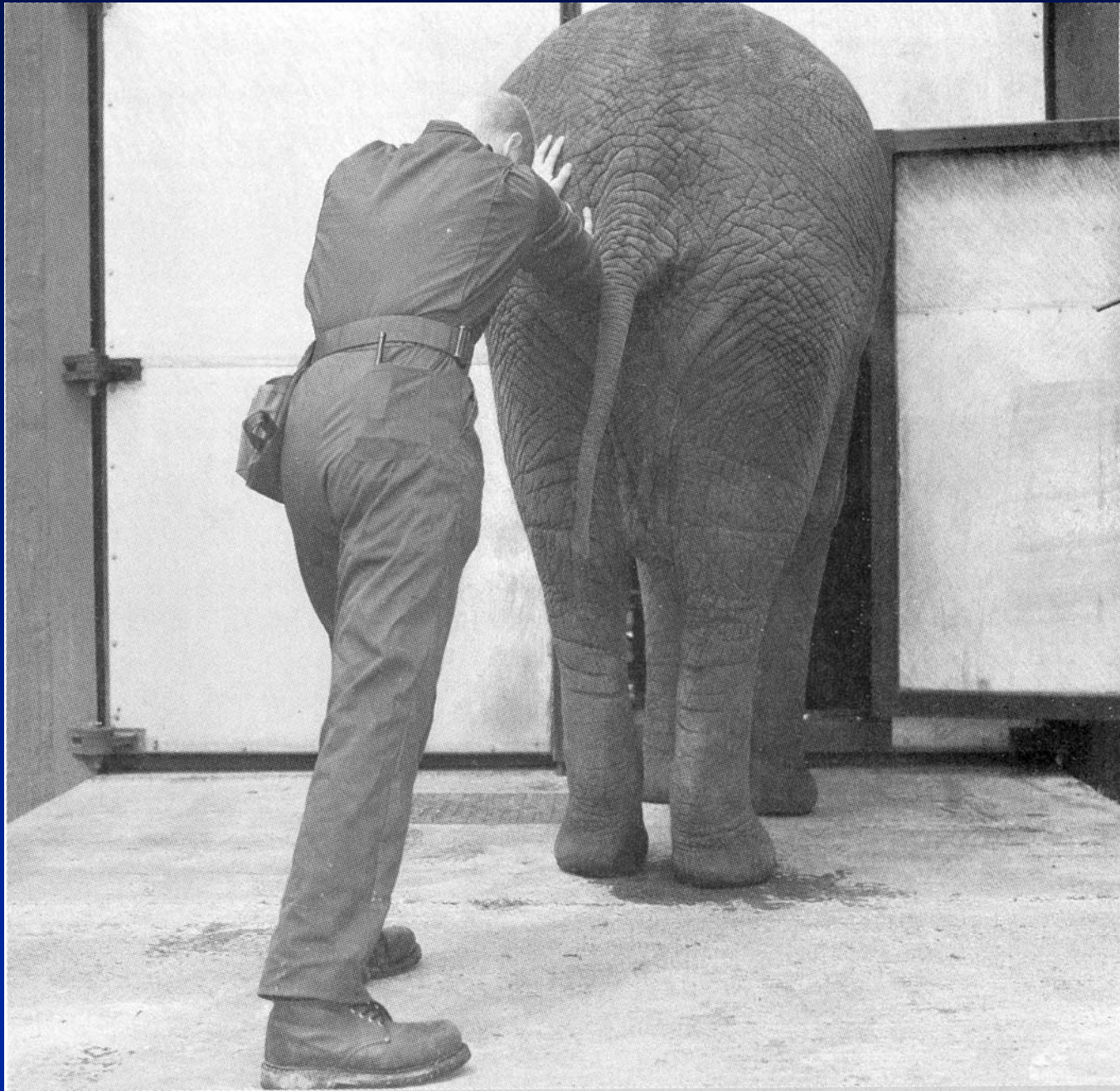


Visual Inspection of  
Injectable Products:  
More than Sorting Good  
from Bad ...

