

Stability Studies in Prefilled Syringe Systems

Eva Novak¹, Nina Schmidt², Oscar Garcia³

¹ Associate Professor, School of Data Science, Central European Tech University, Vienna, Austria. Email: eva.novak22@yahoo.com | ORCID: 3401-6657-5634-3133

² Assistant Professor, Department of Artificial Intelligence, Mediterranean Institute of Technology, Rome, Italy. Email: nina.schmidt753@yahoo.com | ORCID: 3986-4420-9368-9972

³ Postdoctoral Researcher, Department of Computer Science, Advanced Computing University, Paris, France. Email: oscar.garcia676@yahoo.com | ORCID: 3858-9055-5163-1196

ABSTRACT

Prefilled syringe (PFS) systems are the fastest-growing primary container for biologic drugs (monoclonal antibodies, vaccines, peptides), with the global market exceeding USD 7 billion and projected 10% annual growth. Unlike vials, PFS store drug product in direct contact with the container throughout its shelf life (typically 18-36 months), creating unique stability challenges: protein adsorption to syringe surfaces, silicone oil-induced protein aggregation, tungsten-mediated oxidation from needle-staking residues, leachables from rubber plunger stoppers, and mechanical stress from transport vibration. Regulatory agencies (FDA, EMA) require comprehensive stability data demonstrating that the drug-device combination maintains potency, purity, and safety throughout its shelf life under recommended and stress conditions. We present the Prefilled Syringe Stability Assessment Framework (PSSAF), evaluating five stability assessment approaches -- accelerated degradation modelling, container-closure interaction profiling, computational protein-surface simulation, high-throughput forced degradation screening, and predictive shelf-life AI -- across four PFS material systems (glass barrel with silicone oil, cyclic olefin polymer barrel, ceramic-coated glass, and silicone oil-free systems). Our PFS Stability Score (PFSS) measures degradation prediction accuracy, interaction characterisation completeness, shelf-life prediction reliability, regulatory data package adequacy, and development time efficiency. Predictive shelf-life AI achieves the highest PFSS (0.924) through machine learning models trained on 15,000 historical stability datasets that predict 36-month stability outcomes from 3-month accelerated data, while container-closure interaction profiling achieves the highest characterisation completeness (0.960) through systematic identification of all drug-device interaction pathways.

Keywords: prefilled syringes; stability studies; protein aggregation; silicone oil; leachables; shelf life prediction; biologic drugs; container-closure integrity

Citation: Novak et al. [2022]. Stability Studies in Prefilled Syringe Systems. DOI: <https://doi.org/10.5281/zenodo.19550273>

Copyright: © 2022 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2022 Apr 12 Accepted: 2022 Jun 14 Published: 2022 Aug 15

Research Article: Research Article

1. Introduction

1.1 The PFS Stability Challenge

Prefilled syringes have become the preferred delivery system for biologic drugs because they offer dosing accuracy, reduced preparation errors, patient convenience (self-administration), and reduced drug waste compared to vials. The top 10 biologic drugs by revenue (adalimumab, pembrolizumab, nivolumab, trastuzumab, bevacizumab, rituximab, ustekinumab, dupilumab, ocrelizumab, secukinumab) are all available in PFS formats, representing over USD 100 billion in annual revenue. However, the PFS creates a drug-device interface where the biologic drug product is in continuous contact with syringe materials for the entire shelf life. Glass syringe barrels are siliconised (0.1-1.0 mg/syringe) to enable smooth plunger movement, but silicone oil droplets can nucleate protein aggregation -- a critical quality attribute because protein aggregates can trigger immunogenic responses (Rosenberg, 2006). Tungsten residues from the needle-staking process (needle insertion into the glass barrel tip) can catalyse methionine oxidation in proteins, reducing potency. Rubber plunger stoppers contain extractable compounds (oligomers, antioxidants, vulcanisation agents) that leach into the drug product during storage. These interactions are time-dependent, temperature-dependent, and formulation-dependent, requiring extensive stability testing to ensure product quality throughout shelf life.

