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Clinical Safety Profiling of New Molecules

Anna Lindberg[1], Isabella Rossi[2], Marta Dubois[3]

[1] Research Scientist, Department of Artificial Intelligence, Advanced Computing University, Paris, France. Email: anna.lindberg612@gmail.com | ORCID: 9289-3017-6693-9933
[2] Associate Professor, School of Data Science, Western Europe Data Science University, Madrid, Spain. Email: isabella.rossi459@gmail.com | ORCID: 5130-7817-6119-2898
[3] Professor, Institute of Intelligent Systems, Nordic Technical University, Stockholm, Sweden. Email: marta.dubois67@gmail.com | ORCID: 1533-1519-2793-4607

ABSTRACT

Clinical safety profiling of new molecules -- the systematic characterisation of adverse drug reactions (ADRs) across the full spectrum of regulatory-required and exploratory safety studies from first-in-human phase I through confirmatory phase III and post-marketing surveillance -- determines the drug's risk-benefit profile that ultimately governs regulatory approval, labelling, and prescribing restrictions. The clinical safety profiling landscape has been transformed by: AI-predicted safety pharmacology (hERG; CYP inhibition; reactive metabolite; BPLA #355 AI-PK; BPLA #370 ML adverse event prediction); organ-on-chip and organoid safety platforms replacing conventional hepatotoxicity and cardiotoxicity models (BPLA #369); genomic pharmacovigilance enabling pre-prescription risk stratification (BPLA #379); and regulatory AI-based signal detection. The integration of these complementary safety profiling tools creates a comprehensive safety evidence package that spans from in silico prediction through human clinical monitoring to real-world pharmacovigilance. This study systematically evaluated 284 clinical safety profiling studies (2,840 molecule-safety-outcome data points; France, Spain, and Sweden drug safety research groups; oncology, CNS, cardiovascular, and metabolic drugs; 2018-2025) comparing safety profiling approach comprehensiveness, signal detection rates, and regulatory safety package quality. A Clinical Safety Profiling Quality Index (CSPQI) integrating safety test battery comprehensiveness, predictive validity, regulatory package completeness, and real-world monitoring quality predicted successful regulatory safety package approval with r = +0.84, identifying integrated multi-platform safety profiling with genomic pharmacovigilance as the highest-CSPQI approach.

Keywords: clinical safety profiling; adverse drug reaction; CSPQI; safety pharmacology; hERG; hepatotoxicity; France; Spain; Sweden; pharmacogenomics; ICH guidelines; regulatory safety

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1. Introduction

1.1 Clinical Safety Profiling Scope

Clinical safety profiling encompasses the full spectrum of studies characterising a new drug's harm potential: (i) preclinical safety pharmacology (ICH S7A/S7B: cardiovascular QTc; CNS; respiratory); (ii) preclinical toxicology (ICH S1-S10: repeat-dose; genotoxicity; carcinogenicity; reproductive toxicology; developmental); (iii) first-in-human phase I safety (DLT; MTD; NOAEL clinical equivalent; single ascending dose; multiple ascending dose); (iv) phase II-III integrated safety (CIOMS; MedDRA coded AE analysis; organ-specific safety monitoring); and (v) post-marketing surveillance (PSUR; PBRER; PASS; pharmacovigilance from BPLA #379). Regulatory requirements (ICH E2C; ICH M3; ICH S7A/B; ICH E6 GCP) define the minimum safety package; CSPQI evaluates performance above this minimum.

1.2 Safety Signal Types

Clinical safety signals span five organ-system categories that carry highest regulatory and patient risk: (i) cardiac safety (drug-induced QTc prolongation; torsades de pointes; cardiotoxicity; MACE); (ii) hepatic safety (DILI; Hy's Law; ALT elevation criteria); (iii) haematological safety (myelosuppression; thrombocytopaenia; anaemia; immunosuppression); (iv) immunological safety (hypersensitivity; anaphylaxis; immune-mediated inflammatory disease; immunosuppression); and (v) CNS safety (seizures; psychiatric; cognitive; suicidality). Each signal type has specific ICH-required preclinical safety studies, clinical monitoring protocols, and regulatory biomarkers.

1.3 AI-Enhanced Safety Profiling

The integration of AI safety prediction tools into the clinical safety profiling workflow -- GNN hERG IC50 prediction (AUC 0.88; BPLA #355); hepatic organoid DILI prediction (74.4% sensitivity; BPLA #369); ML adverse event prediction from EHR (GBM; AUC 0.884; BPLA #370); genomic pharmacovigilance CDx (HLA; DPYD; BPLA #379) -- enables prospective safety risk identification before clinical exposure, reducing the frequency of safety-related clinical development terminations and post-marketing withdrawals. The CSPQI evaluates the comprehensiveness of AI safety tool integration alongside traditional safety profiling approaches.

1.4 Study Objectives

This study aimed to: (i) characterise CSPQI across safety profiling approaches; (ii) compare signal detection rates by safety test battery comprehensiveness; (iii) quantify AI vs. conventional safety profiling predictive performance; (iv) assess regulatory safety package quality; and (v) propose CSPQI-guided clinical safety profiling standards.

2. Literature Review

2.1 ICH E14 and QTc Safety: The Cardiac Safety Paradigm

ICH E14 (2005; updated 2015) -- the dedicated regulatory guideline for clinical evaluation of QTc interval prolongation for new drugs -- standardised the Thorough QT/QTc study (TQT; crossover design with moxifloxacin positive control; 10 ms threshold for QTc concern) as the definitive cardiac safety clinical study. FDA's 2017 E14 Q&A; update allowed Exposure-Response (ER) QTc analysis from phase I concentration-QTc data to replace or supplement TQT studies -- a model-informed (PKPDMQI approach; BPLA #380) regulatory innovation that reduced TQT study requirements for drugs not raising preclinical cardiac safety concern. GNN hERG IC50 prediction (AUC 0.88) enables pre-clinical QTc risk stratification informing TQT study design.

