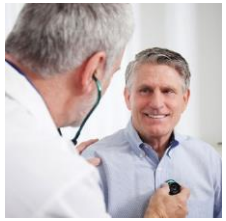
European Federation of Pharmaceutical Industries and Associations

# CMC Strategy Forum Europe 2021

# Polysorbate Degradation and Mitigation / Control Strategy Considerations

Klaus Wuchner & Linda Yi on behalf of Polysorbate Workstream, 18th Oct 2021






EFPIA MQEG Biomanufacturing Satellite Session

# Thanks

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Gianluca Rinaldi, Merckgroup

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Sarah M Richer, Lilly

Sebastian Peuker, Bayer

Shawn Cao, Amgen

Sonal Saluja, Biogen

Sylvain Huille, Sanofi

Tingting Wang, Lilly

Virginie LeBrun, Lonza

**To date 16 Companies**

**22 active team members**

# From industry survey to position paper

## PS Industry Survey (137 questions, 27-page survey)

A. Use of surfactants for biological products, incl. new grade PS – general aspects

B. Polysorbate raw material for cGMP use

C. PS handling during cGMP manufacture

D. Degradation of polysorbate in biological products (including proteins and synthetic peptides) and placebos

E. Analytical methods for of polysorbate in products

F. Mechanistic Understanding of PS degradation and detectability

G. Model systems/Predictive models

H. Mitigation strategies

I. Safety / toxicology

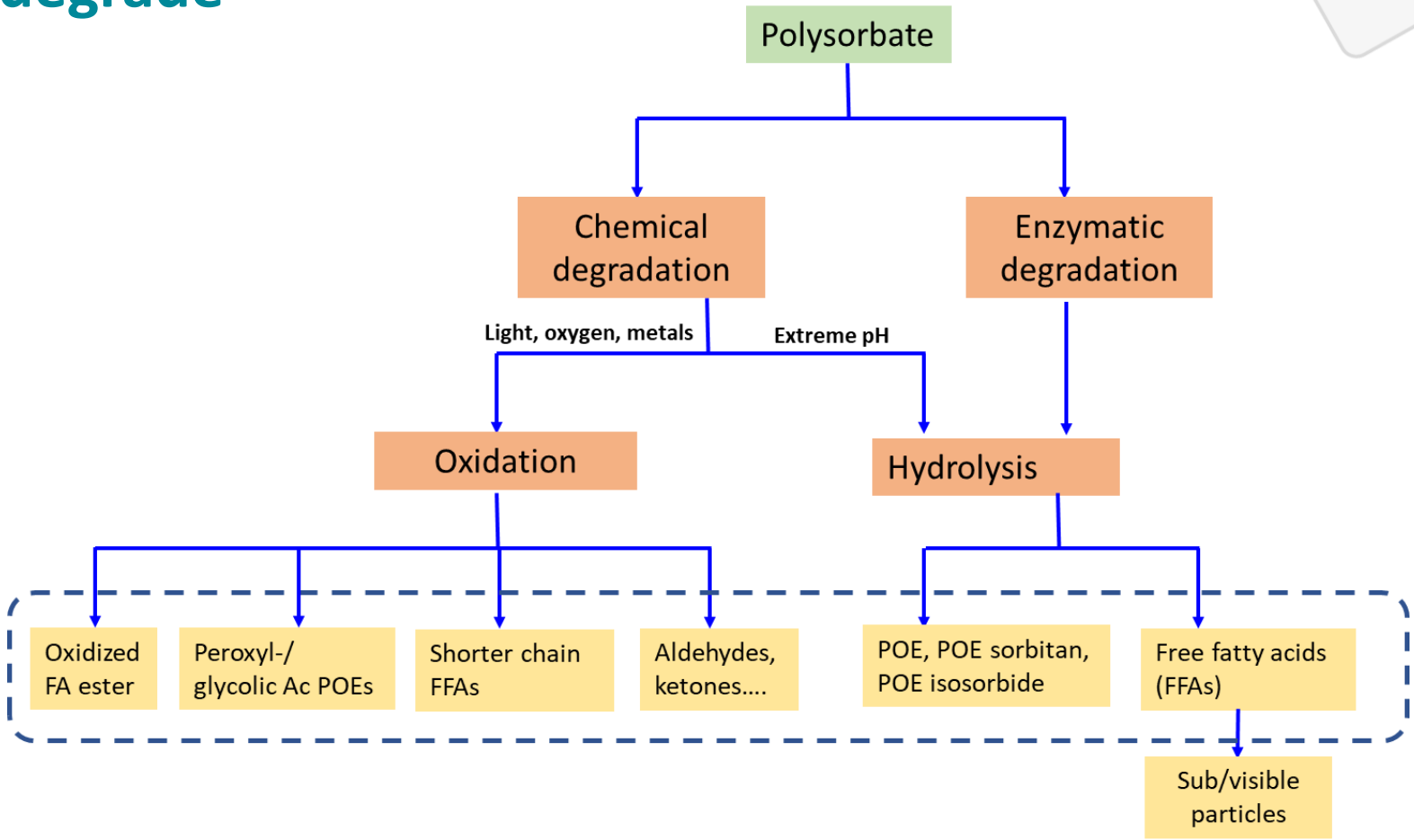
J. Regulatory interactions related to PS / PS degradation / Particle Formation / Specifications