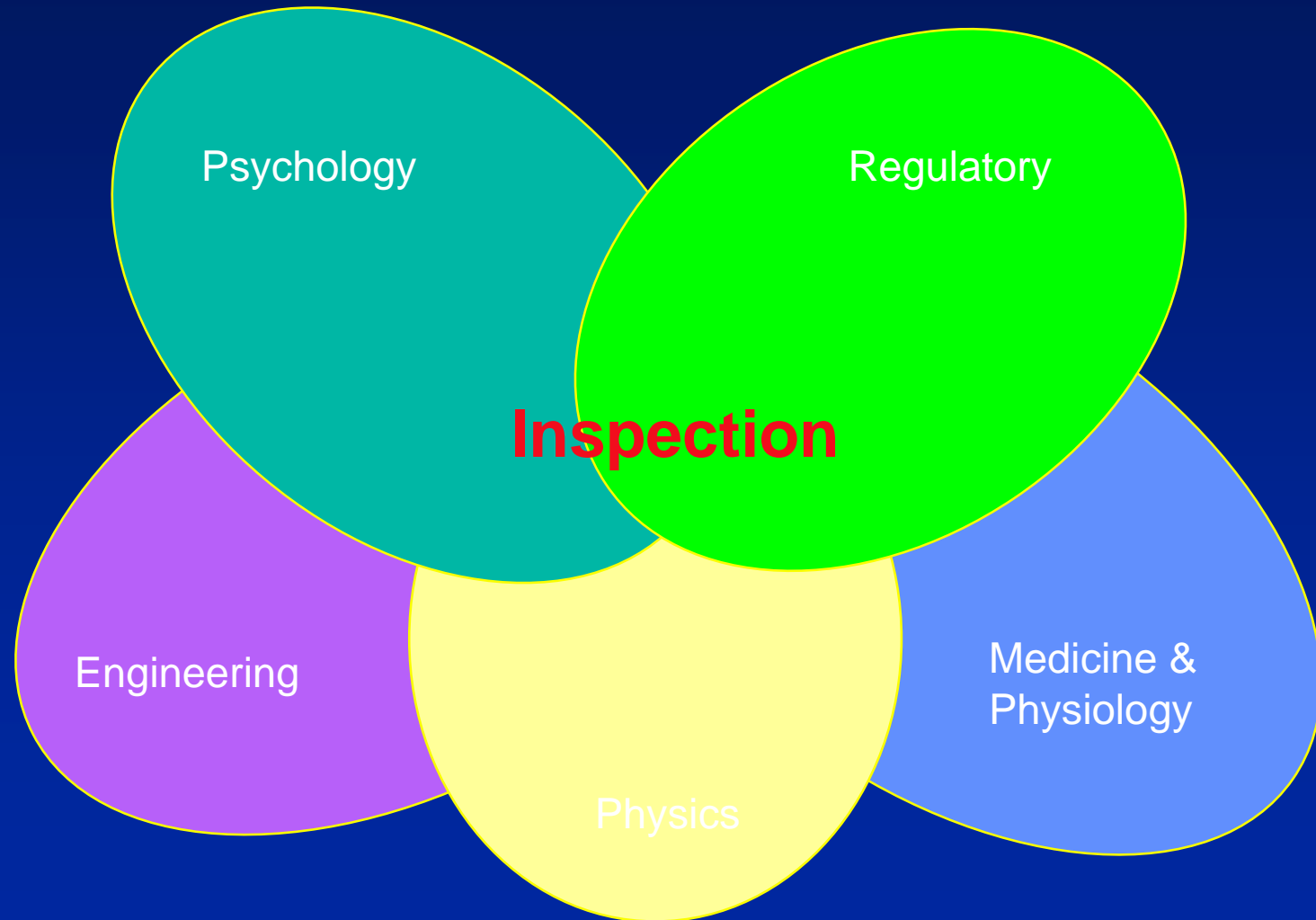
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John G. Shabushnig, Ph.D.  
Pfizer Global Quality Technical Services  
February 9, 2005



# Inspection Influences

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# Why Inspect?

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- Compendial Requirements
- Regulatory Requirements
- Physiological Implications
- Chemical and Microbiological Implications

# US Pharmacopoeia

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- **USP XXVII: <1> Injections - Foreign Matter and Particles**

Every care should be exercised ... to prevent contamination with microorganisms and foreign material. Good pharmaceutical practice requires also that each final container ... be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected.

# US Pharmacopoeia

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- **USP XXVII: <1> Injections - Packaging**

The container is made of material that permits inspection of the contents. ...

