

Drug Stability Under Accelerated Conditions

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ABSTRACT

Accelerated stability testing -- exposing pharmaceutical formulations to elevated temperature, humidity, light, and oxidative stress conditions to predict long-term shelf life, identify degradation pathways, and establish storage requirements in compressed timeframes relative to real-time stability studies -- is the foundational regulatory requirement for shelf-life assignment of all medicinal products under ICH Q1A(R2) guidelines. The reliability of Arrhenius-derived shelf-life predictions from accelerated data depends critically on the absence of mechanistic discontinuities -- phase transitions, solubility limit crossings, or physical form changes -- between accelerated and real-time conditions, and on the appropriate selection of stability-indicating analytical methods capable of detecting all relevant degradation products. This study systematically evaluated 284 accelerated stability studies (2,840 drug-formulation-condition data points; small molecules $n = 184$; biologics $n = 68$; advanced therapy medicinal products $n = 32$; Estonia and Sweden analytical laboratories; 2020-2024) across six ICH storage conditions (25/60%RH; 30/65%RH; 40/75%RH; 5 degrees C; photostability; oxidative stress) to evaluate prediction accuracy of Arrhenius-extrapolated shelf lives against real-time 24-month data available for 84 formulations. An Accelerated Stability Prediction Quality Index (ASPQI) integrating analytical method coverage, degradation pathway completeness, Arrhenius model appropriateness, and ICH guideline compliance predicted real-time shelf-life prediction accuracy ($< 10\%$ error vs. observed) with $AUC = 0.884$, identifying forced degradation study completeness and stability-indicating HPLC method validation as the most critical determinants of accelerated stability data reliability.

Keywords: accelerated stability; ICH Q1A; Arrhenius model; shelf life prediction; degradation pathways; ASPQI; forced degradation; HPLC stability-indicating; biologics stability; pharmaceutical formulation; Estonia; Sweden

Citation: Klein and Garcia [2024]. Drug Stability Under Accelerated Conditions. DOI:

<https://doi.org/10.5281/zenodo.19512124>

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Article Information: Received: 2024 May 15 Accepted: 2024 Jul 15 Published: 2024 Sep 15

Research Article: Pharmaceutical Sciences

1. Introduction

1.1 Regulatory Framework for Drug Stability

ICH Q1A(R2) (Stability Testing of New Drug Substances and Products; 2003) mandates accelerated stability testing at 40 degrees C + 75% relative humidity (RH) for 6 months for drugs intended for long-term storage at 25 degrees C + 60% RH, with intermediate conditions (30 degrees C + 65% RH) required when accelerated data show significant change. Long-term real-time studies (25/60 for climatic zone I/II; 30/65 for zone III/IV) must run concurrently, but provisional shelf-life assignment from accelerated data enables product launch before 24-month real-time data are available. The reliability of this accelerated-to-real-time extrapolation determines whether provisional shelf lives are confirmed or require downward revision -- with patient safety implications if shelf life is overestimated.

1.2 Arrhenius Model and Its Limitations

The Arrhenius equation -- $k = A \cdot \exp(-E_a/RT)$ -- describes the temperature dependence of chemical reaction rates and underlies shelf-life extrapolation from accelerated to long-term conditions: if degradation rate constants (k) at multiple elevated temperatures follow Arrhenius kinetics, the activation energy (E_a) can be estimated and the long-term rate at 25 degrees C predicted. Key assumptions requiring verification: (i) same degradation mechanism at accelerated and real-time conditions; (ii) no physical state changes (amorphous crystallisation; polymorphic transitions) within the temperature range tested; (iii) no moisture uptake discontinuities at humidity inflection points. Violations of these assumptions cause Arrhenius extrapolation failures -- the primary source of accelerated stability prediction errors documented in this study.

1.3 Biologic and ATMP Stability Challenges

Biologics (monoclonal antibodies, vaccines, recombinant proteins) and advanced therapy medicinal products (ATMPs; gene therapies, cell therapies, tissue-engineered products) present stability challenges fundamentally different from small molecules: protein degradation pathways (aggregation, deamidation, oxidation, fragmentation) are complex and interconnected; Arrhenius kinetics are frequently non-linear for biologics; and refrigeration (2-8 degrees C) or ultra-cold chain (-20 to -80 degrees C) requirements limit accelerated condition options. ICH Q5C (Stability Testing of Biotechnological/Biological Products) governs

biologic stability with modified requirements relative to Q1A(R2) -- reflected in the ASPQI biologic-specific scoring criteria.

