Visual Inspection of Injectable Products:

Myth Busting …

John G. Shabushnig, Ph.D.
Insight Pharma Consulting, LLC
insight!
johnshabushnig@aol.com
January 2025

Agenda

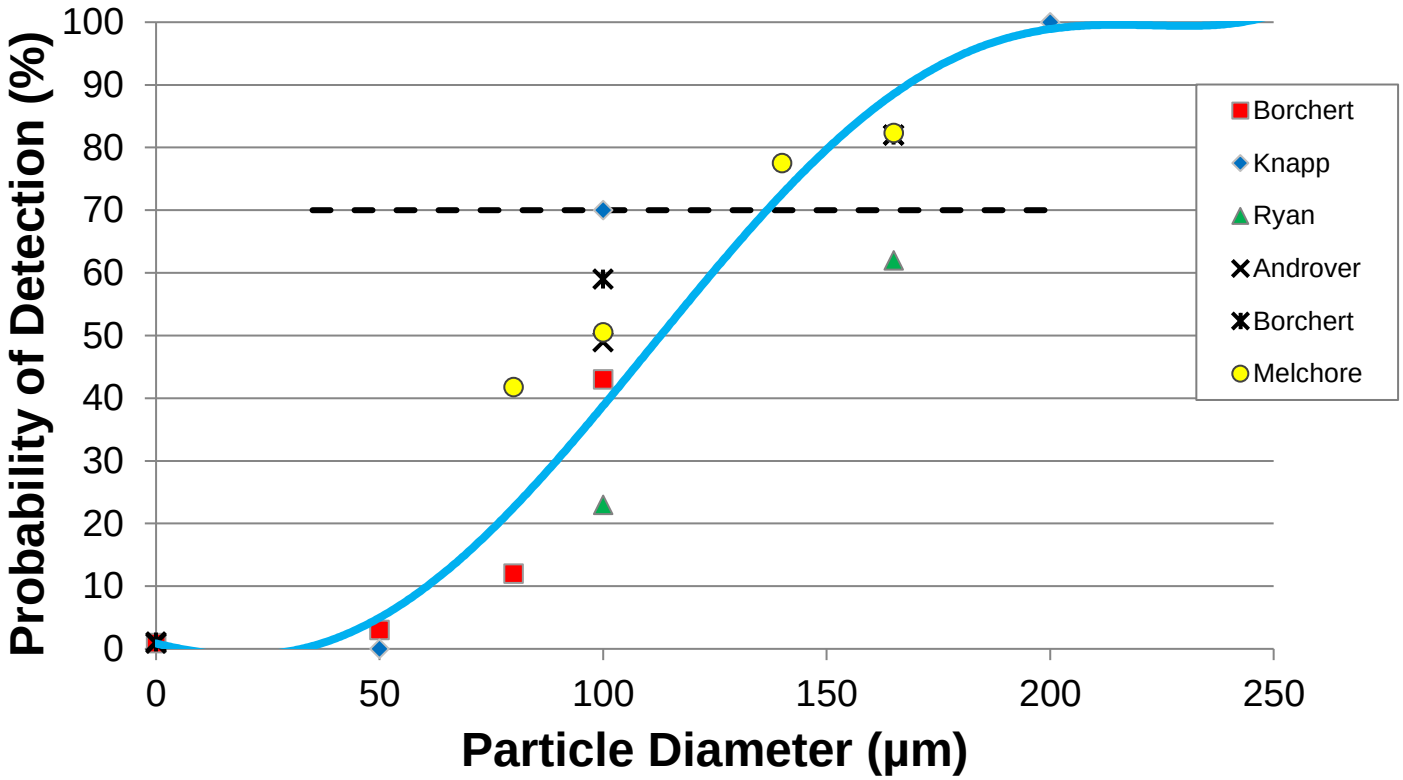
- Inspection Myths
- Conclusions
- References and Acknowledgements

