



Visual Inspection of Injectable Products: Myth Busting ...

John G. Shabushnig, Ph.D.
Insight Pharma Consulting, LLC



johnshabushnig@aol.com
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Agenda

- Inspection Myths
- Conclusions
- References and Acknowledgements



Inspection Myths



An Introduction to Visual Inspection

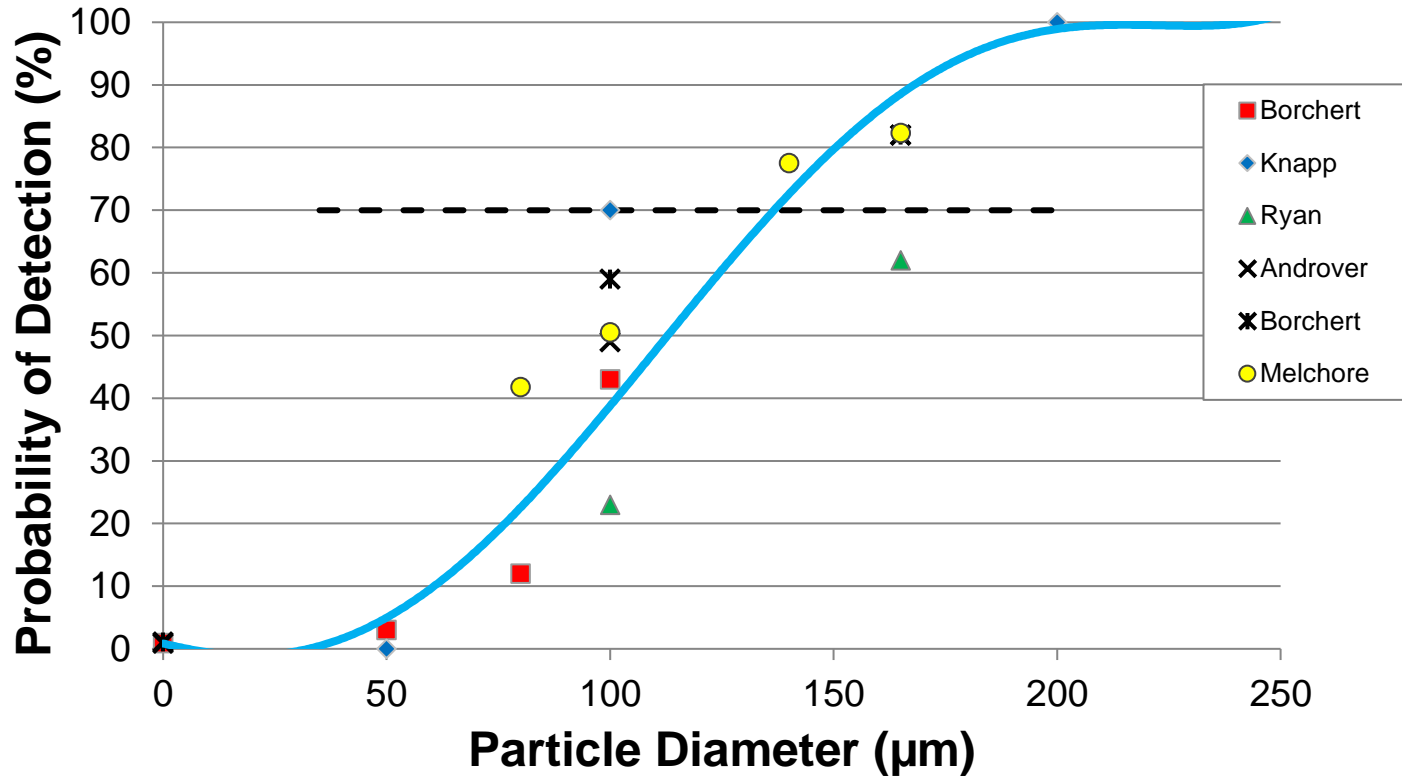


Inspection Myth #1

- 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



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 $\geq 10 \mu m$ generally have a detection probability $< 100\%$.

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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

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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



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 - Inspectors will move head position to minimize eye-strain during extended inspection, reducing apparent magnification.
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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.

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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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Papers

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- Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products
 - Bukofzer, S., Ayres, J., Chavez, A., Devera, M., Miller, J., Ross, D., Shabushnig, J., Vargo, S., Watson, H., and Watson, R., *PDA J Pharm Sci and Technol* 69, 123-139 (2015)



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 - 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

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 - 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



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- 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



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- 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)
 - <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*
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Regulatory & Compendial

- European Pharmacopeia / Pharm Europa (EP)
 - 2.9.19 *Particulate Contamination: Sub-Visible Particles*
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 - 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 (DRAFT Dec 2021)
- 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

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 - 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.antaressvision.com
- Brevetti C.E.A., S.p.A.
 - Sovizzo, Italy www.brevetti-cea.com
- Bonfiglioli Engineering, S.r.l.
 - Vigarano Pieve, Italy www.bonfiglioliengineering.com
- Dabrico, Inc.
 - Kankakee, IL www.dabrico.com
- Eisai Machinery Co., Ltd. (Bosch)
 - Tokyo, Japan www.eisai-mc.co.jp/english
- 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 Maschinenbau, GmbH (Korber)
 - Munich, Germany www.seidenader.de
- Unchained Labs (Rap.ID Particle Systems)
 - Pleasanton, CA www.unchainedlabs.com
- Victor International Marketing, Inc.
 - Morristown, NJ, www.victorinternational.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.
 - Wheeling, IL www.mmlabs.com
- RJ Lee Group
 - Monroeville, PA www.rjlg.com
- SoloHill Engineering, Inc
 - Ann Arbor, MI www.particlestandards.com



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Questions



Remember, everyone is an inspector ...