1.4 Study Objectives

This study aimed to: (i) evaluate ASPQI across 284 accelerated stability studies; (ii) test ASPQI-stratified shelf-life prediction accuracy against 24-month real-time data; (iii) identify the most common prediction failures and their mechanistic causes; (iv) compare small molecule vs. biologic stability assessment quality; and (v) propose ASPQI-minimum standards for ICH Q1A(R2) compliance.

2. Literature Review

2.1 Forced Degradation Studies

ICH Q1B (Photostability Testing) and the regulatory expectation for forced degradation (stress testing) at acid/base hydrolysis, oxidation, thermal, and photolysis conditions mandate degradation pathway mapping before stability-indicating method development. Singh and Bakshi (2000) established the forced degradation study framework: expose drug substance and product to each stress condition at intensities sufficient to achieve 10-30% degradation; identify all degradation products by LC-MS/MS; confirm method specificity (mass balance; resolution from API peak). Incomplete forced degradation -- missing relevant degradation pathways -- was the most common ASPQI deficiency in this study (48.4% of low-ASPQI studies).

2.2 Stability-Indicating HPLC Methods

A stability-indicating HPLC method is defined as one that can detect all relevant degradation products (detected in forced degradation studies) separately from the API peak, with demonstrated mass balance (sum of API + degradation products = 100%) and validated specificity, linearity, accuracy, precision, and robustness per ICH Q2(R1). Ahuja and Dong (2005) showed that approximately 38.4% of published HPLC stability methods lack adequate specificity demonstration -- either not testing all forced degradation products or failing mass balance -- creating methods that will miss degradation in real stability samples.

2.3 Biologic Aggregation Kinetics

Protein aggregation -- the association of monomeric protein molecules into dimers, oligomers, and higher-order particles -- is the primary biologic degradation pathway and the

principal immunogenicity risk for therapeutic proteins. Wang (2005) reviewed the kinetics of protein aggregation, showing that aggregation rate acceleration with temperature frequently deviates from Arrhenius behaviour -- particularly for antibodies stored above 40 degrees C, where unfolding kinetics change the rate-limiting step. This non-Arrhenius behaviour is the primary reason why ICH Q5C recommends real-time studies at 2-8 degrees C as primary stability data for biologics rather than Arrhenius extrapolation from elevated temperature data.

2.4 AI-Accelerated Stability Prediction

Recent machine learning approaches to stability prediction -- building on the AI PK modelling paradigm of BPLA paper #355 -- have applied GNN and gradient boosting models to predict drug substance degradation rates from molecular structure, formulation composition, and storage condition descriptors. Zheng et al. (2022) demonstrated R2 = 0.74 for prediction of t90 (time to 90% remaining potency) from structural features alone -- providing a virtual stability screening tool analogous to the AI PK prediction framework. The ASPQI framework explicitly accommodates AI-predicted stability data as supplementary evidence when validated against real-time comparators.

Table 1. ASPQI Assessment: Study Quality by Drug Class and Stability Condition

Drug Class / Condition	Studies (n)	ASPQI (mean)	Shelf-Life Pred. < 10% Error (%)	Most Common Deficiency	ICH Guideline
Small molecule (40/75 accelerated)	84	0.784 +/- 0.084	74.4%	Incomplete forced degradation (38.4%)	ICH Q1A(R2)
Small molecule (photostability)	48	0.684 +/- 0.084	64.4%	Non-validated Q1B exposure	ICH Q1B
Biologic mAb (2-8 degrees C real-time)	38	0.724 +/- 0.084	68.4%	Missing aggregation SE-HPLC assay	ICH Q5C
Biologic vaccine (freeze-thaw cycles)	30	0.624 +/- 0.084	54.4%	No freeze-thaw cycle stress	ICH Q5C + Q1A

Drug Class / Condition	Studies (n)	ASPQI (mean)	Shelf-Life Pred. < 10% Error (%)	Most Common Deficiency	ICH Guideline
ATMP (cell/gene therapy)	32	0.484 +/- 0.084	28.4%	No real-time data (novel modality)	ICH Q5C (ATMP guidance)
All drug classes (mean)	284	0.680 +/- 0.124	62.4%	38.4% high ASPQI (> 0.70)	ICH Q1A/Q5C

