Hot Topics from the 2019 VIF

Markus Lankers, PhD
September 2019

Hot Topics from the 2019 VIF

- US FDA comments on visible particles and VI
- Application of AI/Deep Learning to VI
- Methods for Difficult to Inspect Parenteral (DIP) products
- Tracking and trending of VI data
- Clinical relevance of particles in injections

US FDA comments on visible particles and VI

Halin Wang presented for the first time at a VIF

- Reanalyzing recall data
- Discussing desired state of visual inspection
- Importance of life cycle

US FDA comments on visible particles and VI

2009 – 2019 Injectable Products Recall Reason Ranking

Rank	Recall Reason	# of Recall Events
1	Lack of Assurance of Sterility/Microbial Contamination/Non-Sterility	299
2	Presence of Foreign Particulate Matter/Crystallization	212
3	Failed stability specifications other than assay	92
4	Labeling Related Errors	78
5	CGMP Deviations	44
6	Lack of Efficacy/Subpotent	40
7	Superpotent Drug	26
8	Defective Container/Delivery System	19
9	Discoloration	11
10	Temperature Abuse	11
11	Incorrect Product Formulation/Excipients	9
12	Chemical Contamination/Cross Contamination	7
13	Correct Labeled Product Mispack	7
14	Lack of Processing Controls	7
15	Marketed Without an Approved NDA/ANDA	5
16	Short Fill	3
17	Resuspension Problems	1

8

Presented by Halin Wang at 2019 VIF

US FDA comments on visible particles and VI

Desired State

FDA

- Rigorous pharmaceutical development studies to prevent product related intrinsic particulates;
- Preventative measures to reduce process related intrinsic particulates;
- Robust visual inspection program to minimize process related intrinsic particulates in the final product;
- Implementation of cGMP requirements to prevent extrinsic particulates;
- Retain samples for stability testing and product complaints;
- Feedback loop for continuous improvement.