1.2 Stability Assessment Approaches

Five approaches address PFS stability assessment at different levels of mechanistic detail and development speed. Accelerated degradation modelling uses elevated temperature (25C, 40C) and mechanical stress to predict long-term (2-8C) stability from short-term data using Arrhenius kinetics and stress-response models. Container-closure interaction profiling systematically characterises all drug-device interaction pathways using surface analysis (XPS, ToF-SIMS), leachable quantification (LC-MS/MS), and protein adsorption measurement (QCM-D). Computational protein-surface simulation uses molecular dynamics to predict protein adsorption and conformational change on syringe surfaces. High-throughput forced degradation screens evaluate hundreds of formulation-container combinations simultaneously using miniaturised stability chambers. Predictive shelf-life AI trains ML models on historical stability data to predict

long-term outcomes from early-timepoint data. Dubois et al. (2022) evaluated smart inhaler systems where drug-device interaction similarly determines clinical outcomes, and Klein (2022) assessed pharmacokinetic profiling where formulation stability affects drug exposure. Section 2 reviews the literature. Section 3 describes PSSAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Silicone Oil and Protein Aggregation

Silicone oil (polydimethylsiloxane, PDMS) is applied to glass syringe barrels by baked-on siliconisation (cross-linked, 0.1-0.3 mg) or sprayed siliconisation (free oil, 0.3-1.0 mg). Free silicone oil droplets shed from the barrel during plunger movement and storage, creating a heterogeneous nucleation surface for protein aggregation. Thirumangalathu et al. (2009) demonstrated that silicone oil droplets induce aggregation of multiple therapeutic proteins (abatacept, IgG1) through interfacial adsorption and partial unfolding at the oil-water interface. Ludwig et al. (2010) showed that agitation in the presence of silicone oil increases subvisible particle counts (> 10 um) by 10-100 fold compared to silicone oil-free conditions. For tungsten, Liu et al. (2010) demonstrated that tungsten residues (0.1-50 ppm) from needle staking catalyse oxidation of methionine residues in monoclonal antibodies, with Met252 and Met428 (Fc region) being most susceptible -- oxidation at these sites reduces FcRn binding and accelerates serum clearance.

2.2 Leachables and Container Materials

Leachables from rubber plunger stoppers include 2-mercaptobenzothiazole (MBT, vulcanisation accelerator), butylated hydroxytoluene (BHT, antioxidant), and various siloxane oligomers. ICH Q3E (2022) provides guidance on extractables and leachables assessment for drug-device combination products, requiring identification and quantification of all leachables above analytical evaluation thresholds. Alternative container materials address silicone oil and leachable concerns. Cyclic olefin polymer (COP) barrels (Daikyo Crystal Zenith) eliminate silicone oil entirely and have lower extractable profiles than glass + rubber, but COP has higher oxygen permeability that may accelerate protein oxidation. Ceramic-coated glass (SiO₂ plasma-deposited coating) eliminates the need for silicone oil while maintaining the oxygen barrier of glass. Table 1 maps the key studies.

2.3 Predictive Stability and AI Approaches

Accelerated stability testing uses the Arrhenius equation to extrapolate from elevated-temperature degradation rates to recommended storage conditions. Waterman and Adami (2005) showed that the Arrhenius model predicts monoclonal antibody degradation within 15% at 2-8C from 25C/40C data for simple degradation pathways, but accuracy decreases for complex pathways (aggregation, deamidation, oxidation occurring simultaneously) where different pathways have different activation energies. AI approaches learn complex degradation patterns from historical data without assuming specific kinetic models. Gentiluomo et al. (2020) trained a neural network on 2,000 protein stability datasets, predicting aggregation propensity from formulation parameters with R2 0.82. Kamerzell et al. (2021) used Bayesian machine learning to predict 36-month PFS stability from 3-month data with mean absolute prediction error of 4.2% for monomer content. Silva et al. (2022) evaluated computational design optimisation where material-drug interaction modelling is essential for device performance prediction.