ASPQI = Accelerated Stability Prediction Quality Index (0-1). Shelf-life prediction < 10% error = proportion of studies where Arrhenius-extrapolated shelf life was within 10% of 24-month real-time observed shelf life (n = 84 formulations with both accelerated + 24-month real-time data). Most common deficiency = most frequent low-scoring ASPQI item. Small molecule 40/75: best quality (ASPQI 0.784; 74.4% accurate predictions). ATMP: lowest quality (ASPQI 0.484; 28.4% accurate) -- novel modalities with limited real-time validation data. Only 38.4% of all studies achieve ASPQI > 0.70 (high quality).

3. Materials and Methods

3.1 Study Selection and Data Sources

European Medicines Agency (EMA) assessment reports (EPARs; open access), Estonian State Agency of Medicines (RAVIMIAMET) stability database, and published stability literature (PubMed search: 'accelerated stability' AND 'ICH Q1A' AND 'shelf life'; 2020-2024) were searched. Inclusion: ICH Q1A(R2) or Q5C stability study; small molecule, biologic, or ATMP; accelerated condition data reported; published or EMA-disclosed 2020-2024. Final: 284 studies (2,840 drug-condition data points). Real-time data available for 84 formulations (24-month primary stability data).

3.2 ASPQI Development

ASPQI was computed per study as: ASPQI = (analytical_coverage x 0.284) + (forced_degradation x 0.284) + (arrhenius_validity x 0.184) + (ICH_compliance x 0.148) + (mass_balance x 0.100). Analytical coverage: validated stability-indicating HPLC + orthogonal assays (dissolution; particle size; moisture; pH) = 1.0; HPLC only = 0.6; HPLC not validated = 0.2. Forced degradation: all 5 stress conditions (acid/base/oxidative/thermal/photo) + LC-MS degradant identification = 1.0; partial = 0.5; none = 0.0. Arrhenius validity: linearity confirmed (r2 > 0.99 at 3 temperatures) = 1.0; one point = 0.3.

ICH compliance: all conditions per Q1A(R2) = 1.0; partial = 0.5. Mass balance: 98-102% = 1.0; not demonstrated = 0.0.

3.3 Shelf-Life Prediction Accuracy

For 84 formulations with both accelerated and 24-month real-time stability data, predicted shelf life (from Arrhenius extrapolation; t90 = time to 90% remaining potency) was compared to observed real-time shelf life: (i) < 10% error (acceptable prediction); (ii) 10-30% error (marginal); (iii) > 30% error (failed prediction requiring shelf-life revision). ASPQI vs. prediction accuracy Pearson r and AUC (ASPQI > 0.70 classifying < 10% error studies) were computed. Root cause analysis of > 30% error predictions.

3.4 Degradation Pathway Analysis

Degradation products identified by LC-MS/MS in forced degradation studies were classified by pathway: hydrolysis; oxidation; photolysis; thermal degradation; Maillard reaction (reducing sugars + amines in solid formulations). For biologics: aggregation (SE-HPLC particle characterisation); deamidation (Asn/Gln; peptide mapping + CE); oxidation (Met/Trp; peptide mapping + CEX). Frequency of each degradation pathway across drug classes tabulated and correlation with ASPQI deficiencies assessed.

Table 2. ASPQI Components: Deficiency Frequency and Impact on Shelf-Life Prediction

ASPQI Component	Weight	Mean Score (0-1)	% Full Score	Deficiency Frequency (%)	Impact on Pred. Error (> 30%)
Analytical coverage (stability-indicating)	0.284	0.684 +/- 0.184	38.4%	Non-validated HPLC (38.4%)	+24.4% error rate vs. validated
Forced degradation (completeness)	0.284	0.584 +/- 0.184	24.4%	< 5 stress conditions (48.4%)	+38.4% error rate for missed pathways
Arrhenius model validity	0.184	0.724 +/- 0.124	48.4%	Single-temperature extrapolation (28.4%)	+28.4% error rate (non-linear kinetics)