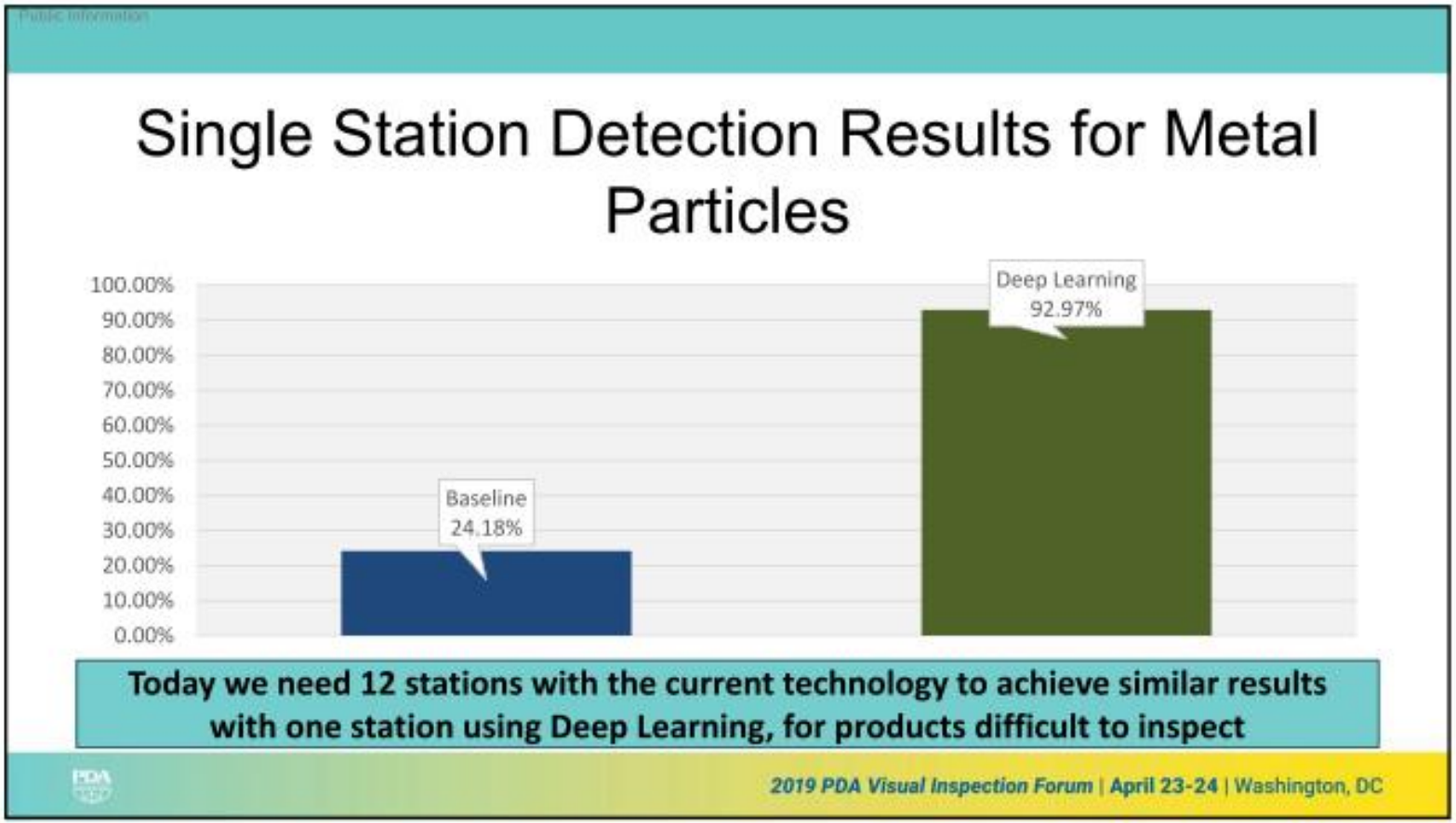
16

16

Application of AI/Deep Learning to VI

- 3 presentations dealing with the potential of AI/ machine learning
- Clarification about integration in cGMP environment
- Outstanding results for selected applications
- Can be seen as an additional tool in the algorithm tool box
- Hybrid approach might be most likely in the (near) future

