Effect of Entrained Air on Automated Visual Inspection of a Virus Vaccine

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Outline

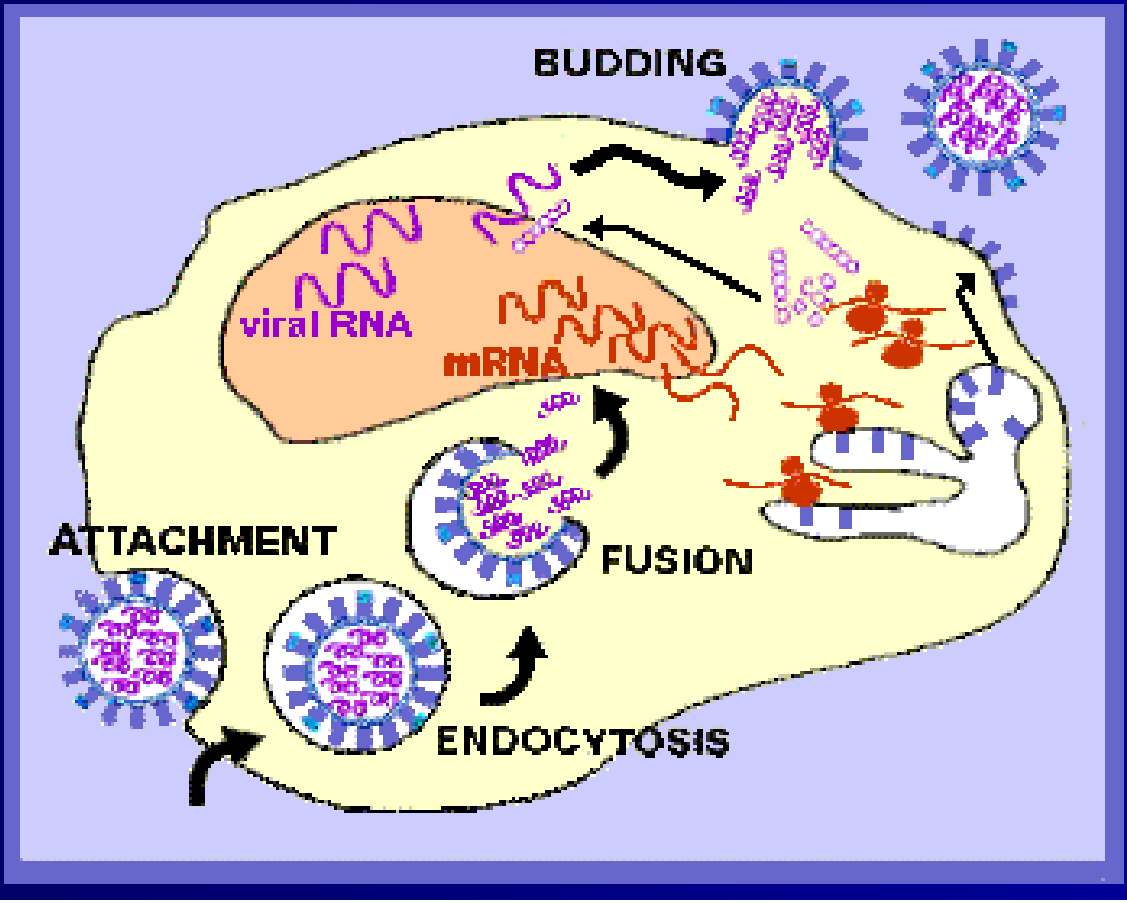
- Introduction
- Virus Biology
- Vaccine Manufacture
- Inspection of Final Containers
- Defective Final Containers
  - Syringes
  - Vials
- Perspective and Challenges
- Case study
- Conclusions

Virus Biology – Origin

- Where did viruses originate?
  - from free-living organisms like bacteria
  - from the host cell DNA or RNA molecules
  - evolved along with the most primitive molecules that first contained self-replicating abilities
- Actually – we don't know!

