

# Visible Particles from Polysorbate Degradation

Cases & Perspectives



# Particles & Parenterals – not best friends

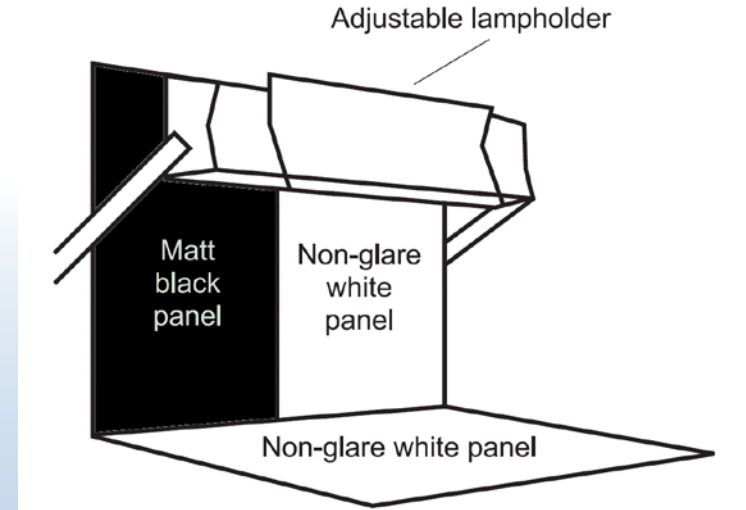
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## Particles...

- represent an obligatory cQA for parenteral products
- are often a focus topic in audits and inspections
- are still the major reason for product recalls
- aspiration of zero visible particles is desirable, but unrealistic

# USP <790> Visible Particulates in Injections – Manual Visual Inspection

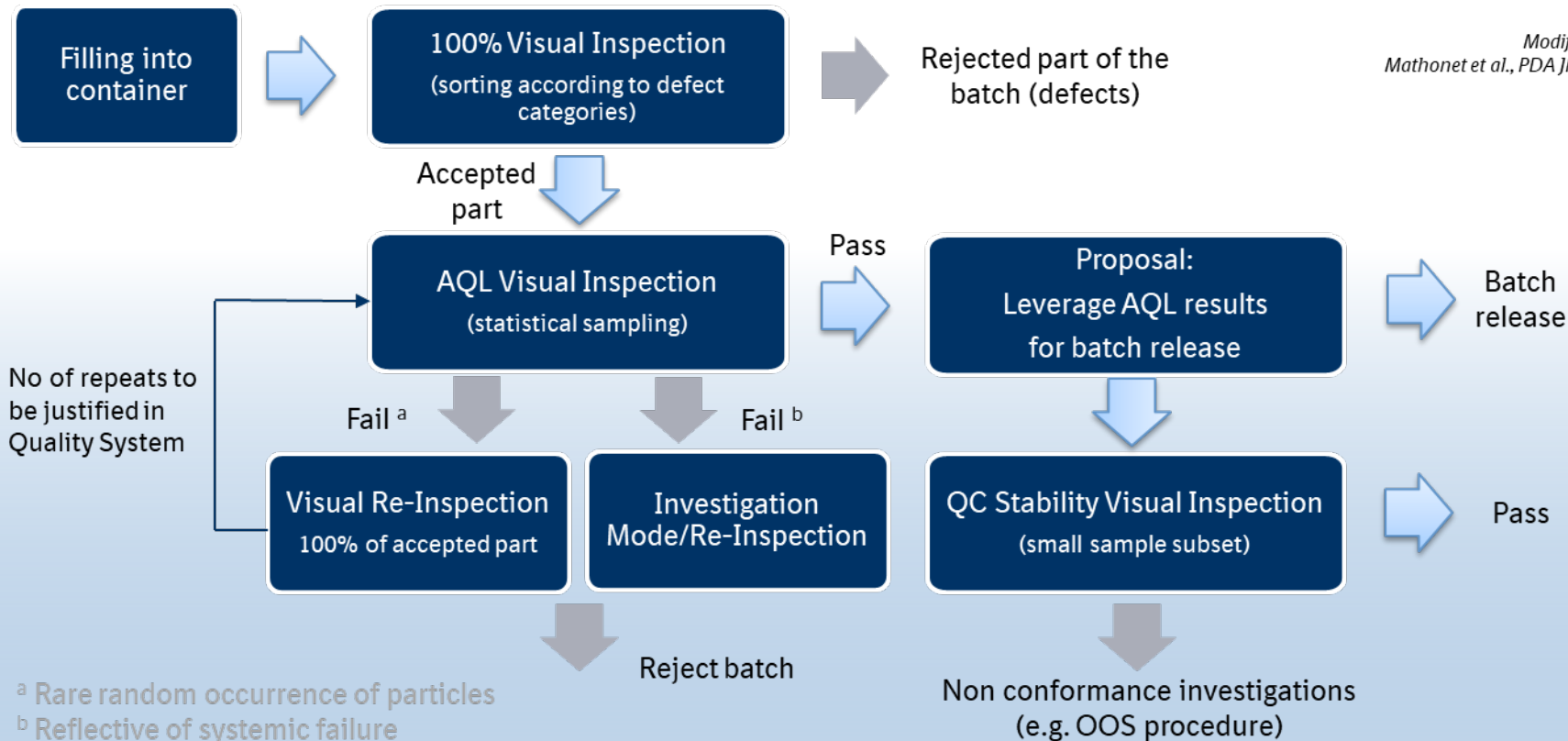
- Standardized procedure: unaided human eye, light box, controlled light intensity (2000 – 3750 lx)
- Analysis upon gentle agitation (e.g. swirling)
- Well trained operators:
  - Periodic eyesight tests
  - Initial and continuous training
  - Performance qualification
  - Periodic performance control