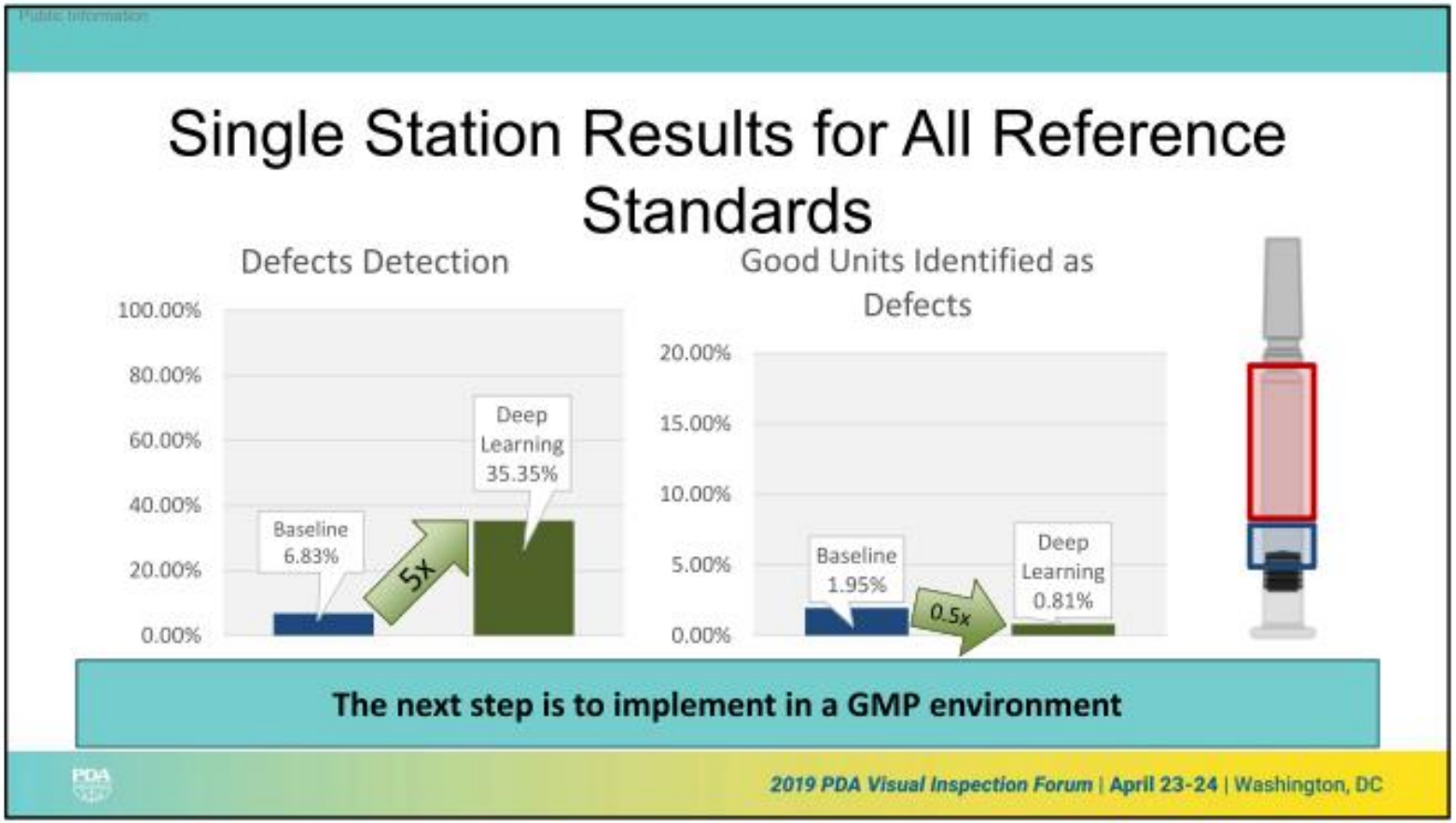
Application of AI/Deep Learning to VI



36

Presented by Jorge Delgado at 2019 VIF

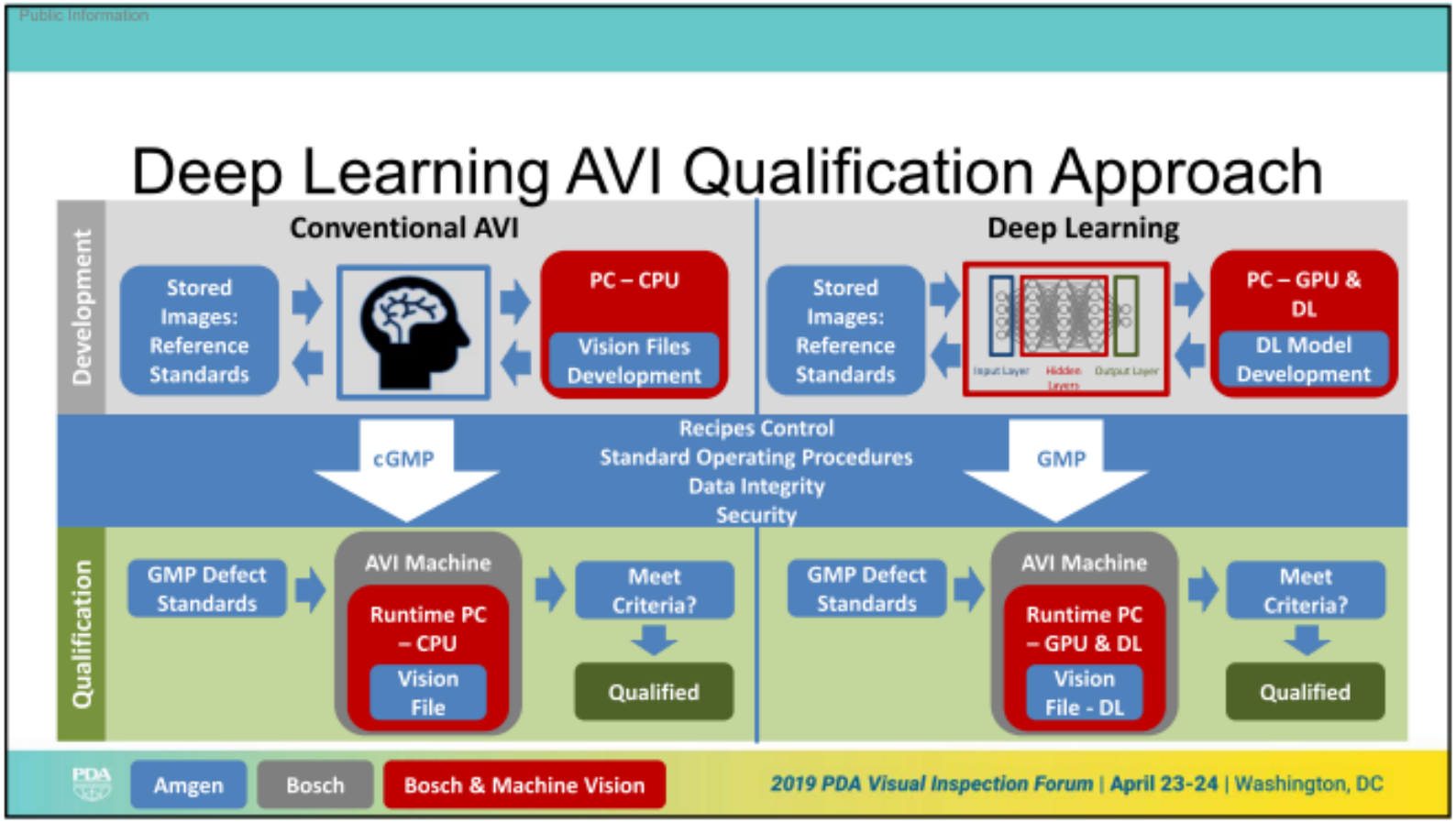
Application of AI/Deep Learning to VI



37

Presented by Jorge Delgado at 2019 VIF

Application of AI/Deep Learning to VI



39

Presented by Jorge Delgado at 2019 VIF

Application of AI/Deep Learning to VI

Real Practical Case

State Of The Art
Computer Vision
Algorithms

solution

Additional
Specialized Area
of Analysis

+19 parameters
4 localization
8 segmentation
7 morphology

Hyper Detection
caused by similar
LDG threshold
activation

Application of AI/Deep Learning to VI

	Computer Vision State of The Art	AI Deep Learning
Method	Multi-ROI analysis	Supervised Learning
Database	200 sequences (36 images)	30k images
Image Type	greyscale	greyscale
Image Resolution	[520,250]	[520,250]
Elaboration Time	~ 70 ms per sequence	~ 50 ms per image
Efficiency	97%	98.5%
False Reject	< 1%	<< 1%
Hardware Architecture	CPU	CPU and/or GPU

Tracking and trending of VI data

- Presentation by Rob Miller

- Overview about trending
- What should be trended: categorization
- Tools for trending
- Setting limits
- Investigations

Tracking and trending of VI data

Will every product presentation have it's own limits? Or will they be Grouped?

- Similar products off the same processing equipment could be grouped into one defect limit set.
- Component manufacturers and historical defect rates should also be considered.

What Categories will be Trended and have Limits?

- Critical, Major, Minor, and Total
- Separate Particulate (esp. if they are considered critical)
- Separate defects that have independent inspection – Leak Detection, NIR moisture

*Defect rates should be the final activity after all inspection activities have been completed. AQL results and repeat inspection data should be included.

