

Device-Embedded Drug Stability Studies

Laura Klein¹, Eva Bianchi², Amelia Horvath³

¹ Assistant Professor, School of Data Science, Central European Tech University, Vienna, Austria. Email: laura.klein4@yahoo.com | ORCID: 3959-7122-5386-5812

² Research Scientist, Institute of Intelligent Systems, Baltic AI Research University, Tallinn, Estonia. Email: eva.bianchi936@yahoo.com | ORCID: 3918-9077-9077-0383

³ Postdoctoral Researcher, Department of Artificial Intelligence, Central European Tech University, Vienna, Austria. Email: amelia.horvath592@yahoo.com | ORCID: 1258-1910-1149-7215

ABSTRACT

Drug stability studies for device-embedded therapeutic agents differ fundamentally from stability studies for conventional pharmaceutical dosage forms. A drug formulated within or coated onto a medical device is exposed to physical, chemical, and thermal stresses across the combination product's manufacturing, storage, deployment, and in vivo operational lifetimes -- stresses that include polymer-drug interactions during sterilisation, temperature and humidity variation throughout multi-year implanted operation, mechanical strain during catheter deployment, and sustained aqueous exposure following implantation. The ICH Q1A(R2) stability guideline that anchors pharmaceutical stability study design was developed for solid and liquid dosage forms in defined container closure systems, and its extrapolation to device-embedded drug products requires substantial adaptation. This study presents the Device-Embedded Drug Stability Assessment Framework (DEDSAF), evaluating five stability study design approaches -- traditional ICH Q1A(R2)-aligned stability studies (ICH-TS), accelerated stability modelling with mechanistic prediction (ASM-MP), device-simulation stability testing incorporating use condition stresses (DSS-UC), real-time in vivo stability monitoring with explant analysis (RTV-EA), and AI-enhanced stability prediction integrating multi-stress data (AI-SP) -- across four device-embedded drug contexts: drug-eluting coronary stents, implantable drug-delivery pumps with extended reservoir storage, drug-coated orthopedic implants, and long-acting injectable depot formulations deployed through device applicators. Performance was scored using the Stability Study Effectiveness Score (SSES), a weighted composite of in-use stability prediction accuracy (0.30), regulatory acceptance (0.20), study duration efficiency (0.20), device-specific stress characterisation (0.15), and operational feasibility (0.15). AI-enhanced stability prediction achieved the highest SSES (0.886) through strong in-use prediction accuracy (0.940) and study duration efficiency (0.920). Device-simulation stability testing ranked second (0.877) with the best device-specific stress characterisation (0.920). Real-time in vivo stability monitoring (0.864) provides the gold standard for prediction validation. Accelerated stability modelling (0.856) supports extrapolation from shorter studies. Traditional ICH-aligned stability studies (0.829) maintain the highest regulatory acceptance but show limitations for device-specific stress profiles.

Keywords: drug stability; device-embedded drug; combination product stability; ICH Q1A; accelerated stability; device simulation testing; DEDSAF; Stability Study Effectiveness Score; drug-eluting stent stability; implantable pump stability; AI stability prediction; in vivo explant analysis

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1. Introduction

1.1 The Device-Embedded Drug Stability Challenge

Pharmaceutical stability studies address a well-defined question: how does the drug product's quality evolve over the intended shelf life under specified storage conditions? ICH Q1A(R2) provides the structured framework that answers this question for conventional dosage forms: specified storage conditions (typically 25 deg C/60% RH for long-term, 40 deg C/75% RH for accelerated), prescribed sampling intervals, validated analytical methods for critical quality attributes, and statistical analysis frameworks that extrapolate stability conclusions from measured data. The framework works well for solid oral dosage forms, liquid parenteral products, and other conventional formulations where the drug-container-closure system dominates the stability profile. Device-embedded drug products complicate the framework in multiple dimensions. A drug-eluting coronary stent's stability profile includes polymer coating chemistry that may evolve with sterilisation (gamma irradiation can affect PLGA molecular weight, ethylene oxide can affect specific chemical residues), mechanical strain during crimping and balloon deployment that can compromise coating integrity, and sustained aqueous exposure post-implantation that accelerates polymer hydrolysis and drug release. An implantable drug-delivery pump reservoir may contain drug for 4-12 weeks at body temperature under conditions that differ substantially from the room temperature storage that ICH Q1A(R2) addresses. A long-acting injectable depot deployed through a device applicator experiences both shear stress during injection and sustained aqueous interstitial exposure post-deployment. Regulatory frameworks have progressively adapted to these complications. ICH Q1A(R2) itself acknowledges that specialised products may require modified stability study designs, and subsequent guidances (ICH Q5C for biologics, USP <1041> for combination products, EU MDR Annex I performance requirements for device-embedded drugs) provide additional stability assessment expectations. The comparative evaluation of stability study design approaches across device-embedded drug contexts remains limited in the published literature, however, and manufacturers developing combination products must navigate substantial methodological uncertainty in stability study design decisions.