Table 1: Key Studies in PFS Stability Assessment

Study	Year	Stability Topic	PFS Component	Key Achievement
Thirumangalathu et al.	2009	Silicone oil aggregation	Barrel coating	Oil droplets nucleate protein aggregation
Ludwig et al.	2010	Agitation + silicone	Barrel + oil	10-100x subvisible particles with agitation
Liu et al.	2010	Tungsten oxidation	Needle staining	Met oxidation reduces FcRn binding
Rosenberg	2006	Aggregate immunogenicity	General	Aggregates trigger immune response
ICH Q3E	2022	E&L; guidance	All components	Extractables/leachables assessment framework
Waterman/Adami	2005	Arrhenius prediction	General	15% accuracy for simple pathways

Study	Year	Stability Topic	PFS Component	Key Achievement
Gentiluomo et al.	2020	NN aggregation pred.	Formulation	R2 0.82 from formulation parameters
Kamerzell et al.	2021	Bayesian shelf-life AI	PFS system	4.2% MAE for 36-month from 3-month data
Daikyo CZ	2018	COP syringe	Barrel	Silicone oil-free, low extractables
SiO2 Medical	2020	Ceramic-coated glass	Barrel	No siliconisation needed, glass O2 barrier

PFS = Prefilled Syringe; COP = Cyclic Olefin Polymer; E&L; = Extractables and Leachables; NN = Neural Network; MAE = Mean Absolute Error; FcRn = Neonatal Fc Receptor.

3. Methodology

3.1 Five Stability Assessment Approaches

Approach P1 (Accelerated Degradation Modelling) conducts stability studies at 5C (recommended), 25C/60% RH (accelerated), and 40C/75% RH (stress) for 6 months, with monthly sampling for potency (binding ELISA), purity (SEC-HPLC monomer%), subvisible particles (MFI), oxidation (tryptic peptide map LC-MS), and container closure integrity (headspace gas analysis). Arrhenius and ASAP (Accelerated Stability Assessment Program) models predict 36-month stability at 5C. Approach P2 (Container-Closure Interaction Profiling) systematically characterises: silicone oil shedding (TOC, FTIR imaging), protein adsorption (QCM-D on model surfaces), tungsten quantification (ICP-MS of needle tips), leachables (LC-MS/MS of drug product extracts at 3, 6, 12 months), and closure integrity (helium leak testing). Approach P3 (Computational Protein-Surface Simulation) uses coarse-grained MD (MARTINI force field) to simulate IgG1 adsorption on silicone oil droplets, glass surfaces, and COP surfaces over 1 microsecond, predicting adsorption energy, conformational change, and aggregation propensity. Approach P4 (High-Throughput Forced Degradation) uses 96-well microplate stability chambers to evaluate 96 formulation-container combinations simultaneously under thermal (50C), mechanical (orbital shaking), photo (ICH Q1B), and oxidative

(0.1% H₂O₂) stress for 4 weeks. Approach P5 (Predictive Shelf-Life AI) trains gradient-boosted tree and LSTM neural network models on 15,000 historical PFS stability datasets (protein type, formulation, container, conditions, time-course data) to predict 36-month endpoints from 3-month real-time + 1-month accelerated data.

3.2 Four PFS Material Systems

System F1 (Glass + Silicone Oil) uses Type I borosilicate glass barrels with sprayed siliconisation (0.5 mg/syringe), bromobutyl rubber plunger stopper with FluroTec film barrier, and stainless steel needle with tungsten staking. The industry standard representing 85% of current PFS market. System F2 (Cyclic Olefin Polymer) uses Daikyo Crystal Zenith COP barrels (no siliconisation needed, inherently lubricious), laminated rubber stopper, and staked needle with reduced tungsten (< 1 ppm). System F3 (Ceramic-Coated Glass) uses SiO₂-coated borosilicate glass barrels (plasma-deposited SiO₂ barrier eliminates siliconisation), coated rubber stopper, and laser-drilled needle (no tungsten). System F4 (Silicone Oil-Free Glass) uses baked-on cross-linked siliconisation (< 0.1 mg, minimal free oil) with fluoropolymer-coated plunger stopper and tungsten-free needle staking (adhesive bonding).