Tracking and trending of VI data

Calculating the Limits – Methods and Analysis

Now you have:

- **Product grouping** that will have separate limits
- **Defined categories** to monitor and trend for excursions
- Consistent and accurate **defect classification** process
- **Data storage** with reporting/exporting capabilities

We can now calculate limits that represent or are:

- Out of Control
- Historically high
- A specified range away from the 3rd quartile
- Above 95% of the data with 95% confidence
- Excessive/Extreme values
- Logical or Visible separation between normal variation and abnormal variation.

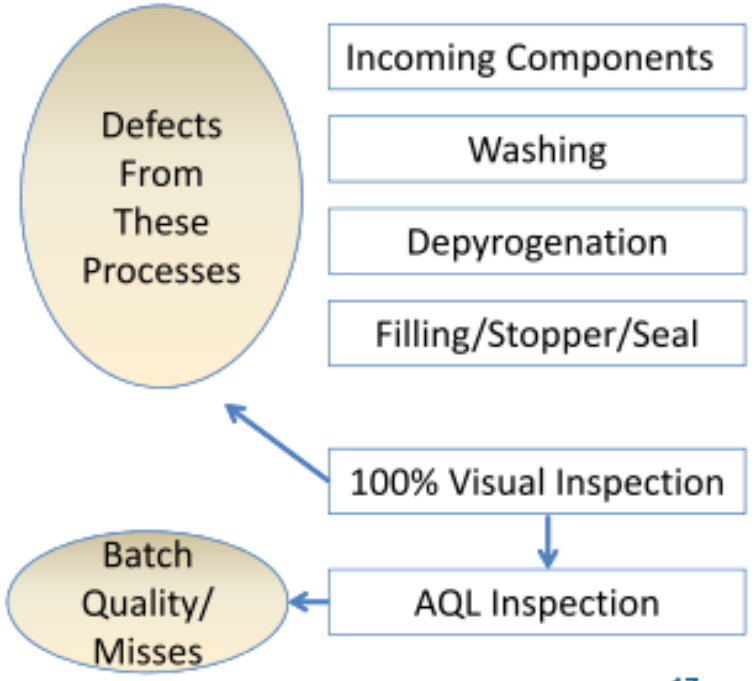
Sample Methods
Mean + 2 or 3 sd
95th Percentile
Box Plot Extreme
Parametric Tolerance Interval
I - Chart
Visualization

8

Tracking and trending of VI data

Exceeding Limits - Investigations

- Exceeding limits does not immediately implicate visual inspection. Inspection found the defects to evaluate.
- Investigation should concentrate on the components/manufacturing process, although VI should be involved to provide defect data and trending.
- Important to have limits that don't clip common cause, so that resources are not wasted, investigations can provide effective corrective actions.
- Proper limits can ensure good opportunity for continuous improvement.



17

Methods for Difficult to Inspect Parenteral (DIP) products

What Defines Difficult to Inspect?

Formulations:

- Deeply Colored Solutions, (opaque)
- Emulsions (two immiscible phases or more, essentially opaque)
- Lyophilized, (reconstitutable, freeze dried solution, opaque)
- Powders/Suspensions, (reconstitutable, recrystallized or spray dried, opaque)
- Biotechnology large molecule (protein), cells, tissue, etc.
- Viscous Solutions (difficult to get particles in motion, latent bubbles)

Container

- Deep cloloured container
- Opaque API or Finished Product Container (no inspection of contents possible)
- Blow Fill Seal (translucent polymer with different shapes)
- Plastic Flexible bags (LVP or SVP) (often pre-printed
- Plastic Syringes (polymeric with varying translucency)
- Small Dosage Size - <1ml (difficult to get particles in motion)

Methods for Difficult to Inspect Parenteral (DIP) products

USP<790> provides a manual inspection procedure and adds an AQL to be conducted at the time of release.