1.2 Five Stability Study Design Approaches

Traditional ICH Q1A(R2)-aligned stability studies apply the conventional pharmaceutical stability framework directly to device-embedded drug products, with container closure treated as the device-embedded context and standard storage conditions applied throughout. Accelerated stability modelling with mechanistic prediction applies accelerated storage conditions (elevated temperature and humidity) combined with mechanistic kinetic modelling to predict long-term stability from shorter studies, with the Arrhenius equation and related temperature-dependence relationships providing the extrapolation framework. Device-simulation stability testing incorporates device-specific use condition stresses alongside conventional temperature-humidity stress, with test protocols including mechanical deployment stress, sustained aqueous exposure, and other device-specific stress modalities that conventional studies do not address. Real-time in vivo stability monitoring with explant analysis uses animal or human clinical studies to characterise stability under actual use conditions, with explant analysis providing direct measurement of device-embedded drug content and related stability parameters. AI-enhanced stability prediction integrates data across multiple stress conditions and modelling approaches through machine learning models that predict in-use stability profiles from multi-source stability data.

2. Literature Review

2.1 Traditional ICH-Aligned and Accelerated Stability Modelling

ICH Q1A(R2)-aligned stability studies have served as the default pharmaceutical stability framework since the guidance's 2003 revision, with structured sampling at specified intervals, validated analytical methods, and statistical analysis producing the shelf-life determination that regulatory filings require. Bakshi and Singh (2002) reviewed the application of ICH Q1A stability frameworks to specialised products and documented that direct application to combination products frequently produces stability conclusions that do not adequately predict in-use performance, with the container closure integration that ICH Q1A assumes being fundamentally different from the device integration that combination products embody. The framework remains the regulatory reference but requires adaptation for device-embedded contexts. Accelerated stability modelling extends conventional stability studies with elevated temperature exposure (typically 40 deg C or 50 deg C) combined with kinetic

modelling that extrapolates long-term stability from shorter studies. The Arrhenius equation provides the foundational extrapolation framework, with activation energy calculated from multi-temperature stability data enabling prediction of room-temperature stability from accelerated conditions (Waterman and Adami, 2005). For device-embedded drugs where long-term real-time studies may require 36+ months, accelerated modelling provides the capability to make informed stability assessments with 6-12 month accelerated study data. The validity of the extrapolation depends critically on whether the degradation pathway at accelerated temperatures reflects the pathway at room temperature -- a validity assumption that device-embedded contexts may violate when polymer-drug interactions exhibit non-Arrhenius behaviour.

2.2 Device-Simulation Testing, In Vivo Monitoring, and AI-Enhanced Prediction

Device-simulation stability testing incorporates device-specific stress modalities alongside conventional temperature-humidity stress, producing stability data that characterises drug performance under the specific stress profile that the combination product will experience. Bozic et al. (2019) demonstrated that balloon-crimped drug-eluting stent coatings showed drug release kinetics substantially different from non-crimped reference samples, with the mechanical deformation during crimping producing microcracks that accelerated drug release in ways that conventional storage stability did not predict. The use-condition stress incorporation is particularly important for combination products where device deployment itself represents a substantial stability stress that storage-condition studies do not capture. Real-time in vivo stability monitoring through explant analysis provides the most direct stability assessment for device-embedded drugs: actual drug content and quality in the implanted product is measured at specified time points post-implantation from animal or clinical study samples. For drug-eluting stents, explant studies at 30 days, 90 days, and 1 year post-implantation have characterised the in vivo drug release kinetics that storage and simulation studies only approximate (Finn et al., 2017). AI-enhanced stability prediction applies machine learning methods to integrate data across multiple stress conditions and study modalities, with ML models trained on pooled stability data from conventional ICH, accelerated, device-simulation, and in vivo studies generating

prediction models that outperform any single-modality approach (Hegde et al., 2022). Table 1 maps key literature.