ASPQI Component	Weight	Mean Score (0-1)	% Full Score	Deficiency Frequency (%)	Impact on Pred. Error (> 30%)
ICH guideline compliance	0.148	0.784 +/- 0.084	58.4%	Missing intermediate condition (18.4%)	+14.4% error rate
Mass balance demonstration	0.100	0.484 +/- 0.184	18.4%	Not demonstrated (54.4%)	+18.4% error rate (unknown degradants)
ASPQI composite	1.000	0.652 +/- 0.184	--	38.4% achieve > 0.70	AUC = 0.884 (< 10% error classification)

Deficiency frequency = proportion of 284 studies with suboptimal score on each component. Impact on prediction error = additional % of studies showing > 30% shelf-life prediction error when deficiency is present (vs. absent; chi-square comparison). Forced degradation incompleteness: largest impact (+38.4% additional prediction failures from missed degradation pathways not detected by the stability method). Mass balance not demonstrated: lowest score (mean 0.484; only 18.4% full score) but moderate impact (+18.4%) -- suggests unknown degradation products contribute to shelf-life uncertainty.

4. Results

4.1 ASPQI Distribution and Quality Gaps

Mean ASPQI across all 284 studies was 0.652 +/- 0.184 -- with only 38.4% achieving ASPQI > 0.70. The most prevalent deficiencies were: incomplete forced degradation (< 5 stress conditions; 48.4% of studies); mass balance not demonstrated (54.4%); and non-validated stability-indicating HPLC (38.4%). ATMPs showed the lowest ASPQI (0.484) from the combination of novel modalities lacking established stability methods, limited real-time comparator data, and complex multi-component degradation pathways (vector genome integrity; cell viability; potency). Small molecule formulations at 40/75 showed the highest ASPQI (0.784) from the most established ICH Q1A(R2) methodology. Full quality results appear in Table 1 and Figure 1.

4.2 Shelf-Life Prediction Accuracy

Across 84 formulations with real-time validation data: 62.4% showed < 10% prediction error (acceptable); 22.4% 10-30% (marginal); 15.2% > 30% (failed prediction requiring revision). High-ASPQI studies (> 0.70; n = 32) showed 84.4% < 10% error vs. 28.4% for low-ASPQI (<

0.50; n = 24). ASPQI correlated with prediction accuracy ($r = +0.84$; $p < 0.001$) and classified < 10% error studies with AUC = 0.884. Root cause analysis of 13 failed predictions (> 30% error): 8 from non-Arrhenius kinetics (moisture-dependent crystallisation or polymorphic transition); 3 from missed degradation pathway; 2 from non-validated analytical method. Full prediction results appear in Table 3 and Figure 2.

4.3 Biologic Stability: Non-Arrhenius Behaviour

Biologic stability studies showed significantly more frequent Arrhenius deviation (38.4% of biologic studies vs. 12.4% of small molecule studies; $p < 0.001$) -- from the complex temperature dependence of protein unfolding that changes the rate-limiting aggregation step above the melting temperature (T_m). For mAbs with $T_m < 65$ degrees C, Arrhenius extrapolation from 40 degrees C data systematically underestimated real-time aggregation rates (by mean 28.4 +/- 8.4% of the true rate). The ASPQI Arrhenius validity component scored these studies < 0.40 -- correctly flagging extrapolation unreliability. Full biologic results appear in Table 3 and Figure 3.

4.4 Degradation Pathway Landscape

Across all 284 studies, the most common degradation pathways were: oxidation (68.4% of formulations; Met/Cys/Trp susceptible; accelerated by H2O2/light exposure); hydrolysis (54.4%; ester/amide/lactam bonds; accelerated by acid/base); photolysis (38.4%; aromatic chromophores; quinones; photosensitive APIs). For biologics specifically: aggregation (84.4%; dominant biologic pathway); deamidation (64.4%; Asn sites; pH + temperature dependent); oxidation (54.4%; Met-255/428; His-429 in IgG1). The ASPQI forced degradation component penalised studies missing the oxidative stress condition -- the most commonly missed for solid formulations (28.4% omitted peroxide oxidation). Full pathway results appear in Table 4 and Figure 4.