• For clear solutions in transparent containers the AQL value of <0.65% is stated (“essentially free” from visible foreign particles).

• Supplemental destructive inspection/testing has been specified for DIP product in USP<1> since 2006. (This has not been a regulatory focus until recently)

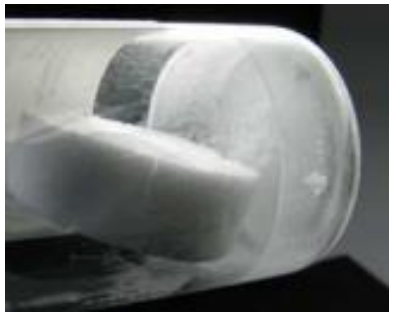
• If the container or product formulation does not allow for a truly effective 100% visual inspection method then the destructive inspection or analytical testing is a regulatory expectation.

Methods for Difficult to Inspect Parenteral (DIP) products

- DIP remains to be a hot topic
- 3 presentations dealing with Difficult to Inspect Products
- Preparation and maintaining of defect sets
  - Specific DIP Issue: stability of defects
- Transition from semiautomated to automated inspection
  - Specific DIP Issues e.g. fill level

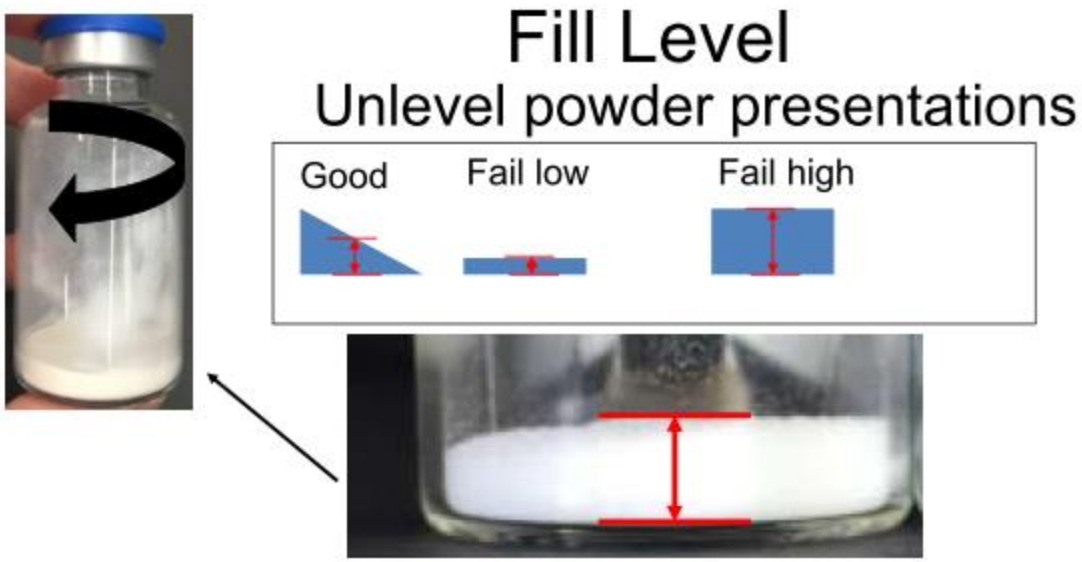
Methods for Difficult to Inspect Parenteral (DIP) products

- Manual manipulation to view as much of the container and product as possible
- Result dust covered inside wall of container
- Samples are degraded before they reach the automated insp ection machine
- Eventually sample must be re-placed