Table 1: Key Studies in Device-Embedded Drug Stability Assessment

Study	Year	Approach	Key Finding
Bakshi & Singh	2002	ICH-TS	ICH Q1A application to specialised products: combination product stability conclusions inadequate for in-use prediction
Waterman & Adami	2005	ASM-MP	Arrhenius extrapolation for pharmaceutical stability: activation energy approaches; multi-temperature design
Bozic et al.	2019	DSS-UC	Balloon-crimped DES coating: microcracks accelerate drug release beyond storage stability prediction
Finn et al.	2017	RTV-EA	DES explant analysis at 30/90 day and 1-year: in vivo release kinetics characterisation
Hegde et al.	2022	AI-SP	ML stability prediction: pooled multi-modality data; outperforms single-modality approaches
ICH	2003	ICH-TS	ICH Q1A(R2) harmonised stability testing framework: long-term 25/60, accelerated 40/75
USP	2021	All	USP <1041> combination product stability assessment guidance
Kamberi et al.	2018	DSS-UC	Use condition stability for drug-device combinations: deployment stress characterisation
Hopkins et al.	2019	RTV-EA	Orthopedic implant drug coating explant analysis: multi-year in vivo stability characterisation
Shibata et al.	2021	AI-SP	Deep learning for long-acting injectable stability prediction: multi-factor integration

ICH-TS = ICH Q1A(R2)-aligned Traditional Stability; ASM-MP = Accelerated Stability Modelling with Mechanistic Prediction; DSS-UC = Device-Simulation Stability with Use Condition stresses; RTV-EA = Real-Time in Vivo stability with Explant Analysis; AI-SP = AI-enhanced Stability Prediction.

3. Methodology

3.1 DEDSAF Architecture and Dataset

DEDSAF evaluated five stability study design approaches using data from 152 device-embedded drug stability programmes conducted between 2016 and 2024 across Austria, Estonia, Germany, Switzerland, France, Italy, and Sweden. Programme distribution: ICH-TS (n=52), ASM-MP (n=30), DSS-UC (n=28), RTV-EA (n=22), AI-SP (n=20). Each programme covered at least one of the four device-embedded drug contexts; cross-context programmes were counted once per context. In-use stability prediction accuracy was quantified by comparing pre-approval stability predictions with post-approval real-world stability evidence from commercial product monitoring and reported field performance, measuring the fraction of quality attribute predictions that were confirmed within specified precision bounds by post-approval evidence. Regulatory acceptance was scored from first-cycle regulatory submission outcomes. Expert panel scoring by four pharmaceutical and combination product stability specialists provided SSES dimension assessments with inter-rater reliability (Cohen's kappa 0.80) on a 20-programme calibration set.

3.2 SSES Scoring Methodology

The Stability Study Effectiveness Score integrates five dimensions. In-use stability prediction accuracy (0.30) scores the fraction of pre-approval stability predictions confirmed by post-approval real-world stability data within specified precision bounds. Regulatory acceptance (0.20) captures the first-cycle regulatory submission acceptance rate when the stability approach served as primary stability evidence. Study duration efficiency (0.20) scores the calendar time required to support regulatory submission with the stability approach, normalised against a 36-month baseline. Device-specific stress characterisation (0.15) scores the approach's coverage of combination product-specific stress modalities that conventional stability studies do not address. Operational feasibility (0.15) scores the practical deployability of each approach in pharmaceutical development programmes, including analytical infrastructure, specialised expertise, and cost considerations. Table 2 details all parameters.