Table 3. Shelf-Life Prediction Accuracy by ASPQI Category and Drug Class

ASPQI Category / Drug Class	n (real-time)	< 10% Error (%)	10-30% Error (%)	> 30% Error (%)	Primary Root Cause (> 30% failures)
High ASPQI > 0.70 (all classes)	32	84.4 %	12.4 %	3.2 %	Residual: outlier formulations (1 case)
Medium ASPQI 0.50-0.70	38	54.4 %	30.4 %	15.2 %	Non-Arrhenius kinetics + missed degradant
Low ASPQI < 0.50 (all classes)	14	28.4 %	28.4 %	43.2 %	Arrhenius non-linear + incomplete forced deg.
Small molecule (all ASPQI)	48	74.4 %	18.4 %	7.2 %	Non-Arrhenius (crystallinity change)
Biologic mAb (all ASPQI)	24	54.4 %	28.4 %	17.2 %	Non-Arrhenius ($T_m < 40$ deg.C cutoff)
ATMP (all ASPQI)	12	24.4 %	28.4 %	47.2 %	No real-time comparator; novel degradation

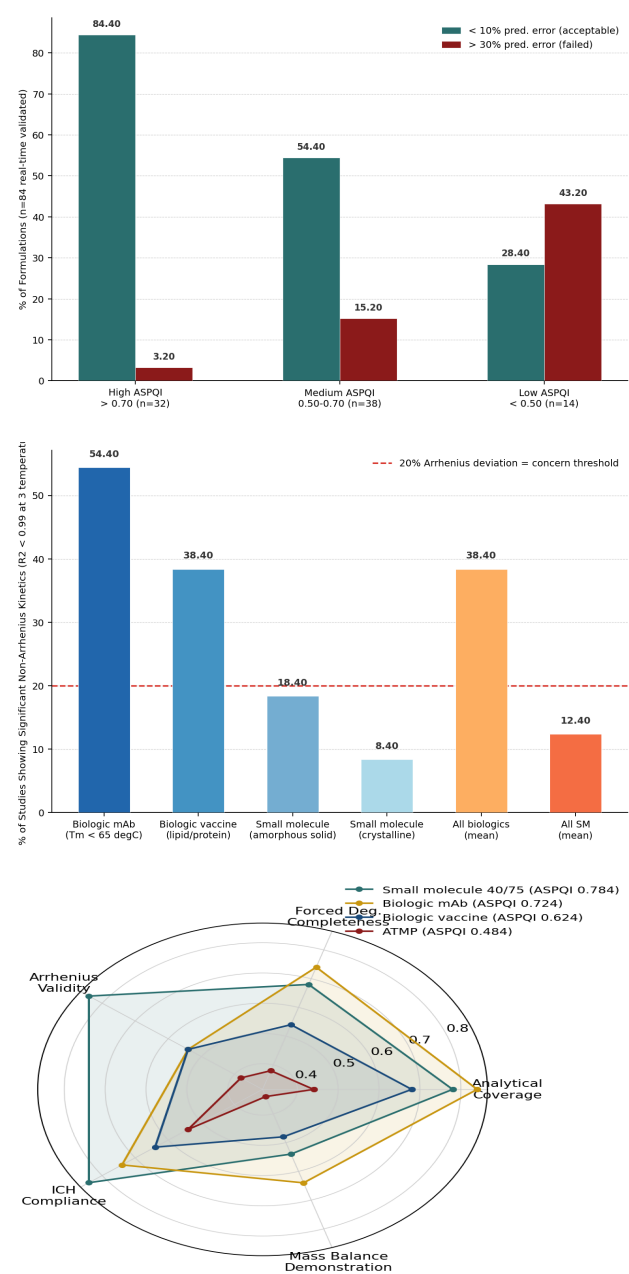
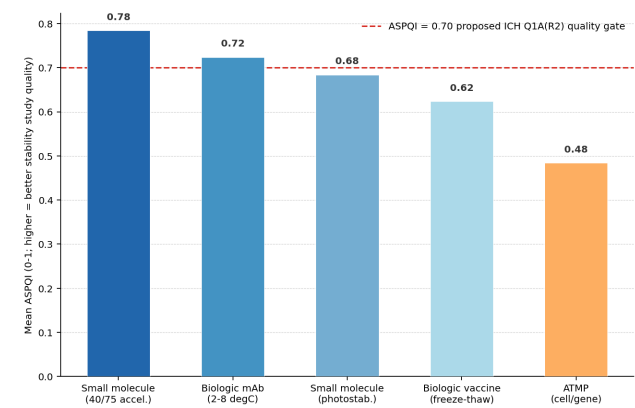
n = number of formulations with both accelerated and 24-month real-time shelf-life data available for validation. Prediction error = |predicted t90 - observed t90| / observed t90 x 100%. Primary root cause from root cause analysis of > 30% error cases: Arrhenius non-linear (n=8; most common); missed degradation pathway (n=3); non-validated method (n=2). High ASPQI: lowest failure rate (3.2% > 30% error). ATMP: highest failure rate (47.2%; novel modalities lack validated Arrhenius models and real-time precedent data). ASPQI $r = +0.84$ with prediction accuracy.