Virus Biology – Replication

- Life cycle of the Influenza Virus



Virus Biology – Disease

- Infections caused by viruses
  - Colds
  - Flu
  - Most coughs and bronchitis
  - Sore throats (except for those resulting from strep throat)
  - Some ear infections

Source: http://www.cdc.gov/getsmart/antibiotic-use/anitbiotic-resistance-faqs.html

Virus Biology

Bacteria vs. Virus

- Bacteria are free-living. A virus must replicate in a host cell.
- Disease-causing bacteria trigger illnesses, such as strep throat, whooping cough, and some ear infections
- Most bacterial diseases can be treated by antibiotics.
- Antibiotics do not treat viral diseases

Virus Biology

Characteristics of novel A(H1N1) virus

- Transmission of novel A(H1N1) is similar to seasonal influenza
- Clinical signs and symptoms similar to seasonal influenza, but with higher rates of nausea/vomiting and diarrhea
- Novel A(H1N1) is genetically different from the A(H1N1) strain included in seasonal influenza vaccines
  - **Receipt of recent (2005-2009) seasonal influenza vaccines is unlikely to elicit a protective antibody response to the novel A(H1N1) virus**
  - **Cross-reactive antibody detected only in adults aged >60 years (33%)**
- Susceptibility
  - **Uniformly resistant to adamantanes (eg, amantadine and rimantadine)**
  - **Susceptible to oseltamivir and zanamivir**
    - **Rare sporadic cases of oseltamivir resistance have been detected worldwide**

http://ecdc.europa.eu/en/files/pdf/Health_topics/090509_AH1N1_Threat_assessment.pdf
http://www.cdc.gov/mmwr/PDF/wk/mm5819.pdf

Vaccine Manufacture

- Growth/propagation of antigen-producing strain
  - Influenza: grown in eggs
- Inactivation and purification
  - Separation of “antigens” from substrates used for propagation.
  - Specific treatment to render “antigens” non-viable

Vaccine Manufacture

- Formulation
  - Combination of “antigens” typically with saline to achieve the desired dose.
- Filling
  - Transfer to the final container under aseptic conditions
- Inspection
  - Examination of 100% of final containers
- Packaging and Distribution

Background Review

- USP <1> Injections
  - Prepared to exclude particulate matter Inspected to the extent possible for “visible particulates Essentially free from visible particulates Every container whose contents shows evidence of visible particulates shall be rejected. The inspection for visible particulates may take place when inspecting for other critical defects
- USP <788> Particulate Matter in Injections
  - Particulate matter consists of mobile, randomly-sourced, extraneous substances, other than ***gas bubbles***....

Source: United States Pharmacopoeia

Background Review

- Automated inspection
  - Machines are fast and consistent; however,
  - Machines cannot discriminate efficiently between a defect such as a bubble or a surfaces blemish (bruise/scuff)
- Human inspection
  - Slow and consistency depends on training, visual acuity, and other human factors; however
  - Humans can fabricate defects and recognize the difference between a bubbles and a particle or other defect

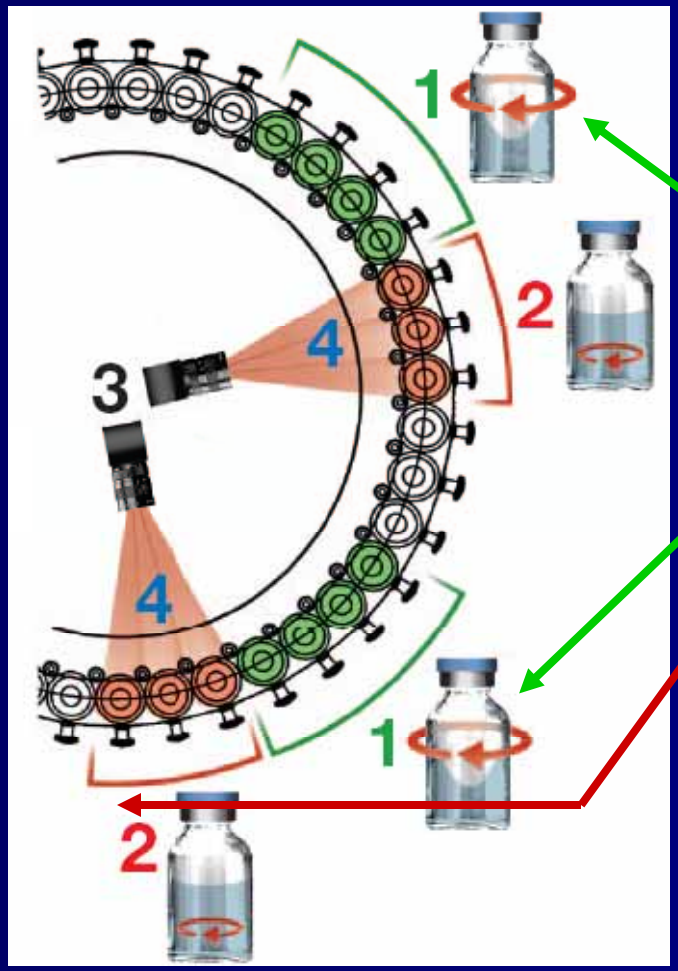
Manufacturing Practices and Trends for Inspection