*Ph. Eur. 2.9.20. "Particulate Contamination: Visible Particles"*

Issue: No clear and harmonized definition of visibility available

# Visual Inspection – Process Flow Scheme for Liquid Products



Modified from:  
Mathonet et al., PDA JPST, 2016



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Case study:  
Visible Particles in Biopharmaceutical  
Development Products

# Case Study: Visible Particles in Biopharmaceutical Development Products

## Initial optical characterization

- Large particles
- Translucent to whitish
- Amorphous shape
- Neutral buoyancy
- Freely moving in solution
- Mainly disappear at RT



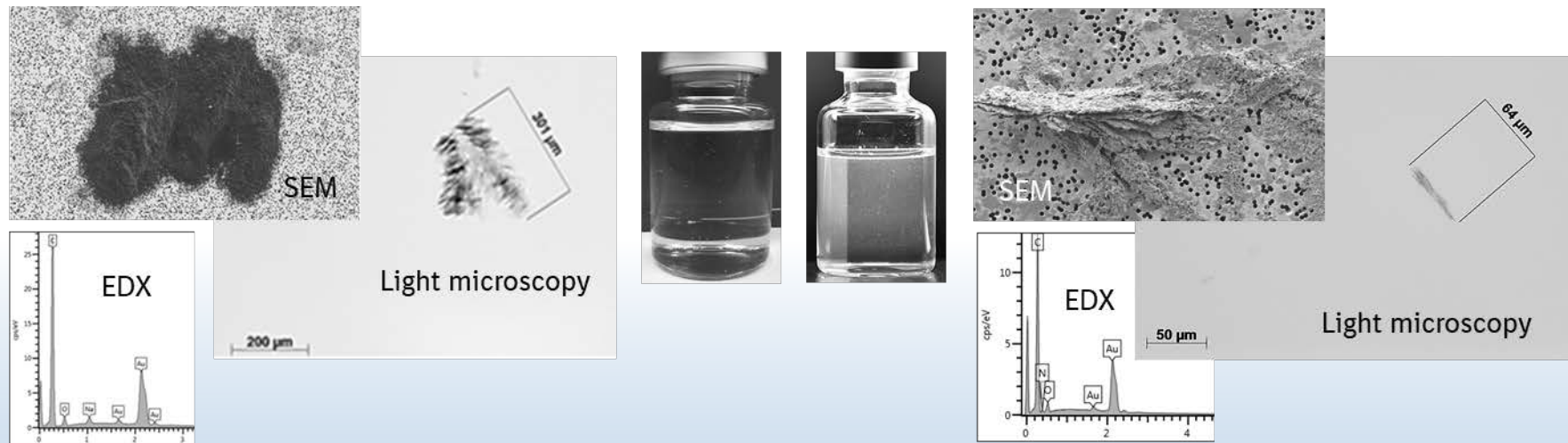
## Initial optical characterization

- Many very small particles (only under enhanced lighting)
- Highly translucent
- Neutral buoyancy
- Freely moving in solution
- Glittering under stray light



Nature of the particles?  
Root cause for formation?