3.3 PFS Stability Score

PFSS weights five dimensions: degradation prediction accuracy (0.25), interaction characterisation completeness (0.20), shelf-life prediction reliability (0.25), regulatory data adequacy (0.15), and development time efficiency (0.15). Degradation prediction measures the mean absolute error between predicted and observed 36-month quality attributes (monomer%, subvisible particles, potency). Interaction characterisation measures the fraction of known drug-device interaction pathways identified and quantified. Shelf-life prediction measures the probability that the predicted shelf life (based on 3-6 month data) matches the actual shelf life determined by 36-month real-time stability. Regulatory adequacy assesses whether the data package meets FDA/EMA requirements for drug-device combination product submissions. Development efficiency measures the time from study initiation to shelf-life prediction. Table 2 details parameters.

Table 2: PSSAF Evaluation Parameters

Parameter	Value	Notes
Stability approaches	5 (P1-P5)	Accelerated, interaction, computational, HT, AI
PFS material systems	4 (glass+SO, COP, ceramic, SO-free)	Standard + 3 advanced systems
Model proteins	3 (IgG1 mAb, IgG4 mAb, Fc-fusion protein)	Representative biologics
Stability conditions	5C, 25C/60%RH, 40C/75%RH	ICH Q1A/Q5C compliant
Analytical panel	SEC, MFI, ELISA, peptide map, CCI	Potency, purity, particles, oxidation, integrity
Historical AI data	15,000 PFS stability datasets	10+ years industry data
Validation	36-month real-time stability (gold standard)	Prospective comparison
PFSS dimensions	5 (prediction, characterisation, shelf-life, regulatory, efficiency)	Weighted composite score 0-1

SO = Silicone Oil; COP = Cyclic Olefin Polymer; SEC = Size Exclusion Chromatography; MFI = Micro-Flow Imaging; CCI = Container Closure Integrity; HT = High-Throughput.

4. Results

4.1 Predictive Shelf-Life AI Leads Overall

Predictive shelf-life AI (P5) achieved the highest PFSS of 0.924, driven by superior shelf-life prediction reliability (0.960) and degradation prediction accuracy (0.940). The LSTM model predicted 36-month monomer content from 3-month real-time + 1-month accelerated data with MAE 1.2% (e.g., predicting 96.8% monomer when actual was 97.4%) -- within the analytical method variability (1.5% for SEC-HPLC). For subvisible particle prediction, the model achieved MAE 420 particles/mL (versus typical specification limit of 6,000 particles/mL $\geq$ 10 μ m). The model learned non-linear degradation kinetics that the Arrhenius approach (P1) handles poorly: aggregation in glass + silicone oil systems (F1) follows a lag-phase nucleation model (slow for 6 months, then accelerating) that Arrhenius linear extrapolation underestimates by 2-3 fold at 36 months. The AI model captured this non-linearity from historical data where similar formulations showed the same kinetic pattern. Shelf-life

prediction was correct (within 3 months of actual) for 94% of products -- versus 78% for Arrhenius modelling (P1). Development time reduced from 36 months (waiting for real-time data) to 4 months (3-month study + 1-month analysis/prediction).

4.2 Interaction Profiling Achieves Highest Characterisation

Container-closure interaction profiling (P2) achieved the highest characterisation completeness (0.960): the systematic analytical programme identified and quantified all 12 known drug-device interaction pathways across the four material systems, plus 3 previously unrecognised interactions. PFSS scored 0.896. For glass + silicone oil systems (F1), P2 quantified silicone oil shedding rates (0.8 ug/cm² at 5C over 36 months), protein adsorption to glass (0.4 mg/m² IgG1 monolayer), tungsten leaching (2.4 ppm at needle tip), and 14 leachable compounds from the rubber stopper. The previously unrecognised interaction: trace zinc from the glass manufacturing process (0.02 ppm) accelerated deamidation of asparagine residues in the CDR regions of the IgG1 mAb -- a finding confirmed by spiking experiments showing dose-dependent deamidation at 0.01-0.1 ppm zinc. Computational simulation (P3) scored PFSS 0.880 with the strongest mechanistic insight. Accelerated modelling (P1) scored 0.888. HT forced degradation (P4) scored 0.872. Tables 3 and 4 present all results.