- Production volume and practice
  - Only 10% of manufacturers produce greater than 100 million units
  - A minority of manufactures (16%) perform inspection in-line with filling
  - Manual inspection rates – 5 to 6 seconds (median)
- Industry trend
  - Automated inspection will increase to improve productivity and quality
  - Tighter regulatory requirements will evolve and impact inspection practices.

Source: A Survey of Industry Practice for the Visual Inspection of Injectable Products[12] (Preliminary Report) Ronald L. Leversee & John G. Shabushnig, Ph.D. October 15, 2008

Inspection of Final Containers

How Visual Inspection Systems Function

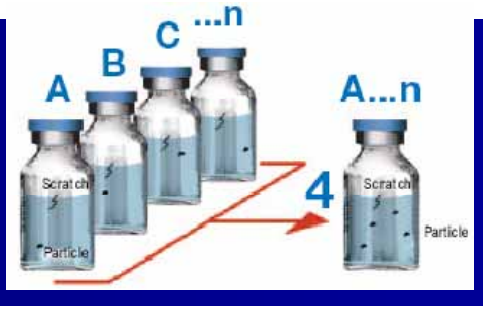


Inspection Machine Seidenader XS

Particle Inspection

Each product is inspected in two particle inspection stations using the image subtraction method:

1. Vials are rotated.
2. The rotation of vial is stopped, the liquid continues to move, particles move with the liquid.
3. A static CCD camera acquires multiple images.
4. The vision processor generates an overlay image to separate all objects which have moved between the images.

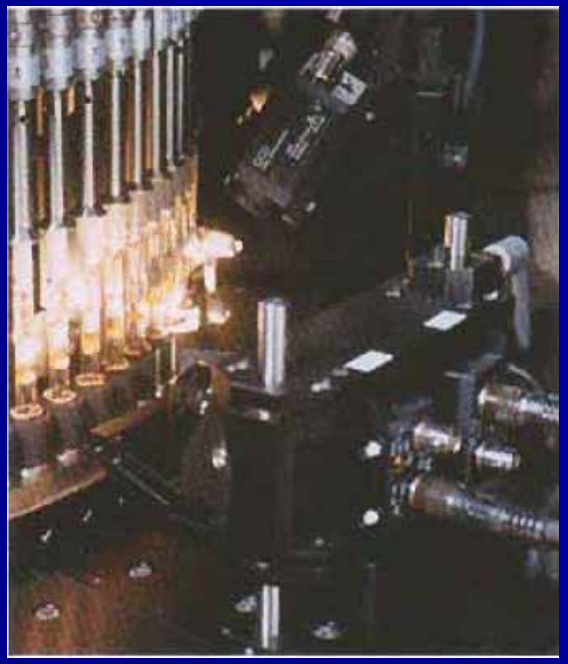


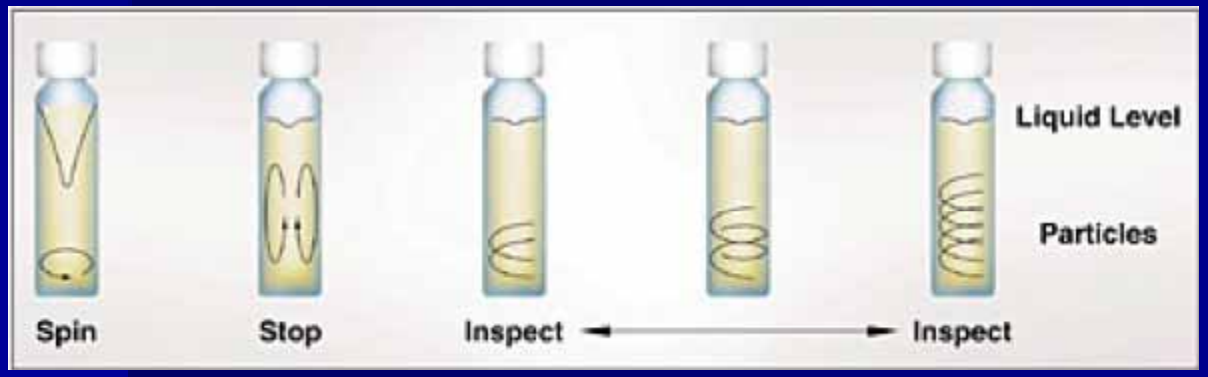
Inspection of Final Containers

How Visual Inspection Systems Function

Particulates:

Non-particulated (cosmetic)





Inspection of Final Containers

Rationale for defect classification

- **Critical**: Nonconformities likely to result in personal injury or potential hazard to the patient – a compromise to container integrity.
- **Major A**: Nonconformities leading to serious container impairments, e.g., a malfunction making packaging unusable.
- **Major B**: Nonconformities leading to container impairments of a lesser degree, for example, reduced efficiency in production.
- **Minor**: Non conformities that do not impact product quality or process capability.
- **N/A:** Imperfections that are considered to be nonapplicable or non-defects and are therefore acceptable.

Inspection of Final Containers
Defects

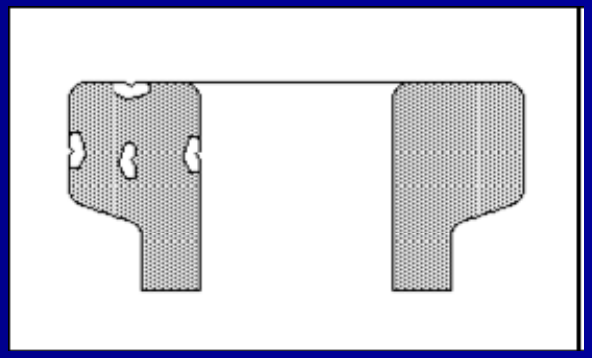
Crack “Critical”

Fracture penetrates completely

Chipped “Major”

Container with a section or fragment broken out (other than sealing surface).

Bubble “Minor”



Public Perspective and Challenges

- "The "fill-finish" step … is a major hurdle on the path to vaccine distribution to providers, and … proves to be a major rate-limiting step in the process of delivering vaccine, especially under pandemic conditions."

  Source: Report to the President on reengineering the Influenza vaccine enterprise to meet the challenges of pandemic Influenza. August 2010

- "Vaccine started rolling out in October and the U.S. eventually ordered 229 million doses from its five licensed makers….."

  Source: Reuters, Tue May 4, 2010

Case Study

- Observation
  - Reject rates for a clear solution product ranged from 15% to 50%.
  - Multiple products
- Technical
  - High volume production (> 100 million units)
  - Inspection in-line with filling.
- Compliance
  - USP <1> and other regulatory requirements
  - Area of intense interest for regulatory authorities.

Case Study – Observation
Actual defect rates

Automated		
Lots Inspected: n = 24		
Acceptable	96.49%	
	Machine Judged Defects (%)	Actual Defects (%)
Critical & Major	1.71%	0.15%
Major (Particulate)	1.72%	0.05%
Minor	0.08%	0.08%
Total	3.51%	0.28%

Semi Automated		
Lots Inspected: n = 7		
Acceptable	98.82%	
	Human Judged Defects (%)	Actual Defects (%)
Critical & Major	0.77%	0.54%
Major (Particulate)	0.05%	0.01%
Minor	0.36%	0.36%
Total	1.18%	0.91%