- **USP XXVII: <1> Injections - Constituted Solutions**

Particulate Matter - Constitute the solution as directed in the labeling ...the solution is essentially free from particles of foreign matter that can be observed on visual inspection.

# US Pharmacopoeia

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- **USP XXIII: <788> Particulate Matter in Injections**

Particulate matter consists of mobile, randomly-sourced, extraneous substances, other than gas bubbles, that can not be quantitated by chemical analysis due to the small amount ...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. ...

# Japanese Pharmacopoeia

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- **JP XIV: 20. Foreign Insoluble Matter Test ...**
  - ... inspect with the unaided eye at a position of light intensity of approximately 1,000 luxes under an incandescent lamp: Injections must be clear and free from readily detectable foreign insoluble matters. As to Injections in plastic containers ... the inspection should be performed with the unaided eyes at a position of light intensity of approximately 8,000 to 10,000 luxes, with an incandescent lamp ...



# EC GMP Annex 1 / WHO Annex 6

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- **Finishing of Sterile Products**

EC 90 / WHO 11.3. 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. ...

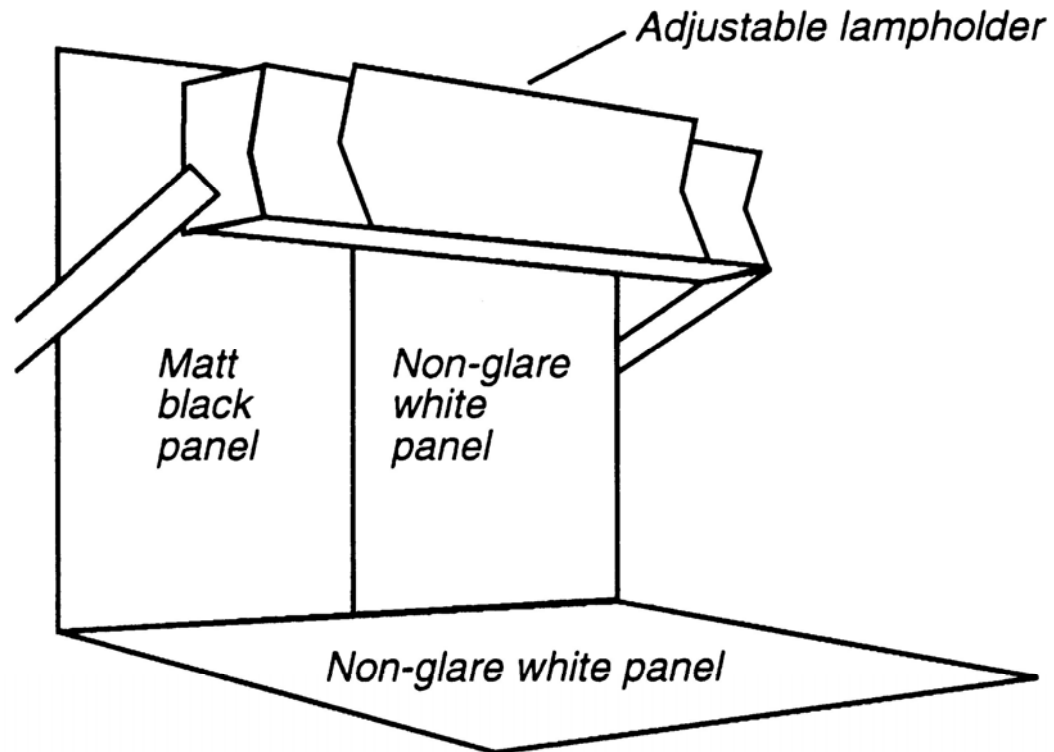
# EC GMP Annex 1 / WHO Annex 6

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- **Finishing of Sterile Products**

EC 90 / WHO 11.3. ... Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

# WHO International Pharmacopoeia



WHO 98430

# WHO International Pharmacopoeia

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- **Apparatus**

- Vertical matte black panel
- Vertical non-glare white panel next to black panel
- Adjustable lamp holder with shaded, white light source and ... a diffuser (... two 13W fluorescent tubes, each 525 mm (20.7 in) in length is suitable). ... illumination at the viewing point is ... between 2,000 and 3,750 lux for clear glass ampoules. Higher values are preferable for coloured glass and plastic containers.