Deep dive of survey results, literature review, lots of team discussion

## Manuscript being drafted: Industry perspective on the use and characterization of polysorbates for biopharmaceutical products

- Part 1 of Survey Report: Current state and common practices for handling and control of polysorbates
- Part 2 of Survey Report: A control strategy preparing for the future

# Polysorbates (PS) in biopharmaceutical formulations may degrade




- PS may degrade via two major pathways, and affect product quality, stability, and shelf life.

# Survey – First indication of PS Degradation in biological products

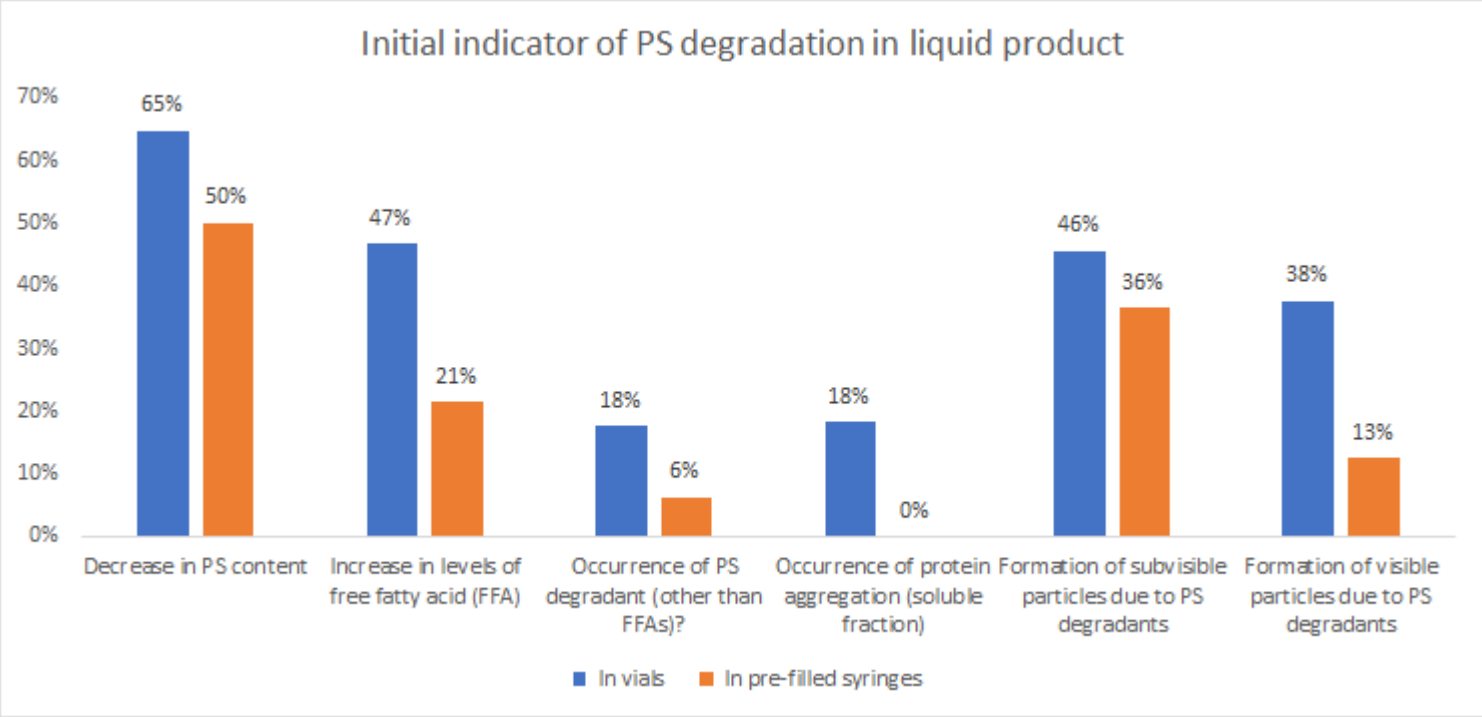



Figure from manuscript in preparation

- "Decrease in PS content" was found to be the first indicator for liquid protein-based products (both vials and pre-filled syringe presentation)
- This was followed by increase in levels of free fatty acids (FFAs) and the formation of subvisible or visible particles
- Occurrence of other PS-related degradation products are less frequent indicators probably because of the lower routine use of specific methods
- Protein aggregation not an indicator for PS degradation

# Mitigation strategies based on PS degradation pathway

Mitigation strategies to eliminate or at least reduce PS degradation are used by most companies, sometimes in a phase appropriate approach (e.g., after successful proof-of-concept)

- Decrease of the PS content below certain threshold was consistently reported to be the trigger for further investigations and mitigation measures
- Formation of unacceptable levels of subvisible or visible particles is one of the main relevant triggers for PS mitigation strategies
- Highly effective mitigation strategies are available for PS oxidation with simpler changes in formulation (e.g., addition of chelator, antioxidant)
- Effective mitigation strategies for enzyme-induced PS hydrolysis are more labor intensive and may involve more dramatic changes (e.g., changes in DS purification process)
- FFAs / PS degradant related particle formation may be acceptable to a certain extend (no tox/safety concerns) if no other CQA is impacted and if appropriate particle controls are implemented
- Switch to a lyophilized drug product presentation (no PS degradation observed) if nothing else helps

# Control Strategy based on PS degradation pathway

Control strategies are in place and are further developed to prevent unacceptable consequences of PS degradation

- PS manufacturers should control FFAs and FA-esters and other low soluble impurities beyond compendial requirements (e.g., C20 esters)