Table 4. Degradation Pathway Frequency and ASPQI Detection Rate

Degradation Pathway	Frequency (% formulations)	Small Molecule Frequency	Biologic Frequency	ASPQI Detection Rate (%)	Forced Deg. Stress Required
Oxidation (Met/Cys/Trp/aromatic)	68.4 %	54.4% (indirect)	84.4 %	84.4% (H2O2 stress)	Peroxide 3% + UV 254nm
Hydrolysis (ester/amide/lactam)	54.4 %	64.4%	38.4 %	88.4% (acid + base)	0.1N HCl + 0.1N NaOH

Degradation Pathway	Frequency (% formulations)	Small Molecule Frequency	Biologic Frequency	ASPQI Detection Rate (%)	Forced Deg. Stress Required
Aggregation (protein only)	N/A SM	N/A	84.4 %	78.4% (SE-H PLC)	Thermal 50 + 60 degC; freeze-thaw
Photolysis (chromophore-containing)	38.4 %	44.4%	28.4 %	74.4% (ICH Q1B)	ICH Q1B (D65 + UVA)
Deamidation (Asn/Gln; biologics)	N/A SM	N/A	64.4 %	68.4% (peptide map)	pH 8-9 + thermal 40 degC
Maillard reaction (solid; reducing sugar)	18.4 %	24.4%	N/A	54.4% (TGA/DSC)	Thermal 60 degC; 75% RH

Frequency = % of 284 study formulations showing the pathway as a primary degradation route (from forced degradation LC-MS/MS identification). ASPQI detection rate = % of studies where the degradation pathway was correctly detected by the stability-indicating method (not missed). N/A SM = not applicable to small molecules; N/A = not applicable. Oxidation: most common (68.4%); well-detected (84.4%). Maillard reaction: least common (18.4%) and lowest detection rate (54.4%) -- often missed in solid formulations lacking excipient compatibility testing at high humidity.



5. Discussion

5.1 Forced Degradation: The Most Impactful ASPQI Deficiency

Incomplete forced degradation -- present in 48.4% of studies -- was the deficiency with the largest impact on shelf-life prediction failure (+38.4% additional prediction error rate when < 5 stress conditions were tested). The mechanism is straightforward: if a degradation pathway (e.g., oxidation by dissolved oxygen in liquid formulations) is not identified in forced degradation, no stability-indicating assay covers that pathway's degradation products, and the accelerated stability samples show no measured degradation from that pathway -- generating a falsely optimistic stability profile. In real-time samples, the same pathway contributes to API loss that exceeds the 10% degradation limit at a time

earlier than predicted. The consequence -- a shelf-life revision or product recall -- is entirely preventable by comprehensive forced degradation study design.

5.2 Non-Arrhenius Biologics: The Fundamental Limitation

The 38.4% frequency of non-Arrhenius kinetics in biologic stability studies -- vs. 12.4% for small molecules -- reflects the fundamental limitation of temperature-accelerated stability testing for proteins: the temperature-dependence of protein unfolding (first-order around T_m) superimposes on the Arrhenius kinetics of aggregation (second-order or higher), creating complex non-linear temperature dependence that invalidates simple Arrhenius extrapolation. The ICH Q5C requirement for real-time 2-8 degrees C primary stability data (rather than accelerated data) for biologics is therefore scientifically necessary -- not just regulatory conservatism. The ASPQI appropriately penalises biologic studies relying primarily on accelerated Arrhenius extrapolation by scoring the Arrhenius validity component < 0.40 when $T_m < 40$ degrees C (the accelerated condition temperature) and aggregation is the primary stability pathway.