# WHO International Pharmacopoeia

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- **Recommended procedure**
  - Gently swirl or invert each individual container, making sure that no air bubbles are introduced, and observe for about 5 seconds in front of the white panel. Repeat ... in front of the black panel.
  - Record the presence of any particles. Repeat the procedure for a further 19 containers.
  - The preparation fails ... if one or more particles are found in more than one container.
  - When ... applied to reconstituted solutions ..., the test fails if particles are found in more than two containers.

# What is the Problem?

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- Ambiguity!
- Definition of “visible”
  - Inspection conditions
    - lighting, background, duration, magnification
  - size, shape and color
- Definition of “essentially free”

# Particulate Matter vs. Foreign Matter

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- Particulate matter is an intrinsic element of the manufacturing process.
- Intrinsic
  - Formulation, Processing Equipment, Primary Package
    - qualified product contact materials (e.g. stainless steel, aluminum, glass, rubber, silicone oil)
- Extrinsic
  - Environmental Contaminants
    - insect parts, hair, fibers, paint, rust

# Foreign Material Concerns

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- **Physiological**

- Most studies have been conducted with LVP's and particles <10um.
  - These are generally trapped in the capillaries of the lungs. Smallest particles found in liver and spleen.
  - Risk of blood vessel blockage from particles >50um.
  - No direct clinical evidence of health risk from limited particle exposure. Animal studies generally conducted with massive particle loads ( $10^5$  -  $10^{12}$ /kg).
- Very few reports of adverse reactions from particles in IM injections.



# Foreign Material Concerns

---

- **Chemical**
  - Single 100um particle in 1mL dose is equivalent to an impurity level of 4 ppm (v/v)
- **Microbiological**
  - Particles can be carriers for microbiological contamination
- **Process Control**
  - Cosmetic assessment of quality

# PDA TR #37 Task Force

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- Review critical variables in the inspection process
- Define visibility (of particulates) through reference inspection method
  - Manual, single container inspection
  - 500 lux, 18% gray background
  - No magnification
  - Inspection duration TBD