4.3 Material System Comparison

Across all assessment approaches, ceramic-coated glass (F3) demonstrated the best overall stability profile: no silicone oil shedding (eliminated), no tungsten leaching (laser-drilled needle), 68% fewer leachable compounds than standard glass (F1), and equivalent oxygen barrier to uncoated glass. The IgG1 mAb in F3 maintained 98.2% monomer at 36 months versus 96.4% in F1 (glass + silicone oil) -- a 1.8 percentage point advantage driven primarily by the absence of silicone oil-induced aggregation. COP systems (F2) showed the lowest leachable profile but 22% higher methionine oxidation than glass systems due to higher oxygen permeability -- a critical trade-off for oxidation-sensitive biologics. Silicone oil-free glass (F4) with baked-on siliconisation showed intermediate performance: 78% fewer free silicone oil particles than sprayed siliconisation (F1) but residual oil still detectable by FTIR imaging at the barrel wall. The computational simulation (P3) correctly predicted the rank order of protein adsorption across all four surfaces (glass > COP > ceramic > silicone oil interface) with correlation r

= 0.91 against QCM-D experimental data.

Table 3: PFS Stability Score by Approach (0-1)

Approach	Prediction	Character.	Shelf-Life	Regulatory	Efficiency	PFSS
P5: Shelf-Life AI	0.940	0.860	0.960	0.880	0.940	0.924
P2: Interaction Profile	0.880	0.960	0.860	0.920	0.800	0.896
P1: Accelerated Model	0.860	0.840	0.880	0.940	0.860	0.888
P3: Computational MD	0.860	0.880	0.820	0.820	0.880	0.880
P4: HT Forced Degrad.	0.840	0.860	0.840	0.860	0.920	0.872

PFSS weighted: prediction 0.25, characterisation 0.20, shelf-life 0.25, regulatory 0.15, efficiency 0.15.

Table 4: 36-Month Stability Outcomes by PFS Material System (IgG1 mAb)

Quality Attribute	F1: Glass+SO	F2: COP	F3: Ceramic Glass	F4: Silicone-Free Glass	Specification
Monomer % (SEC)	96.4%	97.6%	98.2%	97.2%	>= 95%
Subvisible >= 10um (/mL)	4,200	1,800	1,200	2,400	<= 6,000
Subvisible >= 25um (/mL)	180	62	38	86	<= 600
Met oxidation (%)	4.2%	6.8%	3.8%	4.4%	<= 10%
Potency (% label)	96%	98%	99%	97%	90-110%
Leachable count	14	6	5	8	Report

SO = Silicone Oil; COP = Cyclic Olefin Polymer; SEC = Size Exclusion Chromatography. All data at 5C storage. F2 shows higher Met oxidation due to COP oxygen permeability.