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

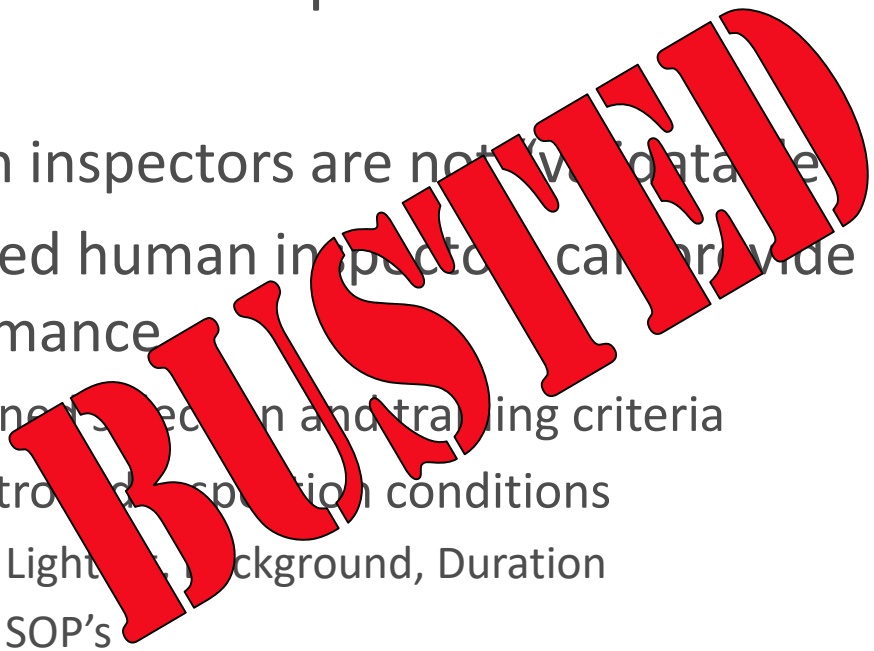
Inspection Myth #1

- 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 <20 µm 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
    - Define selection and training criteria
    - Control inspection conditions
      - Light, Background, Duration
      - SOP’s



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.

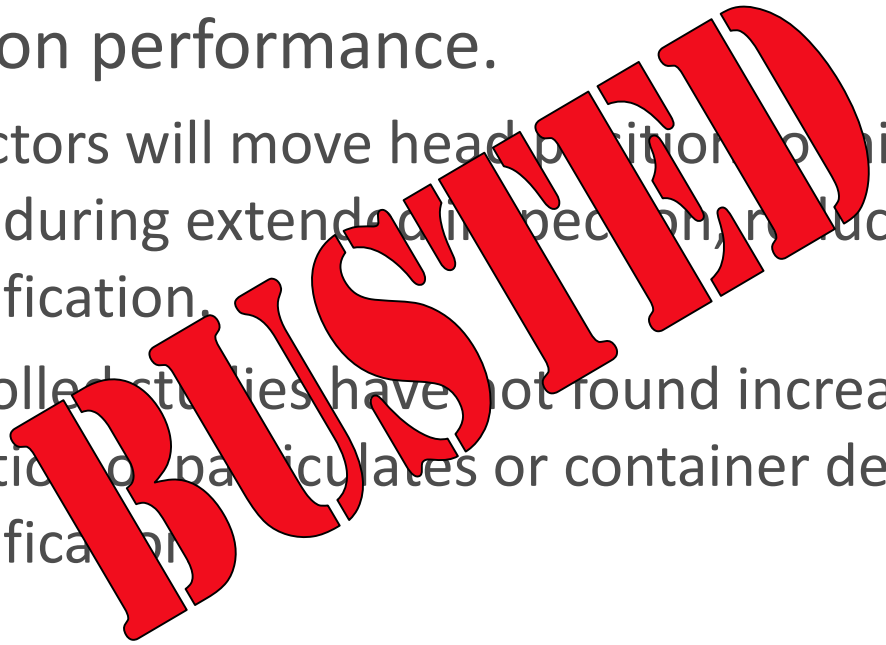
Detection Rate with Magnification

	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, lyo test set, n=1000, 3x mag

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.