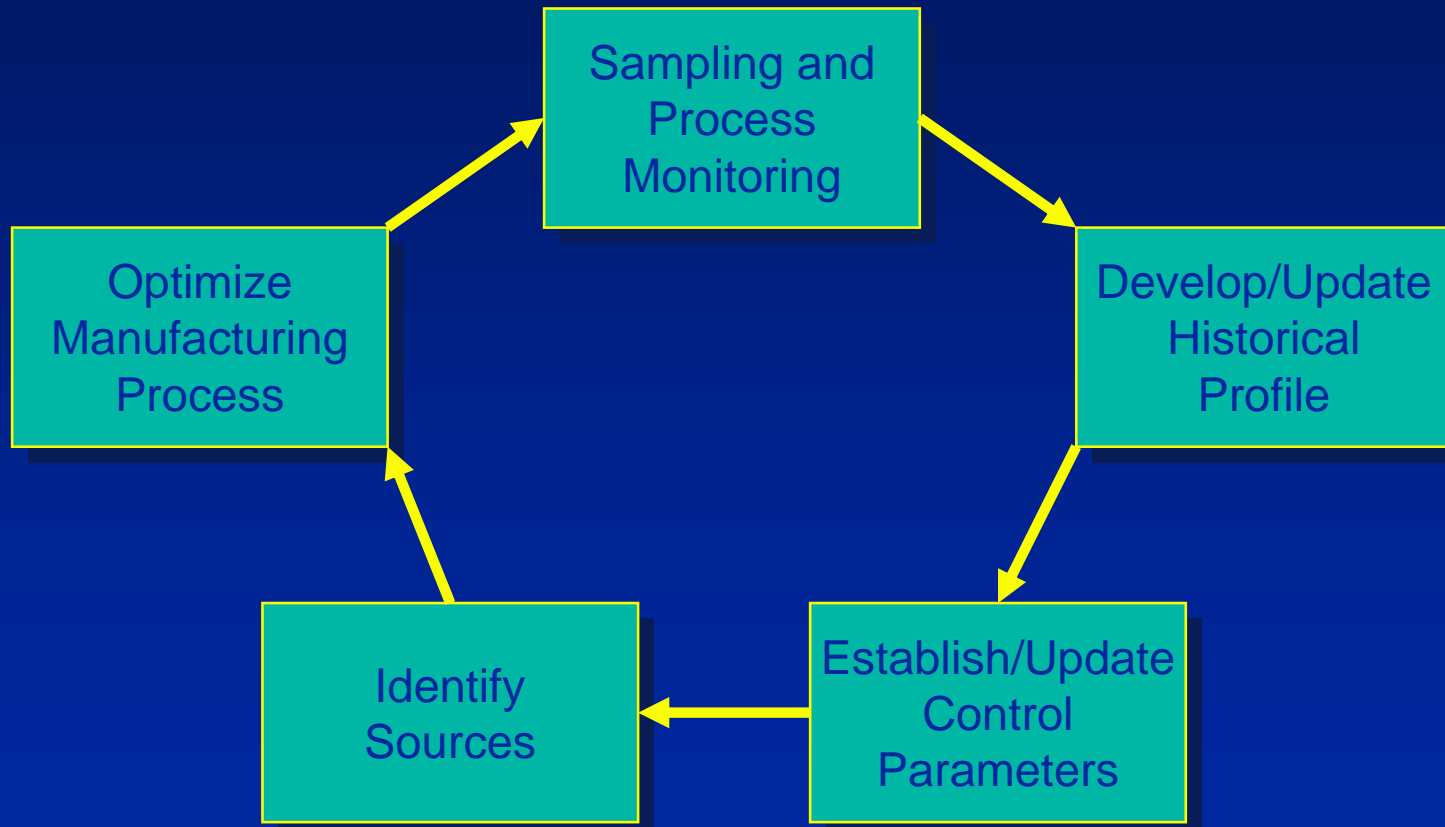
# PDA TR #37 Task Force

---

- Review impact of probabalistic inspection results on acceptance sampling plans and associated AQL values.
- Review particle identification methods and their use in a risk-based inspection plan.

# Particulate Risk Management Program Life Cycle

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# Developing Historical Profiles

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- Particle frequency or the number of rejected units
- Particle classification
  - common categories of matter
  - source of particles
    - Indigenous or intrinsic to the process
    - Foreign or extrinsic to the process
- Particle size