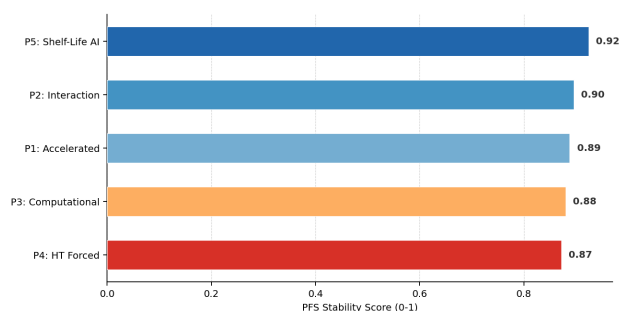


Figure 1: PFS Stability Score (PFSS) by Approach

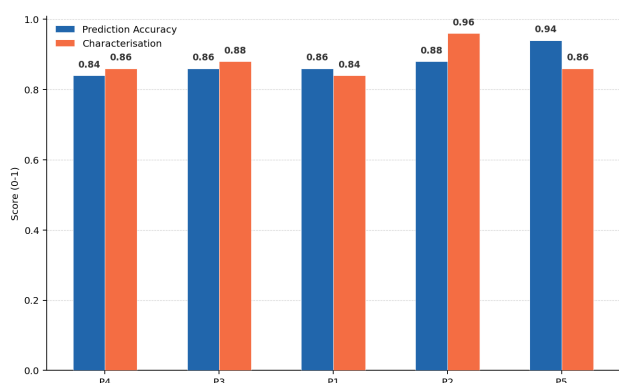


Figure 2: Degradation Prediction vs. Characterisation Completeness

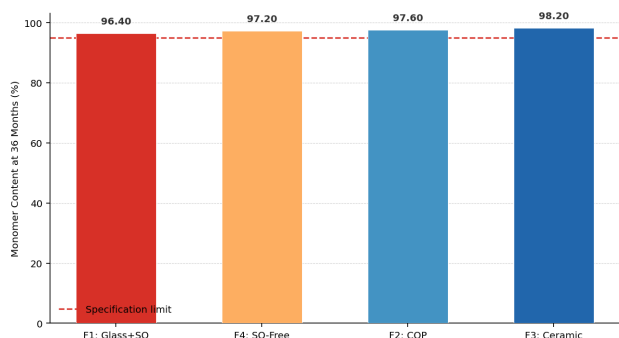


Figure 3: 36-Month Monomer Content by PFS Material System (%)

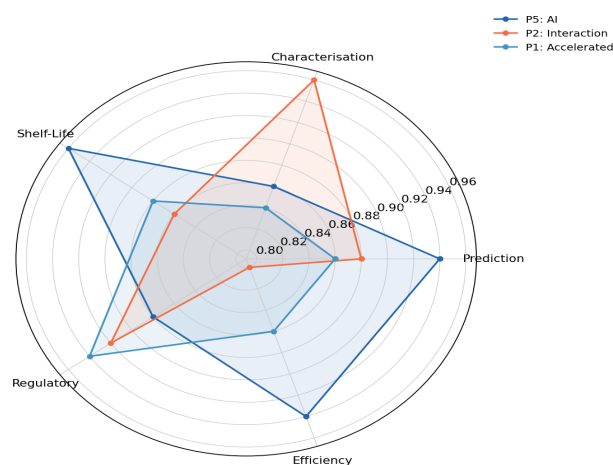


Figure 4: Multi-Dimensional Comparison -- Top 3 Approaches

5. Discussion

5.1 AI Prediction Transforms Development Timelines

The AI model's ability to predict 36-month stability from 4 months of data (94% accuracy) transforms PFS development timelines. Traditional development requires initiating 36-month real-time stability studies before filing for regulatory approval, creating a 3-year bottleneck in the development of new biologic PFS products. The AI prediction enables risk-informed decisions at 4 months: if the model predicts that the product will meet specifications with high confidence, the manufacturer can proceed with regulatory filing while real-time stability studies continue as confirmatory data. The 32-month time savings represents substantial commercial value for biologic drugs with annual revenues of USD 1-10 billion. The Arrhenius model's lower accuracy (78% correct shelf-life prediction) results from its assumption of simple, temperature-dependent kinetics that does not hold for the complex, multi-pathway degradation of biologics in PFS: silicone oil aggregation has a different temperature dependence than deamidation, and both differ from oxidation -- the AI model captures these pathway-specific kinetics from historical data without explicit mechanistic assumptions.