# Case Study: Particle Forensics – Morphology & Elemental Composition

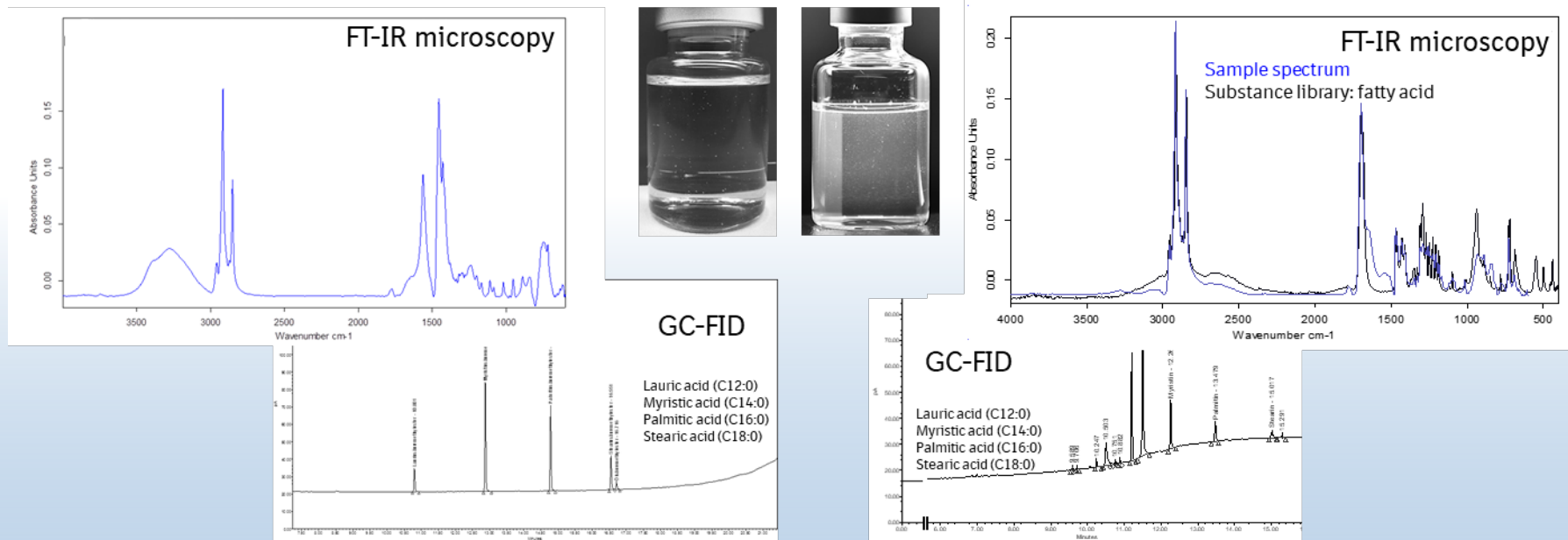


Most particles around 300µm  
Attached fibred and crystalline structures  
Fragile, partially dissolved during preparation

Particle size below 70µm (→ subvis. methods)  
Atypical thin needle like shape, possibly crystalline  
Stable at RT and upon filtration/washing