# Particulate Sources

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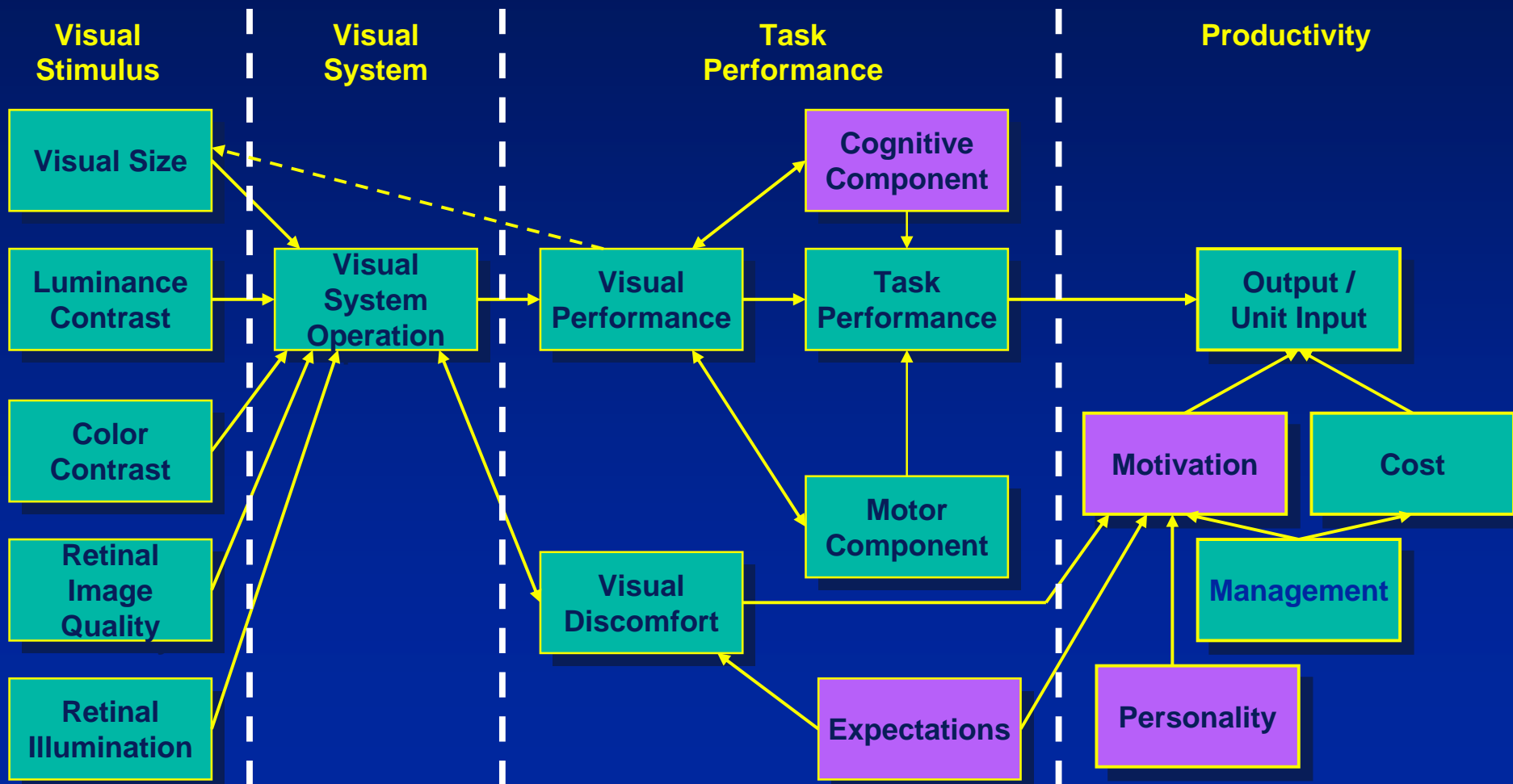
- Particles originate from specific sources:
  - Bulk drug substance
  - Utilities, Water, HVAC, Gases
  - Manufacturing Equipment
  - Processing or Filling Equipment
  - Environment
  - Personnel
  - Cleaning Processes
  - Container / Closure Systems

# Preventive Measures

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- **Filtration**
  - In-line during filling
  - At point of use
- **Vial and Stopper Washing Equipment Design and Operation**
- **Cleanroom Design and Operation**
  - Isolator/Barrier Technology
- **Inspection Technology**

# Inspection



From G. Salvendy, Handbook of Human Factors and Ergonomics, 2<sup>nd</sup> Edition



# Critical Inspection Parameters

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- **Lighting**
  - Illumination Intensity
  - Uniformity and Flicker
  - Type
- **Background**
  - Black / White
  - 18% Gray
- **Presentation and Manipulation**
- **Pace**