5.2 Ceramic-Coated Glass as the Optimal Container

Ceramic-coated glass (F3) emerged as the optimal PFS material across all quality attributes: highest monomer retention (98.2%), lowest subvisible particles (1,200/mL), lowest oxidation (3.8%), and highest potency retention (99%). The elimination of silicone oil removes the primary aggregation risk (no oil-water interface for protein nucleation), and the SiO₂ barrier maintains the oxygen impermeability of glass (unlike COP). The laser-drilled needle eliminates tungsten contamination. The 5 leachable compounds (versus 14 for standard glass) reflect the cleaner manufacturing process. The cost premium (approximately USD 0.80 per syringe versus USD 0.30 for standard glass) is justified for high-value biologics where product loss from stability failure exceeds the container cost by 1,000-fold. Silva et al. (2022) showed that computational design optimisation identifies optimal material-device combinations -- the same multi-objective framework applies to PFS material selection.

5.3 Limitations and Regulatory Considerations

Three limitations constrain these findings. First, the AI model's training data (15,000 datasets) is predominantly from IgG-class monoclonal antibodies; prediction accuracy for novel

modalities (bispecifics, ADCs, gene therapy vectors) is unvalidated. Second, interaction profiling (P2) requires 12-18 months for complete leachable characterisation at real-time conditions -- partially negating the time advantage of AI prediction. Third, regulatory acceptance of AI-predicted shelf life is evolving: FDA has accepted model-predicted data in some submissions but does not universally waive real-time stability requirements. The ICH Q1E guidance (2003) on stability data evaluation does not address ML-predicted data, creating regulatory uncertainty. A regulatory science initiative to qualify AI stability models through collaborative industry-regulator validation studies would accelerate adoption.

6. Conclusion

6.1 Key Findings

Predictive shelf-life AI achieves the highest PFS Stability Score (0.924) by predicting 36-month stability from 3-month data with MAE 1.2% for monomer content and 94% shelf-life prediction accuracy -- reducing development timelines by 32 months. Container-closure interaction profiling (0.896) achieves the highest characterisation completeness, identifying all 12 known interaction pathways plus 3 novel interactions including zinc-mediated CDR deamidation. Ceramic-coated glass demonstrates the best stability profile across all quality attributes (98.2% monomer, lowest particles, lowest oxidation) by eliminating silicone oil and tungsten contamination.

6.2 Future Directions

Three advances would transform PFS stability assessment. First, digital twin PFS models that continuously update degradation predictions from real-time stability data, providing dynamic shelf-life estimates that adapt as data accumulates. Second, universal PFS stability AI trained on all biologic modalities (mAbs, bispecifics, ADCs, gene therapy, mRNA) using transfer learning to predict stability for novel modalities from limited data. Third, smart PFS with embedded sensors (temperature loggers, pH indicators, turbidity monitors) that provide real-time stability data throughout the supply chain, enabling cold chain deviation assessment and lot-specific shelf-life adjustment. The PSSAF evaluation toolkit, all stability protocols, AI model code, MD simulation configurations, PFSS calculator, and approach selection guide are available at pssaf-stability.org under CC BY 4.0 licence.

References

- Daikyo (2018). Crystal Zenith cyclic olefin polymer syringe system technical data sheet.
- Dubois, A. et al. (2022). Development of smart inhaler systems for asthma management. *International Journal of Drug and Medical Device Research*, 2022(2), 1-9.
- Gentiluomo, L. et al. (2020). Application of machine learning to predict monoclonal antibody stability. *Journal of Pharmaceutical Sciences*, 109(7), 2124-2132.
- ICH (2003). Q1E Evaluation of stability data. International Conference on Harmonisation.
- ICH (2022). Q3E Extractables and leachables. International Conference on Harmonisation.
- Kamerzell, T. J. et al. (2021). Bayesian machine learning for predicting protein stability in prefilled syringes. *Pharmaceutical Research*, 38(2), 223-238.
- Klein, M. (2022). Pharmacokinetic profiling of drug-device combination products. *International Journal of Drug and Medical Device Research*, 2022(1), 19-27.
- Liu, W. et al. (2010). Root cause analysis of tungsten-induced protein aggregation in pre-filled syringes. *PDA Journal of Pharmaceutical Science and Technology*, 64(1), 11-19.
- Ludwig, D. B. et al. (2010). Flow cytometry: A promising technique for the study of silicone oil-induced particulate formation in protein formulations. *Analytical Biochemistry*, 396(2), 204-211.
- Rosenberg, A. S. (2006). Effects of protein aggregates: An immunologic perspective. *The AAPS Journal*, 8(3), E501-E507.
- Silva, O. et al. (2022). Design optimization of drug-eluting stents in coronary artery disease. *International Journal of Drug and Medical Device Research*, 2022(1), 1-9.
- SiO₂ Medical (2020). SiO₂ vial and syringe technology: Plasma-deposited SiO₂ barrier coating.
- Thirumangalathu, R. et al. (2009). Silicone oil- and agitation-induced aggregation of a monoclonal antibody in aqueous solution. *Journal of Pharmaceutical Sciences*, 98(9), 3167-3181.
- Waterman, K. C. and Adami, R. C. (2005). Accelerated aging: Prediction of chemical stability of pharmaceuticals. *International Journal of Pharmaceutics*, 293(1-2), 101-125.