**Observed particles are very likely of non-proteinaceous composition**

# Case Study: Particle Forensics – Chemical Composition

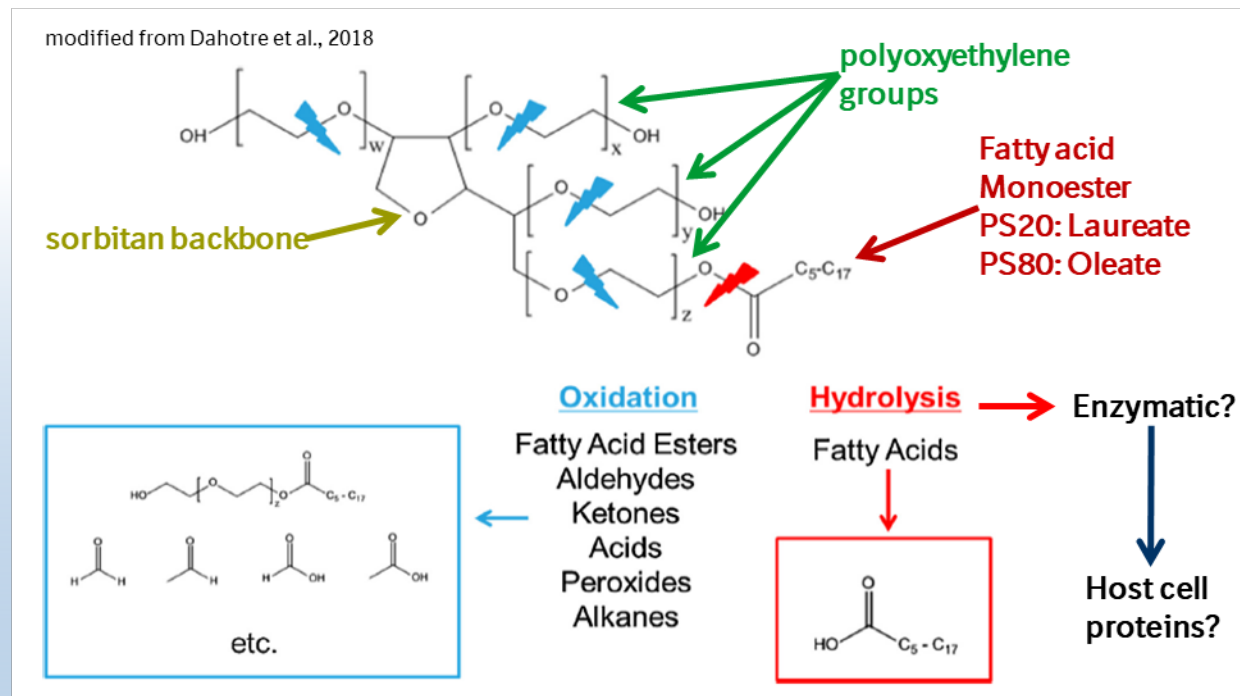


No typical protein spectrum, strong match with long chain fatty acids  
Fatty acid composition of particles typical for polysorbate 20



# Case Study: Source of Free Fatty Acids – most likely PS20

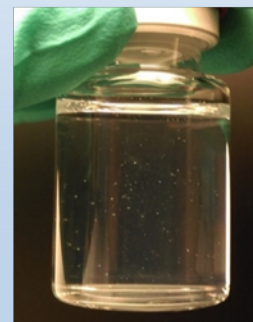
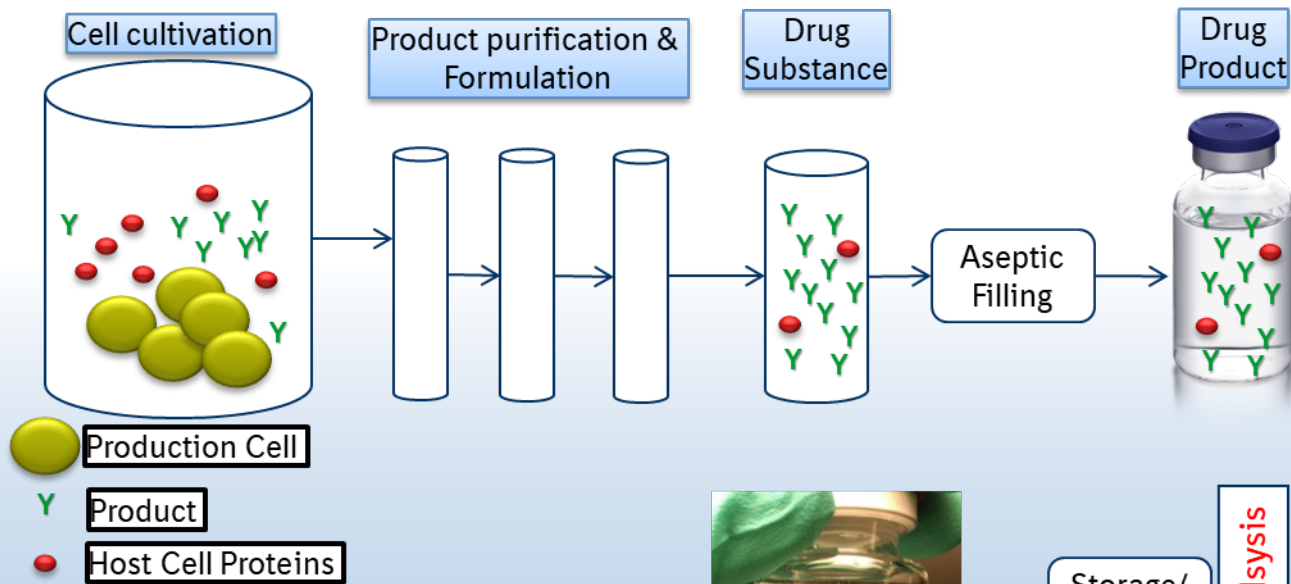
Polysorbates can be degraded via different mechanisms