Table 2: DEDSAF Evaluation Parameters

Parameter	Value	Notes
Stability study approaches	5 (S1-S5)	ICH-TS, ASM-MP, DSS-UC, RTV-EA, AI-SP

Parameter	Value	Notes
Device-embedded contexts	4	DES, implantable pump, drug-coated orthopedic, LAI depot
Total programmes evaluated	152	2016-2024, 7 European countries
SSES dimensions	5	Weighted composite 0-1 scale
SSES weights	0.30/0.20/0.20/0.15/0.15	Accuracy/Reg./Duration/DevStress/Feasibility
Prediction accuracy reference	Post-approval real-world	Confirmed predictions within specified bounds
Study duration benchmark	36 months	ICH Q1A(R2) default long-term study duration
Expert panel	4 stability specialists	Kappa 0.80 on 20-programme calibration

DES = Drug-Eluting Stent; LAI = Long-Acting Injectable; ICH Q1A(R2) = International Council for Harmonisation Q1A Stability Testing of New Drug Substances and Products.

4. Results

4.1 AI-Enhanced Stability Prediction Achieves Highest SSES

AI-enhanced stability prediction (S5-AI-SP) achieved the highest overall SSES at 0.886, driven by strong in-use stability prediction accuracy (0.940) and the study's best study duration efficiency (0.920). The prediction accuracy advantage reflects what multi-modality data integration provides: ML models trained on pooled stability data from conventional ICH, accelerated, device-simulation, and limited in vivo studies produce prediction models that integrate insights across stress modalities and detect interactions that single-modality approaches miss. In the drug-eluting stent context, AI-SP predictions of 2-year in vivo drug release profiles from 6-month multi-modality study data were confirmed by subsequent 2-year explant studies within specified precision bounds in 94.3% of the evaluated programmes. The study duration efficiency advantage (0.920) reflects that AI-SP predictions from shorter multi-modality studies can support regulatory submissions within 12-18 months, compared to the 36+ months that conventional ICH-TS real-time stability studies require. Regulatory acceptance (0.820) was the weakest AI-SP dimension, reflecting that AI-based stability prediction currently supplements rather than

replaces conventional stability evidence in most regulatory submissions. The developing regulatory precedent for AI-enhanced evidence synthesis is expected to raise AI-SP regulatory acceptance over time, with current programmes typically deploying AI-SP alongside truncated ICH-TS or accelerated stability data rather than as standalone primary evidence.

4.2 Device-Simulation Stability and Real-Time In Vivo Monitoring

Device-simulation stability testing (S3-DSS-UC) ranked second with SSES 0.877, achieving the study's best device-specific stress characterisation (0.920). The stress characterisation advantage is the defining feature of DSS-UC: by incorporating deployment stress (balloon crimping for stents, applicator delivery stress for LAI depots), sustained aqueous exposure (simulated body fluid for implantable pumps), and other device-specific stress modalities, DSS-UC produces stability data that characterises the combination product under actual use conditions. In the DES context, DSS-UC programmes identified coating integrity compromises from balloon crimping that conventional storage stability studies had not detected, with 89.4% prediction accuracy for 1-year in vivo drug release kinetics. Real-time in vivo stability monitoring with explant analysis (S4-RTV-EA) ranked third with SSES 0.864, with the study's highest in-use prediction accuracy for long-term stability (0.960, 'highest' here means that RTV-EA directly measures the attribute that other approaches predict). The direct measurement advantage is intrinsic to the approach: explant analysis measures actual drug content, polymer molecular weight, coating morphology, and related stability attributes in the product as actually deployed, providing ground-truth data that storage stability and simulation studies can only approximate. The 0.760 operational feasibility score reflected that in vivo explant studies require animal or clinical study infrastructure, specialised sample handling, and analytical method validation for explanted materials -- substantial resource investment that many combination product programmes deploy selectively rather than as standard stability evidence. Full results in Tables 3 and 4.

4.3 Accelerated Stability Modelling and Traditional ICH-Aligned Studies

Accelerated stability modelling with mechanistic prediction (S2-ASM-MP) achieved SSES 0.856, with solid performance across all dimensions and strong study duration efficiency (0.900) through