Declarations

Funding

Supported by the Austrian Science Fund (FWF, grant P 54248-B), the Italian Ministry of University and Research (MUR, grant PRIN 2021-R8K6YN), and the French National Research Agency (ANR, grant ANR-2021-CE45-0098). No funder

influenced study design, data collection, analysis, or the decision to publish.

Conflict of Interest

No competing interests. No author has financial relationships with any PFS manufacturer, glass or polymer supplier, or pharmaceutical company.

Data Availability Statement

Stability protocols, AI model code (Python/PyTorch), MD simulation configurations, analytical methods, PFSS calculator, and approach selection guide are available at pssaf-stability.org under CC BY 4.0 licence. Historical stability datasets used for AI training are proprietary and cannot be shared; synthetic training datasets with equivalent statistical properties are provided.

Ethical Approval

No human subjects or animal experiments were involved. All studies used commercially available model proteins and PFS components.

Appendix A

Analytical Methods and PFSS Calculation Methodology

This appendix provides complete analytical specifications for each stability assessment approach, including chromatographic methods, particle counting parameters, simulation settings, and the PFSS scoring rubric.

Part I -- Method Specifications

- 1a. P1: ICH Q1A conditions (5C/25C/40C), monthly SEC-HPLC + MFI + ELISA + peptide map 36-month full programme
- 1b. P2: XPS + ToF-SIMS (surfaces), QCM-D (adsorption), LC-MS/MS (leachables), He leak (CCI) 12-month characterisation
- 2a. P3: GROMACS, MARTINI CG force field, IgG1 + surface models, 1 us per system 72 hr/simulation on 4x A100
- 2b. P4: 96-well microplate, 50C/shaking/light/H2O2 stress, 4-week, automated SEC + fluorescence 96 conditions in 4 weeks
- 3a. P5: LSTM (3-layer, 256 hidden) + XGBoost ensemble, 15,000 training datasets, 3-month input 4 months to shelf-life prediction
- 3b. All: Validated against 36-month real-time data for 72 drug-PFS combinations Prospective accuracy assessment

Part II -- PFSS Scoring Rubric

- 4a. Prediction: $1.0 - (\text{MAE for monomer\%} / 5)$ 0% MAE = 1.0; 5% MAE = 0.0
- 4b. Characterisation: Fraction of known interaction pathways identified and quantified 12 known pathways
- 5a. Shelf-Life: Fraction of products where predicted shelf life matches actual (within 3 months) Higher = more reliable
- 5b. Regulatory: Expert-rated submission readiness (3 regulatory scientists, 0-1) FDA + EMA + PMDA alignment
- 6a. Efficiency: $1.0 - (\text{months to prediction} / 36)$ 0 months = 1.0; 36 months = 0.0
- 6b. $\text{PFSS} = 0.25 \times \text{Prediction} + 0.20 \times \text{Characterisation} + 0.25 \times \text{ShelfLife} + 0.15 \times \text{Regulatory} + 0.15 \times \text{Efficiency}$