



# Visual Inspection of Injectable Products: Myth Busting ...

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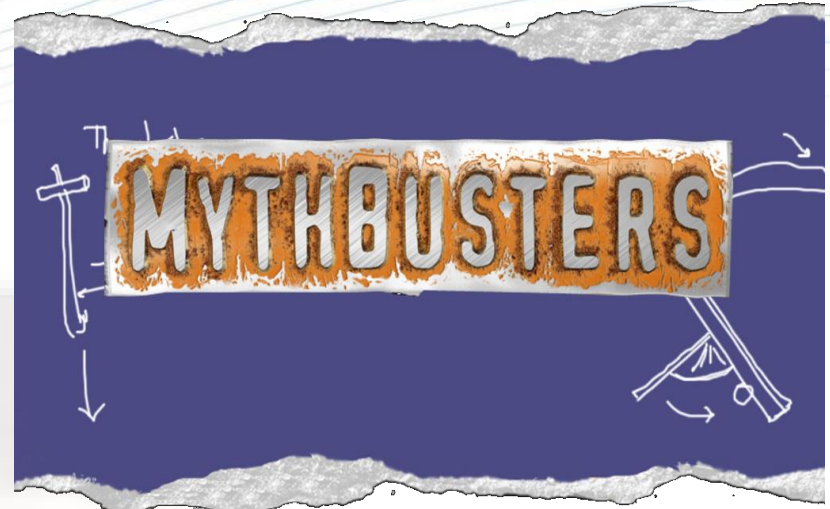