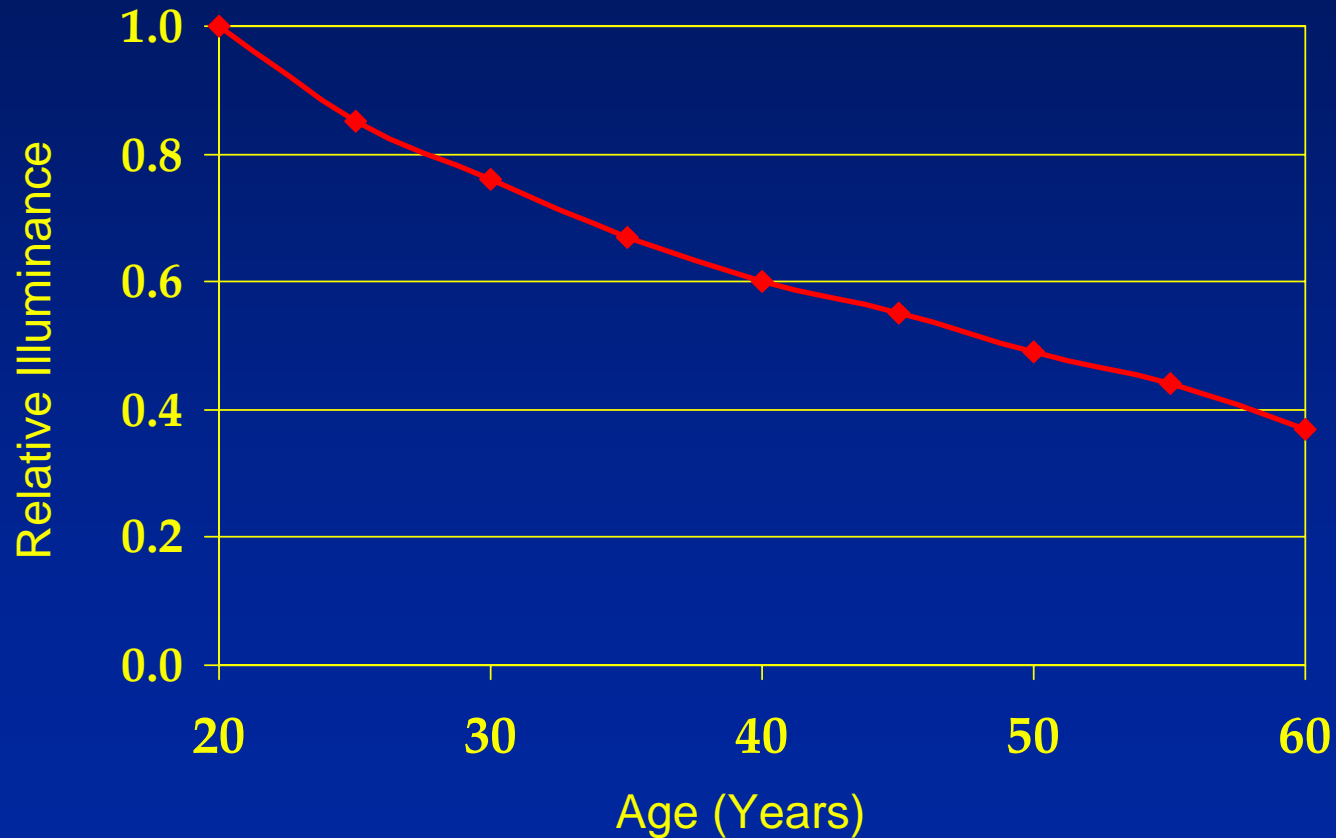
# Illumination Intensity

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- JP
  - 1,000 lux
- WHO
  - 2,000-3,750 lux
- IESNA
  - “Difficult Inspection”, visual tasks of low contrast and small size. 1,000 lux
  - “Exacting Inspection”, visual tasks near threshold. 3,000-10,000 lux

# Aging and Relative Illuminance

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From IESNA Lighting Handbook, 9<sup>th</sup> Edition

# Illumination Type

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- Incandescent
  - No flicker
- Fluorescent
  - Possible flicker
    - HF Ballast
  - Diffuse
- Tyndall
  - Directional
  - Crack detection

# Lighting

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	<u>2003</u>	<u>1996</u>
• Fluorescent .....	56%	45%
• Incandescent .....	15%	25%
• Both .....	26%	25%
• Intensity at container:		
- 65-750 ft-candles / 215 ft-candles median		
- 90-500 ft-candles / 225 ft-candles median		
- 600-7,000 lux / 2,000 lux median		
- 850-4,650 lux / 2,100 lux median		

# Manual Inspection

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	<u>2003</u>	<u>1996</u>
• Paced .....	56%	80%
• Magnification .....	31%	45%
- (1.3-5x, 2x avg.)		
• Clip/Grouped .....	22%	30%
- number per group (2-15, 6.5 avg.)		
• Polarizer .....	4%	25%

# Manual Inspection Rate

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- Molded Glass Vials

- 1 to 10 mL ..... 0.7-4 sec / 2 sec median  
1-20 sec / 6 sec median
- 11 to 100 mL ..... 1-28 sec / 6 sec median  
0.5-20 sec / 7 sec median
- >100 mL ..... 1-4 sec / 3 sec median  
1-20 sec / 7 sec median