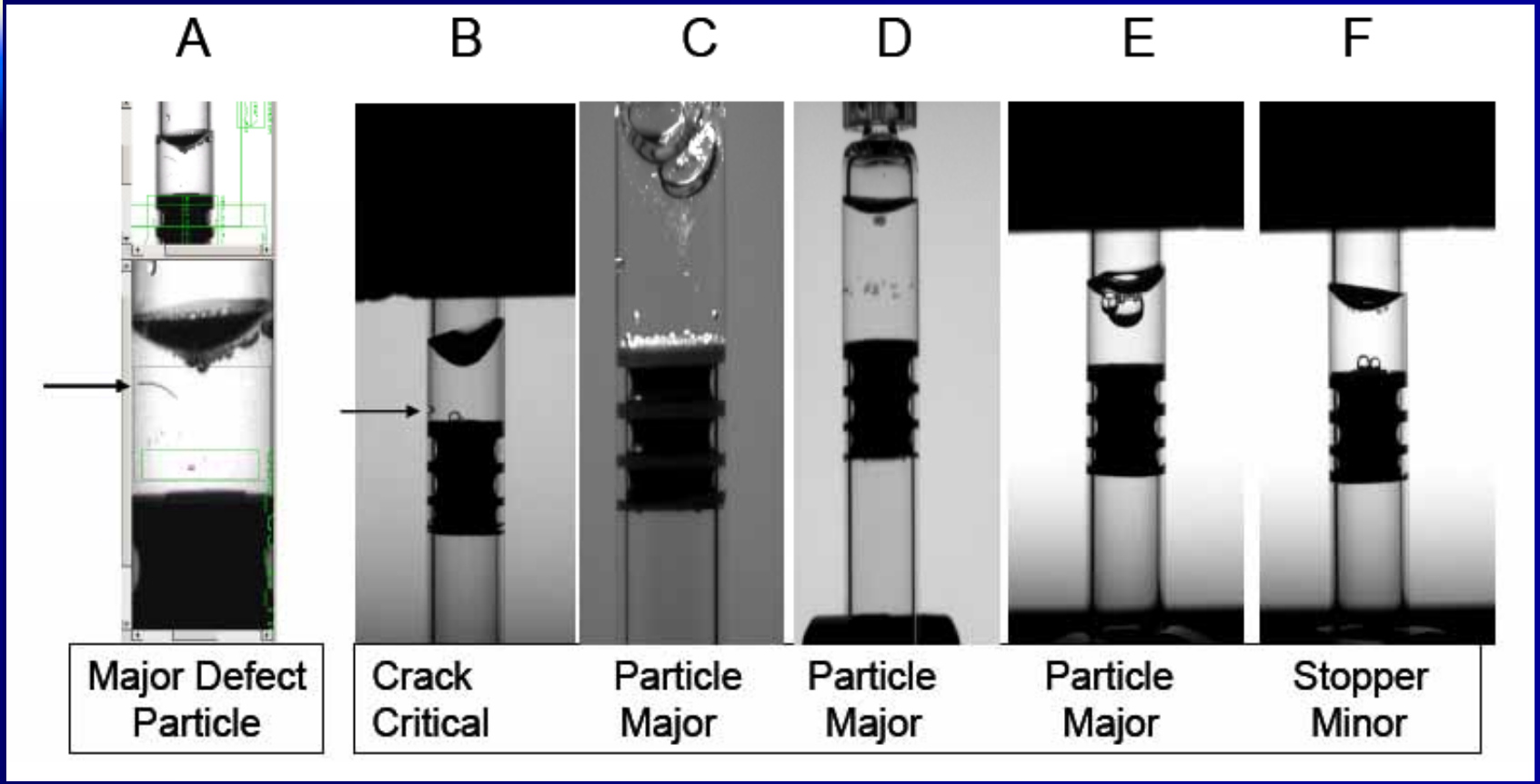
Case Study – Observation
Actual defect rates

Lots Inspected: n = 1		
Acceptable	85.18% (n = 68,462)	
	Machine Judged Defects (%)	Actual Defects (%)
Non-Particulate		
Critical	11.069%	0.045%
Major		0.834%
Minor		3.531%
Major (Particulate)	3.751% (n = 2568)	0.004% (n = 3)
Total	14.82% (n = 10,266)	4.41% (n = 3,022)