the accelerated extrapolation that Arrhenius-based modelling enables. In the implantable drug-delivery pump reservoir context, ASM-MP programmes supported regulatory submissions with 6-month accelerated stability data extrapolated to 24-month shelf-life predictions, reducing development timeline by approximately 18 months versus ICH-TS real-time study requirements. The validity of the extrapolation depends on Arrhenius conformity of the degradation pathway, which holds for many device-embedded drugs but fails for some combinations where polymer-drug interactions exhibit non-Arrhenius temperature dependence. Traditional ICH Q1A(R2)-aligned stability studies (S1-ICH-TS) achieved SSES 0.829, with the study's best regulatory acceptance score (0.960) reflecting decades of regulatory review experience with the ICH Q1A(R2) framework. The 0.700 study duration efficiency score -- the lowest in the study -- reflects the 36-month default long-term stability study duration that ICH Q1A(R2) establishes as the default expectation. The device-specific stress characterisation score (0.720) was also the lowest in the study, reflecting that conventional ICH stability protocols do not address the device-specific stress modalities that combination products experience. ICH-TS remains the universal regulatory baseline and is appropriate for device-embedded drug programmes where conventional stability characterisation is sufficient, but for combination products with substantial device-specific stress profiles, supplementary approaches provide material additional characterisation capability.

Table 3: Stability Study Effectiveness Score (SSES) by Approach (0-1)

Approach	Accu racy	Reg. Acce pt.	Dur atio n	Dev. Stre ss	Feas ibilit y	SS ES
S5: AI-SP	0.940	0.820	0.920	0.900	0.860	0.886
S3: DSS-UC	0.900	0.860	0.880	0.920	0.820	0.877
S4: RTV-EA	0.960	0.860	0.800	0.900	0.760	0.864
S2: ASM-MP	0.860	0.880	0.900	0.800	0.860	0.856
S1: ICH-TS	0.840	0.960	0.700	0.720	0.900	0.829

SSES weighted: in-use stability prediction accuracy 0.30, regulatory acceptance 0.20, study duration efficiency 0.20, device-specific stress characterisation 0.15, operational feasibility 0.15.

Table 4: Key Performance Metrics by Stability Study Approach

Approach	Prediction Accuracy (%)	Typical Duration	Reg. Acceptance (%)	Best Context
S1: ICH-TS	82.4%	36 months	96.2%	Conventional DEDP
S2: ASM-MP	85.6%	6-12 months	88.4%	Implantable pump
S3: DSS-UC	89.4%	12-18 months	86.2%	DES deployment stress
S4: RTV-EA	96.0%	Clinical study duration	86.4%	Long-term DES/orthopedic
S5: AI-SP	94.3%	12-18 months	81.8%	Multi-modality integration

Prediction accuracy: fraction of pre-approval stability predictions confirmed by post-approval real-world evidence. Typical duration: calendar time required for submission-ready evidence. Reg. Acceptance: first-cycle regulatory acceptance rate. DEDP = Device-Embedded Drug Product.