# Agenda

- Inspection Myths
- Conclusions
- References and Acknowledgements



# Inspection Myths



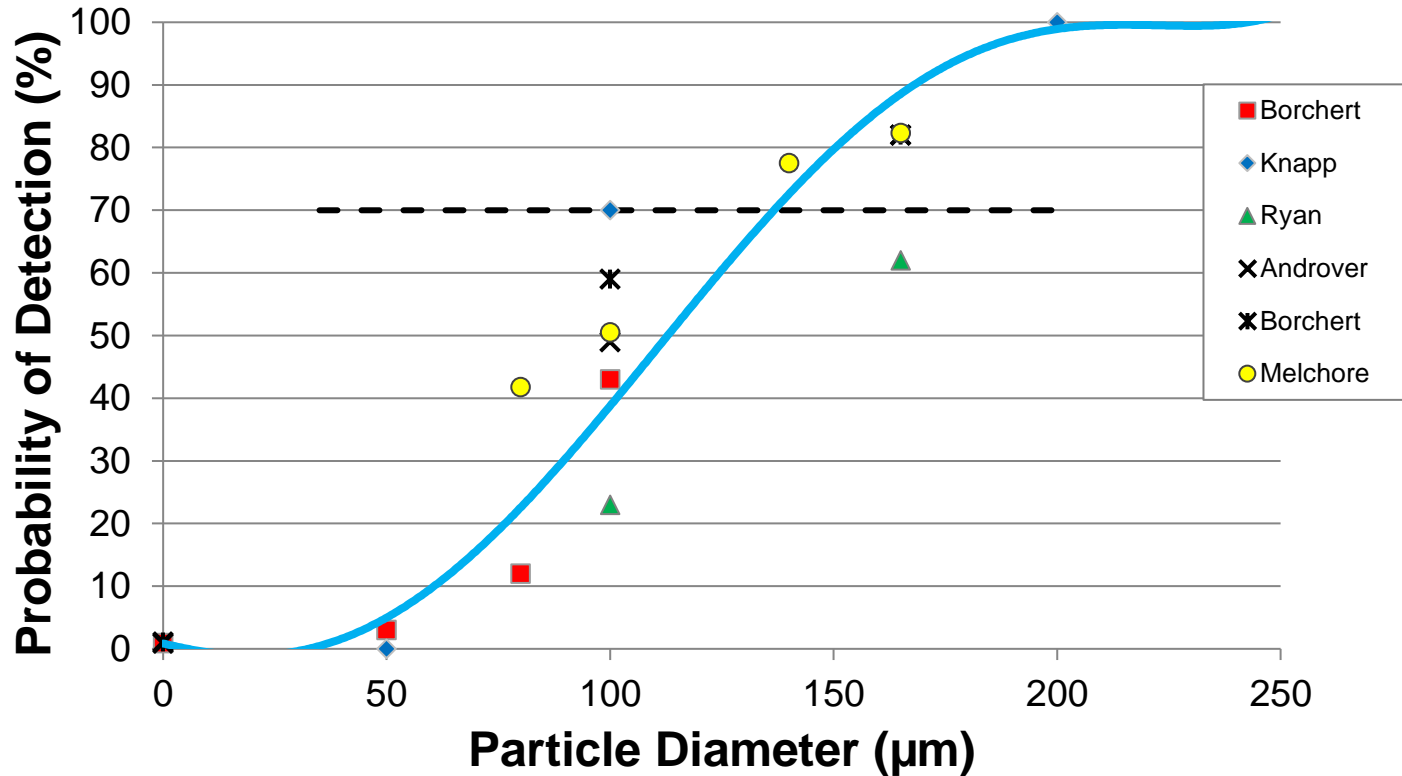


# Inspection Myth #1

- 100% inspection means detection and elimination of all visible defects (e.g. particulate matter, cracks, etc.)
  - Inspection is a probabilistic process.
  - Detection probability is dependant on inspection conditions and defect characteristics.
  - Particles <200 um generally have a detection probability <100%.



# Human Inspection Performance



From Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995

An Introduction to Visual Inspection

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# Inspection Myth #1

- 100% inspection means detection and elimination of all visible defects (e.g. particulate matter, cracks, etc.)
  - Inspection is a probabilistic process.
  - Detection probability is dependant on inspection condition and defect characteristics.
  - Particles  $\geq 10 \mu\text{m}$  generally have a detection probability  $< 100\%$ .

**BUSTED**



# Inspection Myth #2

- Human manual inspection is a “validatable” process.
  - Human inspectors are not “validatable”
  - Qualified human inspectors can provide reliable performance
    - Defined selection and training criteria
    - Control of inspection conditions
      - Light, Background, Duration
      - SOP’s

**BUSTED**





# Inspection Myth #3

- Magnification always improves human manual inspection performance.
  - Inspectors will move head position to minimize eye-strain during extended inspection, reducing apparent magnification.
  - Controlled studies have not found increased detection of particulates or container defects with 3x magnification.



# Detection Rate with Magnification

	5 mL		30 mL	
	No Mag	Mag	No Mag	Mag
Product	50.0%	37.5%	18.6%	18.6%
Container	37.5%	37.2%	45.4%	44.6%
Closure	62.3%	54.2%	72.5%	68.2%
All Defects	50.6%	46.0%	53.6%	51.4%
Good	0.5%	0.9%	2.0%	0.6%

Semi-automated inspection at 55 VPM, Iyo test set, n=1000, 3x mag



# Inspection Myth #3

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  - Inspectors will move head position to minimize eye-strain during extended inspection, reducing apparent magnification.
  - Controlled studies have not found increased detection of particulates or container defects with 3x magnification.

**BUSTED**



# Inspection Myth #4

- If you use a sampling plan with an AQL of 0.1% and do not exceed the acceptance number in your sample, the defect rate in your batch will not exceed 0.1%.
  - AQL is the Acceptable Quality Level and is the defect rate where the rejection probability is 5%. 95% of batches with this defect rate will be accepted. This is a measure of the risk of rejecting good batches.
  - The UQL is the Unacceptable Quality Level and is the defect rate where the rejection probability is 90% for the batch.

**BUSTED**



# Conclusions



# Conclusions

- Current industry performance is generally at or beyond the limits of medical risk.
- Compendial guidance is ambiguous, but getting better.
- “Zero defects” is a valuable goal, not a practical limit for particulate matter.
- Need to develop practical limits based on risk assessment and process capability measures.





# References and Acknowledgements



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  - Julius Z. Knapp, et. al., Marcel Dekker ©1997
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  - Ed. Mark S. Rea, 9<sup>th</sup> Edition, ©2000
- Guide to Acceptance Sampling
  - Wayne A. Taylor, Taylor Enterprises, Lake Villa, IL, ©1992



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- PDA Technical Report No. 43 (Revised 2013): Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing: Covering Ampoules, Bottles, Cartridges, Syringes and Vials (2013)
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  - Subpart B – Organization and Personnel
    - 211.25 Personnel qualifications
  - Subpart C – Buildings and Facilities
    - 211.42 Design and construction features
    - 211.56 Sanitation
  - Subpart D -Equipment
    - 211.63 Equipment design, size and location
    - 211.65 Equipment construction
    - 211.67 Equipment cleaning and maintenance
    - 211.68 Automatic, mechanical, and electronic equipment