Case Study – Investigation

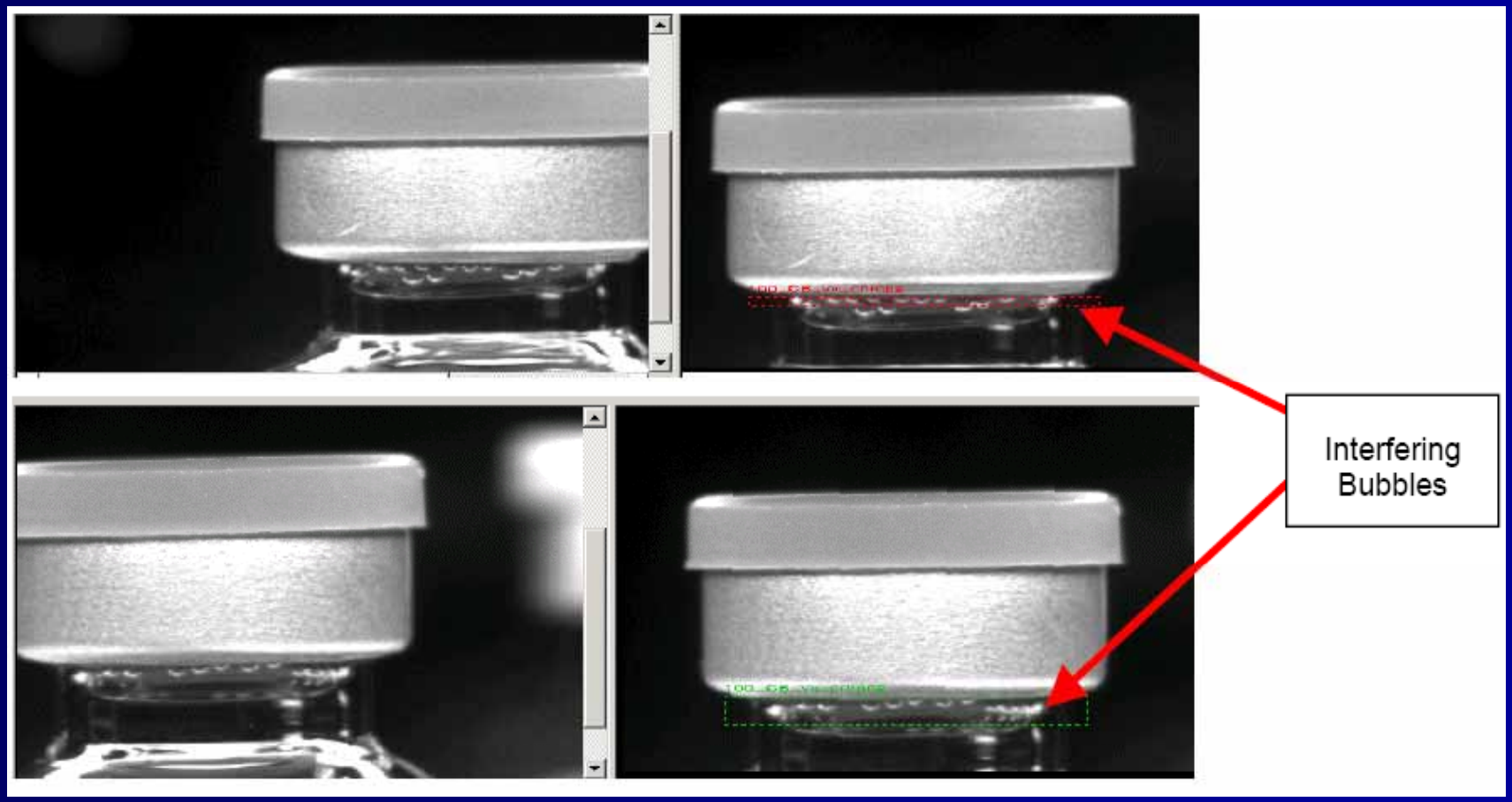
- Bubbles interfere with automated inspection and cause inaccurate inspection results
- Automated inspection machines cannot distinguish between a defect and a bubble.
- Bubbles are mistaken for all defect categories
  - Critical
  - Major
  - Major Particulate
  - Minor

Case Study – Observation
Rejected syringes



A. Particulate (defect); B – F No observable defect

Case Study – Observation
Rejected vials



Machine reject – malformed crimp (bubbles)