Inspection Myth #4

- If you use a sampling plan with an AQL of 0.1% and do not exceed the accept 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

Papers

- Good Practices in Visual Inspection
  - CG Drury, J Watson; Federal Aviation Administration, Flight Standards Service (2002), www.faa.gov
- Visual Inspection: A Review of the Literature
  - JE See; Sandia National Laboratories Report SAND2012-8590. (2012) www.sandia.gov
- Rare Items Often Missed in Visual Searches
  - J Wolfe, T Horowitz, and N Kenner; *Nature*, 435, 439-440 (2005)

Papers

- Generalized Methodology for Evaluation of Parenteral Inspection Procedures
  - JZ Knapp and HR Kushner, *J. Parent. Sci & Techn.* 34 (1), pgs. 14-61 (1980)
- Implementation and Automation of a Particle Detection System for Parenteral Products
  - JZ Knapp and HR Kushner, *J. Parent. Sci & Techn.* 34 (5), pgs. 369-393 (1980)
- 2023 PDA Visual Inspection Survey
  - J Shabushnig, R Miller, R Watson; Parenteral Drug Association, May 2023

Papers

- Intravenous Fluids: A Solution Containing Such Particles Must Not Be Used
  - JM Garvan and BW Gunner, *Med J Austr.* 2, pgs. 140-145 (1963)
- The Harmful Effects of Particles in Intravenous Fluids
  - JM Garvan and BW Gunner, *Med. J. Austr.* 2, pgs. 1-6 (1964)
- Particles in Intravenous Solutions; A Review
  - WH Thomas and YK Lee, *New Zealand Med. J.* 80, pgs. 170-178 (1974)
- Foreign Particle Embolism in Drug Addicts: Respiratory Pathophysiology
  - FG Douglas, et al, *Annals Int. Med.* 75, pgs 865-872 (1971)

Papers

- Potentially Hazardous Effects of Introducing Particulate Matter into the Vascular System of Man and Animals
  - AM Jonas, *Proceedings of the Safety of Large Volume Parenteral Solution Symposium*, Washington D.C., July 28-29, 1966
- Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products
  - S Bukofzer, J Ayres, et al; PDA J Pharm Sci and Technol 69, 123-139 (2015)
- Applying Machine Learning to the Visual Inspection of Filled Injectable Drug Products
  - R Veillon, J Shabushnig, et al; PDA J Pharm Sci and Technol, in press (2023)

Papers

- Visible Particulates in Injections – A History and a Proposal to Revise USP General Chapter *Injections* <1>
  - RE Madsen, RT Cherris, JG Shabushnig and DG Hunt, Pharmacopeial Forum, 35(5) pgs. 1383-1387, Sept-Oct 2009.
- Particulate Matter in Injectable Drug Products
  - Stephen E. Langille, *PDA J Pharm Sci and Technol,* 67 (3) pgs. 186-200 (2013)
- Considerations for Design and Use of Container Challenge Sets for Qualification and Validation of Visible Particulate Inspection
  - James A. Melchore and Dan Berdovich, *PDA J Pharm Sci and Technol*, 66 (3) pgs. 273-284 (2012)

Books and Journals

- Visual Inspection and Particulate Control
  - D. Scott Aldrich, Roy T. Cherris and John G. Shabushnig, DHI Press ©2016, PDA Bookstore
- Control of Particulate Matter Contamination in Healthcare Manufacturing
  - Thomas A. Barber, CRC Press ©1999
- Pharmaceutical Particulate Matter; Analysis and Control
  - Thomas A. Barber, Interpharm Press ©1993
- Particulate Matter; Sources and Resources for Healthcare Manufacturers
  - Michael J. Groves, Interpharm Press ©1993

