Recalls, as a function of the associated risk:
  - Class I, Class II, Class III, Market withdrawal, Medical device safety alert