# Manual Inspection Rate (cont.)

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- **Tubing Glass Vials**

- 1 to 10 mL ..... 0.7-60 sec / 8 sec median

- 0.5-20 sec / 7 sec median

- 11 to 100 mL ..... 1-60 sec / 15 sec median

- 0.5-20 sec / 8 sec median

- **Glass Ampoules** ..... 4-42 sec / 4 sec median

- 3-20 sec / 11 sec median



# Inspection Standards

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# MYTHBUSTERS

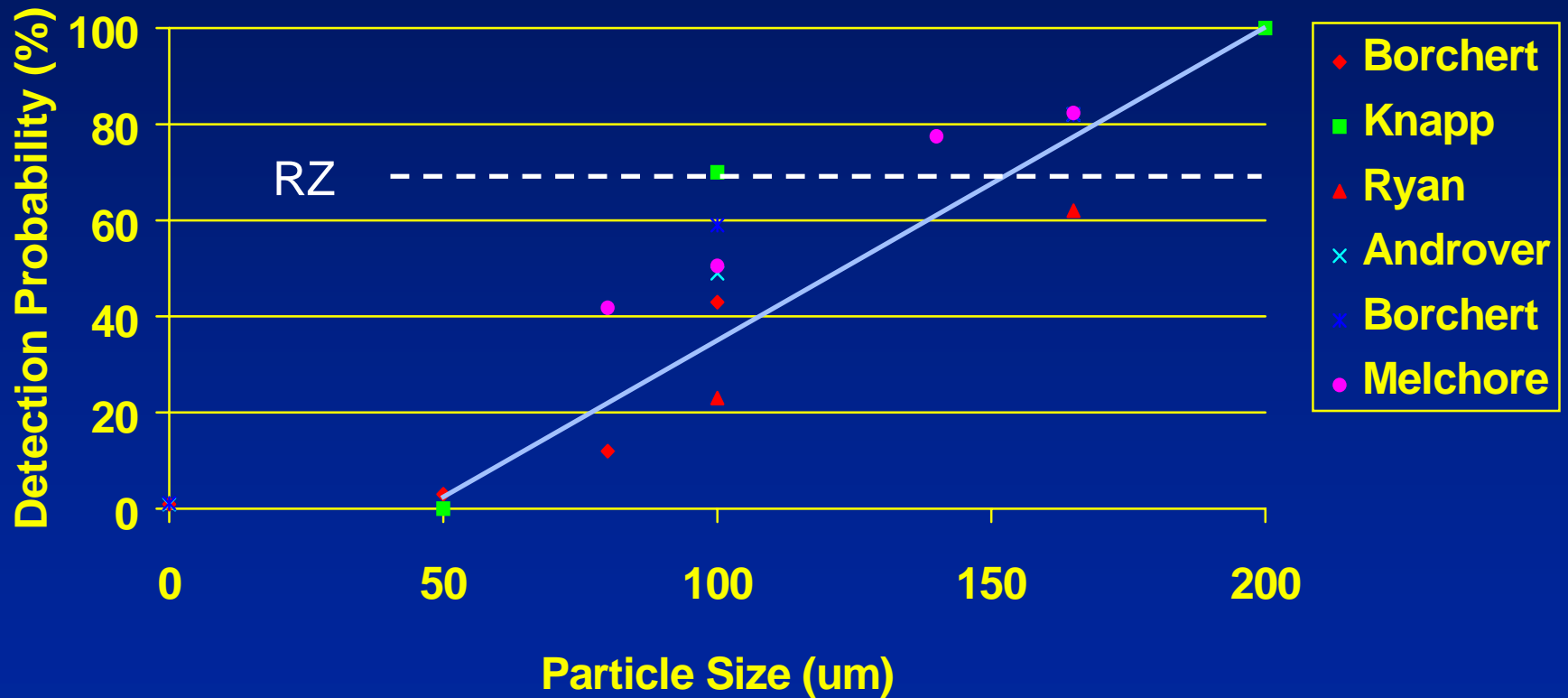


# Inspection Myth #1

---

- 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 <200um 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 condition and defect characteristics.
  - Particles  $< 100 \mu\text{m}$  generally have a detection probability  $< 100\%$ .

# Inspection Myth #2

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

# Inspection Myth #3

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- 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

---

- 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 particular or container defects with 3x magnification.

# Conclusions

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- Current industry performance is generally at or beyond limits of medical risk.
- Compendial guidance is ambiguous.
- “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.

# Acknowledgments

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- PDA TR #37 Task Force
  - Julius Z. Knapp – R&D Associates
  - Roy T. Cherris – Bridge Associates International
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- Rap.ID Particle Systems, GmbH
  - Markus Lankers

**BEAUTIFUL,  
BUT OBSOLETE.**