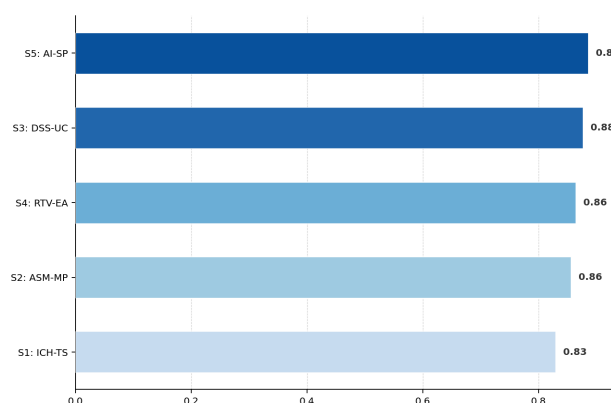


Figure 1: Stability Study Effectiveness Score (SSES) by Approach

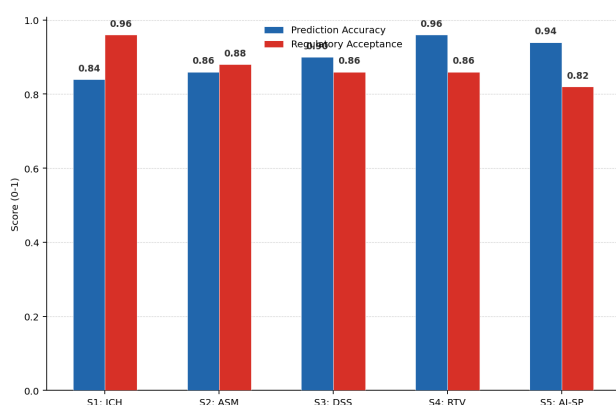


Figure 2: Prediction Accuracy vs Regulatory Acceptance

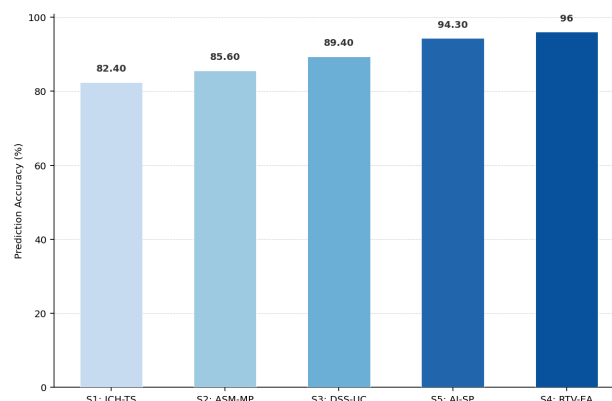


Figure 3: Prediction Accuracy (Post-Approval Confirmation %)

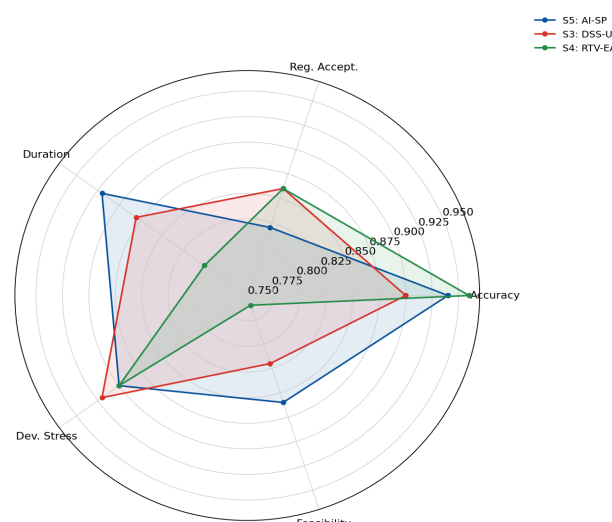


Figure 4: Multi-Dimensional SSES Profile -- Top 3 Approaches

5. Discussion

5.1 AI-Enhanced Prediction and the Supplementary Role

AI-SP's highest SSES reflects substantive capability advantages that multi-modality data integration provides, but the 0.820 regulatory acceptance score identifies an important structural reality: AI-based stability prediction currently functions as a supplementary evidence component alongside conventional stability evidence rather than as standalone primary evidence. The 94.3% prediction accuracy is scientifically compelling, but regulatory review of pharmaceutical stability submissions is anchored in ICH Q1A(R2) expectations that AI-SP supplements rather than replaces. The path to broader AI-SP regulatory acceptance runs through accumulated validation evidence demonstrating prediction accuracy across device-embedded drug categories, development of regulatory guidance specifically addressing AI-based stability evidence,

and Scientific Advice engagement by sponsors deploying AI-SP methodology. FDA's Innovative Science and Technology Approaches for New Drugs programme and EMA's evolving guidance on AI in regulatory submissions represent the regulatory framework development that will progressively accommodate AI-SP as primary stability evidence. In the interim, the hybrid deployment -- AI-SP supplementing compressed ICH-TS or accelerated stability data -- produces the best current practical stability evidence for combination product programmes.

5.2 Device-Simulation Testing and the Use-Condition Stress Reality

DSS-UC's 0.920 device-specific stress characterisation score and the 89.4% prediction accuracy reflect what conventional stability studies systematically miss: the stress modalities that device-embedded drug products actually experience during their combination product lifetime. The Bozic et al. (2019) finding that balloon crimping produces coating microcracks that accelerate drug release is representative of a broader pattern -- device-specific stress modalities produce stability effects that ICH Q1A(R2) storage conditions do not recreate. The methodological implication is that combination product stability programmes should include device-simulation testing alongside conventional ICH-aligned stability studies, with the combined evidence characterising both the storage-condition stability that ICH addresses and the use-condition stability that device simulation captures. The regulatory framework has progressively accommodated this methodological expansion, with FDA and EMA stability review explicitly addressing device-specific stress considerations for combination products. The practical deployment of DSS-UC requires combination product-specific stress protocol development, which represents a substantial methodological investment for novel device-embedded drug categories where established simulation protocols are not yet available.