- Maintenance of consistent quality of PS raw material is important: using smaller PS container size, consistent protection from light and oxygen and reduced sampling and testing are advantageous (avoid opening of PS containers until addition to product stream)
- If no PS content decrease is observed during long term storage conditions, PS content will be controlled at release, but not during stability once sufficient batch history is available
- If PS degradation is observed, its degradation is acceptable if no other CQA is impacted (PS content to be monitored during release and stability)
- End of shelf-life characterization stress studies and PS boundary studies may help to justify PS degradation and stability specifications
- Alternative surfactants (e.g., not prone to enzymatic degradation) are explored but there is still a lack of well characterized and acceptable suitable stabilizers for parenteral use

# Questions

- Although PS is used for parenteral products and often received from supplier (not directly from manufacturer), a reduced sampling and testing of PS starting material (e.g., no ID test on all containers, no complete (re)-testing of compendial requirements on each PS batch) will help to maintain high quality of the PS as delivered by manufacturer – what is your view and which elements should be part of the validated process?

- What's the expected data package to accept to a certain extend PS degradation if PS degradation occurs but without a meaningful impact on other CQAs?

- Provided that PS degradation related (subvisible or even visible) particles are well characterized and no other types of particles (e.g., protein particles) occur during DP storage, would this be acceptable and which data package and procedural controls would be necessary?

- Alternatives to PS are very scarce, and the regulatory hurdles very high:
  - How could we enhance the establishment of an alternative surfactant?
  - What would be the minimal /maximal work/investment and the timing behind?
  - How could we work together (as an industry) and with agencies to establish PS alternatives?

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Thank you

# Purpose and activities of working group

- Started in 2019
- “Industry for industry” best practices covering entire life-cycle of PS
- Work out common strategies to mitigate risks
- Exchange of scientific information
- Evaluate the risk/benefit profile of all-oleate Polysorbate 80
- Understand better PS quality through technical discussions with main PS manufactures
- Industry survey to benchmark use of PS, gaps, analytical methods and regulatory expectations, end to end approach