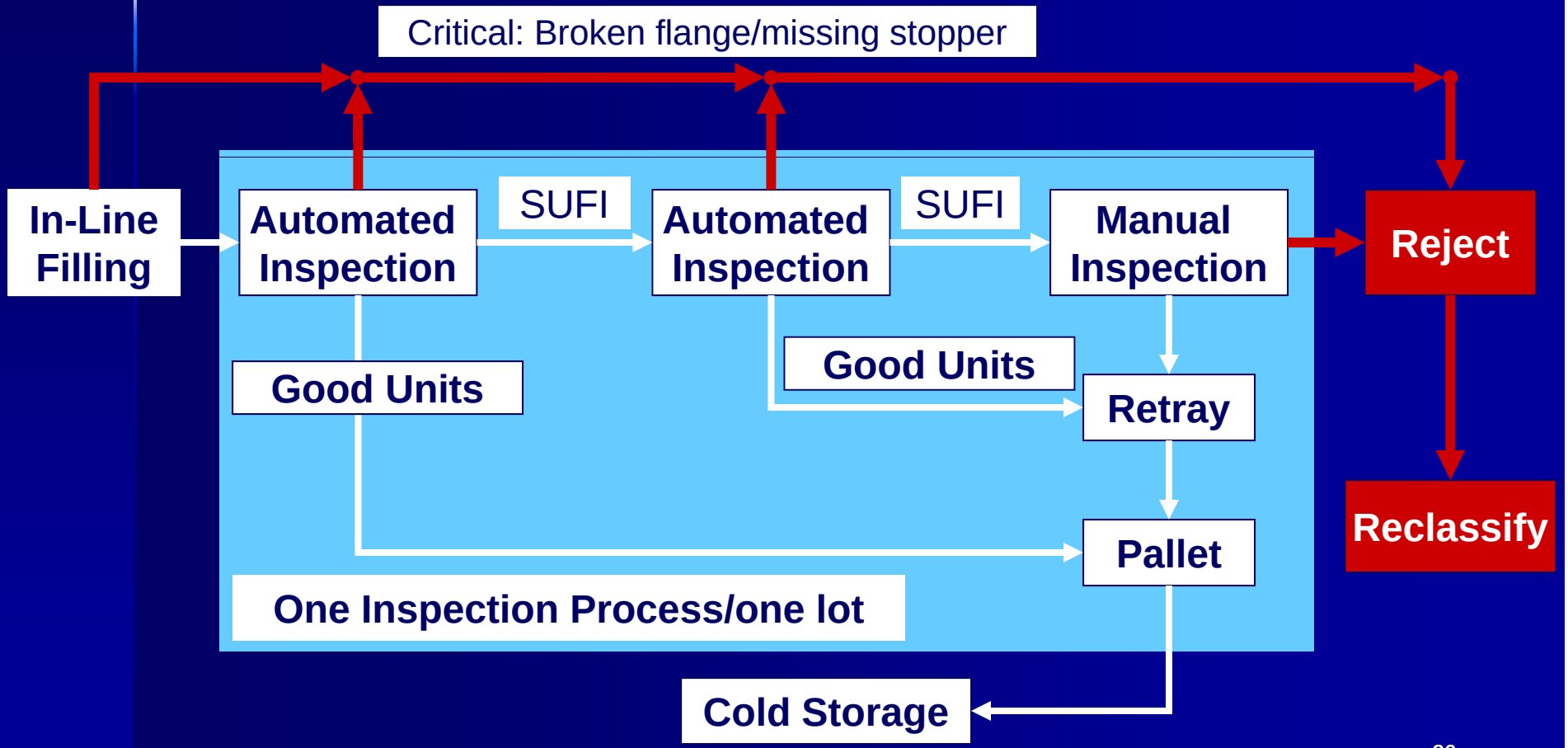
Case Study – Response

- Delay between fill and inspection reduced bubbles
  - impractical for inspection in-line with filling.
- Three-step inspection process
  - **Step 1 –** Segregate final containers and classify as ***Suitable Units for Further Inspection*** (SUFI).
  - **Step 2 –** Automated inspection of units segregated in Step 1.
  - **Step 3 –** Human inspection of units segregated from Step 2.

Case Study – Quality Considerations

- Technical basis and rationale
- Process definition
- Product segregation
- “Rejection” is definitive
- Lot Acceptance Criteria (AQL)
  - Defined and consistent
- Operator training
- cGMP documentation

Case Study – SUFI Process Flow



Case Study – Trial Run

Lots Inspected: n = 1 (280,141 syringes)	Cumulative Totals		
	Step 1	Step 2	Step 3
Acceptable	241,299	259,445	267,092
SUFI	36,829	17,805	N/A
Rejected	2,013	2,891	13,049

Acceptable	86.1%	92.6%	95.3%
SUFI	13.1%	6.4%	N/A
Rejected	0.7%	1.0%	4.7%

Note: Stopper improperly placed ≈ 4%

Conclusions

- Automated inspection machines are qualified to detect particulates equal to or better than human inspectors.
  - Actual rates for particulates in syringes range from 0.004% 0.05%
- Bubbles affect automated inspection and can misrepresent true defect rates
  - Critical: side wall “crack.”
  - Major: particulate and *non-particulate*
  - Actual defect rates are less than 1%.

Conclusions

- Multi-step inspection increases efficiency by preserving final containers that are not defective.
- Human inspection verifies actual defects.
  - Human inspection forms the basis for automated inspection.
- Rejected units that are predominantly defective greatly increases the effectiveness of reclassification and remediation.

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