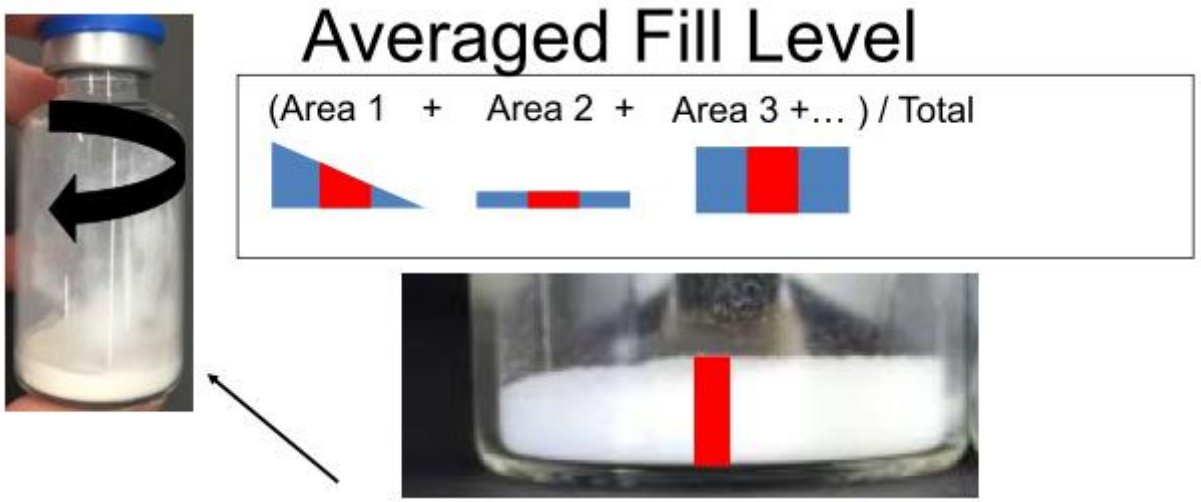


Methods for Difficult to Inspect Parenteral (DIP) products

Product: antibiotic sterile powder



Methods for Difficult to Inspect Parenteral (DIP) products



Clinical relevance of particles in injections

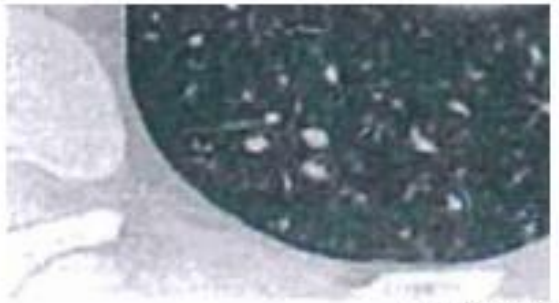
Doug Ross (MD) summarized clinical data

- Clinical data for humans show a certain tolerance for particles
- However, examples with deadly outcome exist by the application of huge amounts of particles
- No real limit in terms of particle number and size can be set
- More nuanced response to particulates

Clinical relevance of particles in injections

Large Load Particulate Harm Data: Drug-drug interactions

- Ceftriaxone and calcium precipitation in neonates' lungs and kidneys with severe to fatal outcomes especially in neonates
- Co-administration of calcium and phosphate - intravenous $CaPO_4$ precipitation in parenteral nutrition solutions.
  - Outcomes-death, PAH, RHF, granulomas w/macrophages and giant cells
  - Amorphous material containing calcium obstructing small vessels.
  - Diffuse <1 mm poorly marginated micronodules. No other organs showed evidence of microvascular emboli.



Reedy 1999

Presented by Doug Ross at 2019 VIF

Clinical relevance of particles in injections

Lesser Load Particulate Harm Data

Adults

- No clinically apparent harm:
  - Lung perfusion scans: ~1,000,000 ^{99m}Tc-labeled particles 10-60µm
  - An adult in the ICU ~10^6 particulates; TPN ~$3x10^6$ ≥2µm

Presented by Doug Ross at 2019 VIF

Clinical relevance of particles in injections

Lessor Particulate Loads

- IV fluids – 4L/day
  - ≤ 100,000 subvisible/day
- IV site phlebitis
  - mitigation with filter use

Falchuk	Incidence of IV-site phlebitis		
	Day 1	Day 2	Day 3
With in-line filter	6.9%	16%	25.5%
Without in-line filter	14.3%	41.3%	57.2%