# Regulatory & Compendial

- US Code of Federal Regulations (CFR) 211 Food and Drugs
  - Subpart E - Control of Component and Drug Product Containers and Closures
    - 211.80– General requirements
    - 211.84 Testing and approval or rejection of components, drug product containers, and closures
    - 211.94 Drug product containers and closures
  - Subpart F – Production and Process Controls
    - 211.100 Written procedures: deviations
    - 211.110 Sampling and testing of in-process materials and drug products
  - Subpart I – Laboratory Controls
    - 211.160 Laboratory controls – general requirements
    - 211.165 Testing and release for distribution



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    - 211.192 Production record review
    - 211.194 Laboratory records
    - 211.198 Complaint files
  - Subchapter F - Biologics
    - 600.10 Personnel
    - 600.11 Physical establishment, equipment, animals, and care



# Regulatory & Compendial

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Manufacture of Sterile Medicinal Products
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- Chinese Pharmacopeia (ChP)
- Japanese Guidance for Industry: Sterile Drug Products  
Produced by Aseptic Processing
- German Pharmaceutical Codex (DAC)
- WHO International Pharmacopoeia
- FDA Warning Letters and 483 Observations
  - FDA website
  - GMP Trends



# Conferences and Meetings

- PDA Visual Inspection of Parenterals Interest Group
- PDA Visual Inspection Forums



# Equipment Vendors

- Antares Vision
  - Brescia, Italy [www.antaressvision.com](http://www.antaressvision.com)
- Brevetti C.E.A., S.p.A.
  - Sovizzo, Italy [www.brevetti-cea.com](http://www.brevetti-cea.com)
- Bonfiglioli Engineering, S.r.l.
  - Vigarano Pieve, Italy [www.bonfiglioliengineering.com](http://www.bonfiglioliengineering.com)
- Dabrico, Inc.
  - Kankakee, IL [www.dabrico.com](http://www.dabrico.com)
- eyetec
  - Antwerp, Belgium [www.eyetec.be](http://www.eyetec.be)
- Syntegon Technology, GmbH (formerly Eisai, Bosch)
  - Waiblingen, Germany [www.syntegon.com](http://www.syntegon.com)
- InnoScan K/S (Stevenato Group)
  - Braband, Denmark [www.innoscan.dk](http://www.innoscan.dk)





# Equipment Vendors

- Optrel (Stevenato Group)
  - Padova, Italy [www.optrelinspection.com](http://www.optrelinspection.com)
- Phoenix Imaging
  - Livonia, MI [www.phoeniximaging.com](http://www.phoeniximaging.com)
- Seidenader, GmbH (Korber)
  - Munich, Germany [www.seidenader.de](http://www.seidenader.de)
- Unchained Labs (Rap.ID Particle Systems)
  - Pleasanton, CA [www.unchainedlabs.com](http://www.unchainedlabs.com)
- Lighthouse Instruments
  - Charlottesville, VA [www.lighthouseinstruments.com](http://www.lighthouseinstruments.com)
- Wilco AG
  - Wohlen, Switzerland [www.wilco.com](http://www.wilco.com)



# Standards Vendors

## Standard Particles:

- Duke Scientific Corp.
  - Palo Alto, CA [www.dukescientific.com](http://www.dukescientific.com)
- Mo-Sci Corp.
  - Rolla, MO [www.mo-sci.com](http://www.mo-sci.com)
- National Institute of Standards (NIST)
  - Gaithersburg, MD [www.nist.gov](http://www.nist.gov)
- Poly Sciences, Inc.
  - Warrington, PA [www.polysciences.com](http://www.polysciences.com)



# Standards Vendors

## Finished Standard Containers:

- Material Analytischer Service (M.A.S.)
  - Freiburg, Germany [www.ma-service.de](http://www.ma-service.de)
- Micro Measurement Laboratories, Inc.
  - Wheeling, IL [www.mmlabs.com](http://www.mmlabs.com)
- Phoenix Imaging
  - Livonia, MI [www.phoeniximaging.com](http://www.phoeniximaging.com)
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  - D. Scott Aldrich (retired)
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  - Markus Lankers



# Questions



Remember, everyone is an inspector ...