Books and Journals

- Liquid & Surface-Borne Particle Measurement Handbook
  - Julius Z. Knapp, et. al., Marcel Dekker ©1997
- Illuminating Engineering Society of North America (IESNA) Lighting Handbook
  - Ed. Mark S. Rea, 9th Edition, ©2000
- Guide to Acceptance Sampling
  - Wayne A. Taylor, Taylor Enterprises, Lake Villa, IL, ©1992

Journals

- PDA Journal of Pharmaceutical Science and Technology
- 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)
- PDA Technical Report No. 76: Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging (2016)
- PDA Technical Report No. 79: Particulate Matter Control in Difficult to Inspect Parenterals (2018)

Regulatory & Compendial

- US Pharmacopoeia (USP)
  - <1> *Injections and Implanted Drug Products (Parenteral) – Product Quality Tests*
  - <771> *Ophthalmic Products – Quality Tests*
  - <787> *Subvisible Particulate Matter in Therapeutic Protein Injections*
  - <788> *Particulate Matter in Injections*
  - <789> *Particulate Matter in Ophthalmic Solutions*
  - <790> *Visible Particulates in Injections*
  - <1787> *Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections*
  - <1788> *Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions*
  - <1790> *Visual Inspection of Injections*

Regulatory & Compendial

- European Pharmacopeia / Pharm Europa (EP)
  - 2.9.19 *Particulate Contamination: Sub-Visible Particles*
  - 2.9.20 *Particulate Contamination: Visible Particles*
  - 5.17.2 *Recommendations on testing of particulate contamination: visible particles (DRAFT)*

- Japanese Pharmacopoeia (JP)
  - 6.06 *Foreign Insoluble Matter Test*
  - 6.07 *Insoluble Particulate Matter Test for Injections*

Regulatory & Compendial

- FDA Guidance for Industry: Inspection of Injectable Products for Visible Particulates (Dec 2021, draft)
- FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)
- US FDA Compliance Program Guidance Manual 7356.002A
- US FDA Advisory: Formation of Glass Lamellae in Certain Injectable Drugs (3-25-2011)

Regulatory & Compendial

- US Code of Federal Regulations (CFR) 211 Food and Drugs

  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

Regulatory & Compendial

- US Code of Federal Regulations (CFR) 211 Food and Drugs

  Subpart J – Records and Reports

  – 211.188 Batch production and control records
  – 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

- EC Guide to Good Manufacturing Practice – Annex 1 Manufacture of Sterile Medicinal Products
- British Pharmacopeia (BP)
- 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.antaresvision.com
- Brevetti C.E.A., S.p.A.
  - Sovizzo, Italy www.brevetti-cea.com
- Bonfiglioli Engineering, S.r.l.
  - Vigarano Pieve, Italy www.bonfigliolienginеering.com
- Dabrico, Inc.
  - Kankakee, IL www.dabrico.com
- eyetec
  - Antwerp, Belgium www.eyetec.be
- Syntegon Technology, GmbH (formerly Eisai, Bosch)
  - Waiblingen, Germany www.syntegon.com
- InnoScan K/S (Stevenato Group)
  - Braband, Denmark www.innoscan.dk

Equipment Vendors

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

Standards Vendors

Standard Particles:

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

Standards Vendors

Finished Standard Containers:

- Material Analytischer Service (M.A.S.)
  - Freiburg, Germany www.ma-service.de
- Micro Measurement Laboratories, Inc. (MML)
  - Wheeling, IL www.mmlabs.com
- Phoenix Imaging
  - Livonia, MI www.phoeniximaging.com
- Prime Results
  - Harrisburg, PA www.prime-results.com
- SoloHill Engineering, Inc
  - Ann Arbor, MI www.particlestandards.com

Acknowledgments

- PDA Task Force
  - Julius Z. Knapp – R&D Associates
  - Roy T. Cherris – Bridge Associates International
  - Russell E. Madsen – The Williamsburg Group, LLC
- Pfizer Inc
  - Stephen J. Borchert (retired)
  - D. Scott Aldrich (retired)
- MIBIC, GmbH
  - Markus Lankers

Questions

Remember, everyone is an inspector …