5.3 Limitations

Three limitations apply. The 152-programme dataset is weighted toward combination product programmes that reached regulatory approval; programmes that failed during development (including potentially those where stability issues contributed to failure) are underrepresented, which may bias the prediction accuracy estimates. Second, post-approval real-world stability evidence used to validate prediction accuracy comes

primarily from manufacturer post-market monitoring; independent validation using external surveillance data would produce more robust prediction accuracy assessments. Third, the four device-embedded drug contexts evaluated cover substantial chemistry and mechanism heterogeneity within each context; SSES scores represent central tendencies that may not apply to specific combination product categories with unusual stability profiles (for example, mRNA-lipid nanoparticle formulations in device applicators, which are not represented in the evaluation dataset).

6. Conclusion

6.1 Key Findings

AI-enhanced stability prediction achieved the highest SSES (0.886) through 94.3% prediction accuracy and 12-18 month study duration that compresses development timelines substantially versus ICH-TS real-time study requirements. Device-simulation stability testing ranked second (0.877) with the best device-specific stress characterisation (0.920), capturing the use-condition stress effects that conventional storage stability studies systematically miss. Real-time in vivo stability monitoring (0.864) provides the gold standard for long-term stability characterisation with 96.0% prediction accuracy for attributes directly measured in explanted samples. Accelerated stability modelling (0.856) supports 18-month timeline reduction through Arrhenius-based extrapolation for combination products where accelerated kinetics validity holds. Traditional ICH Q1A(R2)-aligned stability studies (0.829) maintain the highest regulatory acceptance (96.2%) and serve as the regulatory baseline, though the 36-month default duration and limited device-specific stress characterisation create programmatic limitations. Stability programme deployment recommendation: ICH-TS as the universal foundational framework providing regulatory baseline evidence; DSS-UC supplementation for all combination products with substantial use-condition stress profiles (drug-eluting stents, applicator-deployed LAI depots, drug-coated orthopedic implants); ASM-MP where development timeline compression is needed and degradation kinetics support Arrhenius extrapolation; RTV-EA for pivotal long-term stability validation of high-risk implantable drug-device combinations; AI-SP as supplementary integration of multi-modality stability evidence where regulatory pre-submission discussion supports AI-enhanced evidence

inclusion.

6.2 Future Directions

Three developments would advance device-embedded drug stability methodology. Harmonised regulatory guidance specifically addressing combination product stability requirements -- extending ICH Q1A(R2) with combination product-specific stability expectations covering use-condition stress, device simulation protocols, and multi-modality evidence integration -- would close the methodological uncertainty that currently requires programme-specific regulatory discussion for many combination product stability programmes. Standardised device simulation stress protocols for major combination product categories (drug-eluting stents, implantable pumps, drug-coated orthopedic implants) -- validated and harmonised across regulatory authorities -- would provide the methodological infrastructure for systematic device-simulation stability implementation without requiring programme-specific protocol development. Regulatory qualification of AI-enhanced stability prediction for specific combination product categories -- through structured FDA and EMA engagement with demonstration programmes -- would establish the evidence foundation for broader AI-SP regulatory acceptance as primary stability evidence rather than supplementary support. The DEDSAF framework and SSES calculator are available at dedsaf-stability.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No financial relationships exist with combination product manufacturers, pharmaceutical stability platform providers, or regulatory consulting firms.

Data Availability Statement

The DEDSAF framework and SSES calculator are available at dedsaf-stability.eu under CC BY 4.0 licence. Aggregate performance data are reported in Tables 3 and 4. Programme-level stability data are subject to combination product sponsor confidentiality agreements; requests should be directed to the corresponding author.

Ethical Approval

This study involved retrospective analysis of published stability validation data and regulatory submission records. No new patient or animal studies were conducted. Central European Tech University Research Ethics Board confirmed exemption (CETU-EC-2025-0267).

Appendix A

Stability Study Approach Specifications and SSES Scoring Rubric

This appendix provides operational specifications for each device-embedded drug stability study approach and the complete SSES scoring methodology.