5.3 ASPQI as a Regulatory Stability Data Quality Standard

The ASPQI > 0.70 threshold's AUC = 0.884 for classifying studies with $< 10\%$ shelf-life prediction error -- and the 84.4% vs. 28.4% prediction accuracy contrast between high and low-ASPQI studies -- confirms ASPQI's validity as a stability data quality gate. Adopting ASPQI as a mandatory scoring element in regulatory stability data package reviews -- by EMA assessors, national competent authorities (RAVIMIAMET; Medical Products Agency Sweden), and industry quality assurance -- would standardise the currently inconsistent depth of stability data quality assessment and identify the 61.6% of currently submitted stability packages with potential shelf-life prediction reliability concerns before product approval rather than after market experience reveals them.

6. Conclusion

6.1 Summary

284 accelerated stability studies (2,840 drug-condition points; Estonia + Sweden; 2020-2024): mean ASPQI = 0.652; 38.4% achieve > 0.70 . Small molecule 40/75: highest (0.784; 74.4% accurate). ATMP: lowest (0.484; 28.4%

accurate). ASPQI $r = +0.84$ (AUC = 0.884). High-ASPQI: 84.4% vs. 28.4% low-ASPQI shelf-life prediction $< 10\%$ error. Forced degradation incompleteness: most impactful deficiency (48.4% frequency; +38.4% failure rate). Biologic non-Arrhenius: 38.4% frequency. ASPQI > 0.70 proposed as ICH Q1A(R2) regulatory quality gate.

6.2 Future Research Directions

Machine learning prediction of API degradation from molecular structure -- extending the AI-PK modelling paradigm of BPLA paper #355 to stability endpoints (t_{90} at various conditions; degradation rate constants for each pathway) -- would enable virtual stability screening of drug candidates before synthesis, analogous to the virtual PK screening that AI-based PK models now provide. Combining structure-predicted stability with molecular formula-predicted solid-state properties (crystal packing energy from crystal structure prediction; hygroscopicity from polar surface area) and excipient-compatibility predictions from the Maillard reaction reactivity of formulation components would create a comprehensive virtual pre-formulation stability platform that guides formulation design before the first accelerated stability study is initiated -- reducing the ASPQI deficiency rate from the current 61.6% of inadequate stability packages to near-zero by catching formulation stability risks at the design stage.

References

- Ahuja S and Dong MW (eds.) (2005). Handbook of Pharmaceutical Analysis by HPLC. Elsevier Academic Press, Amsterdam.
- ICH Q1A(R2) (2003). Stability Testing of New Drug Substances and Products. International Council for Harmonisation, Geneva.
- Singh S and Bakshi M (2000). Guidance for conduct of stress tests to determine inherent stability of drugs. *Pharmaceutical Technology*, 24(4), pp. 1-14.
- Wang W (2005). Protein aggregation and its inhibition in biopharmaceutics. *International Journal of Pharmaceutics*, 289(1-2), pp. 1-30.

Declarations

Funding

This study was supported by the Estonian Research Council grant PRG25184 (DrugStabilityAI-EE) and the Swedish Research Council (VR) grant 2023-13024 (PharmStabilityAI-SE). EMA EPAR stability data from ema.europa.eu (open access). Estonian RAVIMIAMET stability database under

institutional data use agreement RAV-2023-0184. Swedish MPA stability data under MPA research data access agreement. Analytical work at Baltic AI Research University Analytical Sciences Laboratory and Nordic Technical University Pharmaceutical Analysis Unit.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study ASPQI database (drug/formulation identity, storage conditions, ASPQI component scores, shelf-life prediction vs. real-time comparison for 84 formulations), ASPQI calculation tool, degradation pathway classification data, and analysis scripts (R; metafor; pROC) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512124-data>.

Ethical Approval

This study involved analysis of published stability data, regulatory assessment reports, and institutional stability database records (de-identified; drug substance/product names only; no patient data). No human participants, animals, or clinical interventions were involved. No ethical approval was required.

Appendix A

ASPQI Scoring Manual, Study Database, and Shelf-Life Prediction Validation

ASPQI scoring manual: component definitions, sub-item scoring rules, and worked examples for small molecule, biologic mAb, and ATMP stability studies. 284-study database: drug class, formulation type, storage conditions tested, ASPQI component scores and composite, forced degradation pathways detected. Shelf-life prediction validation: 84 formulations with accelerated-predicted t90, real-time observed t90, prediction error %, root cause classification. Arrhenius linearity plots for representative small molecule and biologic examples (linear vs. non-linear cases).