Fatty acid component	USP42 (%)
C6:0	≤1.0
C8:0	≤10.0
C10:0	≤10.0
C12:0	40.0–60.0
C14:0	14.0–25.0
C16:0	7.0–15.0
C18:0	≤11.0
C18:1n-9	≤11.0
C18:2n-6,9	≤3.0

PS20 is a complex mixture, not a well-defined substance

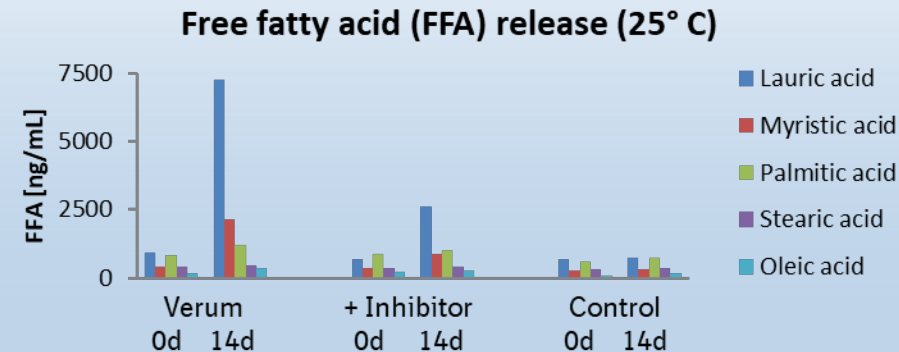
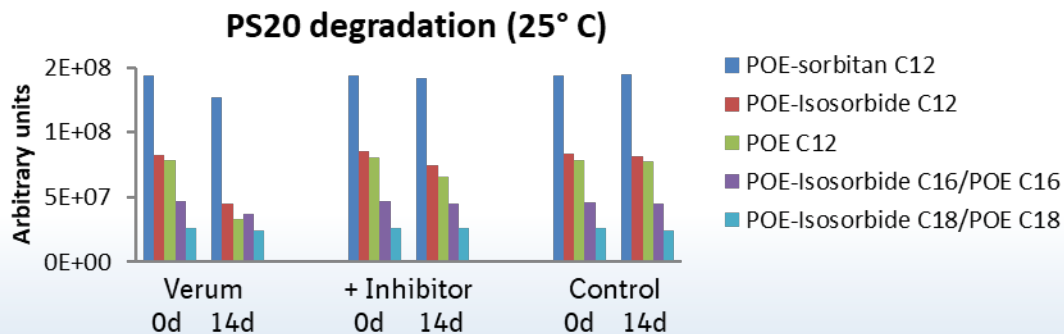
# Case Study: Root Cause within the Manufacturing Process?



Storage/  
Stability

polysorbate hydrolysis

# Case Study: Mechanism of PS20 Degradation



near-complete inhibition of PS hydrolysis by Serine Hydrolase Inhibitor:



confirmation of enzyme as main root cause for polysorbate degradation

# Case Study: Visible Particles in Biopharmaceutical Development Products



Nature of the particles:  
mainly fatty acids, partly dissolve at RT

Root cause for formation  
enzymatic PS20 degradation

# Acknowledgements

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Ingrid Auernhammer

Florian Baiz

Martin Dass

Thomas Ehrmann

Beate Eyrich

Cornelia Gapp

Patrick Garidel

Julia Groß-Rother

Felix Halbach

Peter Happersberger

Silke Hövel

Werner Kliche

Marius Löffler

Theresa Müller

Dagmar Rädcl

Katrin Reinhardt

Markus Riegger

Thomas Schwab

Maik Veelders

Peter Wanja

Till Wenger

Robert Wild

Justine Witosch

and many more...



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