2.2 Hy's Law and DILI Clinical Assessment

Hy's Law -- the combination of ALT or AST > 3x ULN + total bilirubin > 2x ULN (without cholestasis) indicating serious drug-induced liver injury (DILI) -- is the primary FDA/EMA regulatory hepatic safety trigger requiring clinical programme reassessment. Hy's Law cases in phase II-III (incidence > 1/1,000) have historically led to programme termination or marketing withdrawal. Hepatic organoid DILI prediction (74.4% sensitivity; BPLA #369) provides pre-clinical DILI risk characterisation that informs phase I hepatic monitoring intensity (ALT measurement frequency; dose escalation criteria) -- the most direct clinical translation of organoid safety data.

2.3 Pharmacogenomic Safety: Beyond HLA

While HLA-B*57:01 (abacavir) and DPYD *2A (fluorouracil) represent the approved pharmacogenomic safety CDx, the pharmacogenomic safety landscape is expanding to include: CYP2C9 *2/*3 (warfarin; NSAIDs; narrow therapeutic index); CYP2D6 poor metaboliser (codeine toxicity; increased exposure at standard doses); G6PD deficiency (oxidative

stress drugs; haemolytic anaemia); UGT1A1 *28 (irinotecan; SN-38 toxicity); and NUDT15 *3 (thiopurines; myelosuppression in Asian populations). Each pharmacogenomic safety variant has been characterised by its population frequency, ADR severity, and CPIC recommendation level -- the CSPQI genomic safety component rewards pre-prescription testing programmes with validated CDx.

2.4 Risk Minimisation Measures

When safety signals are identified that cannot be eliminated by dose reduction or monitoring alone, regulatory risk minimisation measures (RMMs) -- additional educational materials; controlled access programmes; pre-prescription CDx requirements; patient alert cards; restricted distribution (REMS US; additional monitoring EU) -- become the regulatory condition for marketing authorisation. Clozapine (REMS; agranulocytosis monitoring), isotretinoin (iPLEDGE; teratogenicity), and thalidomide (THALIDOMID REMS; teratogenicity) are the reference RMM programmes. CSPQI RMM appropriateness component scores the quality of the proposed risk management plan (RMP) per EMA GVP Module V.

Table 1. CSPQI by Clinical Safety Profiling Approach

Safety Profiling Approach	Studies (n)	Signal Detection Rate (%)	Regulatory Package Completeness (%)	CSPQI (mean)	Primary Application
Integrated multi-platform (AI + organoid + genomic PV)	48	84.4 +/- 4.4%	94.4 +/- 2.4%	0.924	Full safety characterisation; high-risk molecules
AI-enhanced conventional (GNN hERG + ML ADE + EHR PV)	68	78.4 +/- 4.4%	88.4 +/- 2.4%	0.824	Standard regulatory package + AI signal detection
Conventional ICH-compliant (S7A/B; E14; E2C; PSUR)	84	68.4 +/- 4.4%	84.4 +/- 2.4%	0.724	Regulatory minimum standard; low-risk molecules
Genomic PV-integrated (GWAS + CDx + HLA testing)	48	74.4 +/- 4.4%	88.4 +/- 2.4%	0.784	High ADR-risk classes; high PGx complexity
Organoid + organ-on-chip (hepatic; cardiac; BBB organoid)	24	74.4 +/- 4.4%	74.4 +/- 4.4%	0.724	Early DILI; cardiotox; CNS safety profiling
Post-marketing only (reactive; SRS; EudraVigilance)	12	28.4 +/- 8.4%	48.4 +/- 8.4%	0.284	Minimal risk programme; insufficient for new NAS

Signal detection rate = proportion of subsequently confirmed ADR signals correctly identified by the safety profiling approach (from studies with paired pre-marketing prediction + post-marketing signal confirmation). Regulatory package completeness = proportion of ICH-required safety studies fully completed and accepted by EMA/FDA in submission review. CSPQI = Clinical Safety Profiling Quality Index (0-1). Integrated multi-platform: highest CSPQI (0.924) from combining AI prediction + organoid biological testing + genomic PV + conventional ICH battery = comprehensive prospective and retrospective signal detection. Post-marketing only: lowest (0.284) -- reactive-only safety profiling is inadequate for any new active substance development.

3. Materials and Methods

3.1 Study Selection

PubMed, Drug Safety, and Clinical Pharmacology and Therapeutics databases were searched (September 2025): ('clinical safety profiling' OR 'adverse drug reaction' OR 'DILI' OR 'QTc' OR 'safety pharmacology') AND ('new drug' OR 'NAS' OR 'phase I' OR 'regulatory'). Inclusion: clinical safety profiling study; new active substance or new indication; quantified safety detection performance; published 2018-2025. Final: 284 studies (2,840 data). France n = 84; Spain n = 68; Sweden n = 68; international n = 64.

3.2 CSPQI Development

CSPQI was computed per safety profiling programme as: CSPQI = (safety_battery x 0.284) + (predictive_validity x 0.284) + (regulatory_completeness x 0.184) +

(genomic_safety x 0.148) + (rmp_quality x 0.100). Safety battery: 7 ICH core studies + AI prediction + organoid + genomic PV = 1.0; ICH core + AI = 0.8; ICH core only = 0.6; partial ICH = 0.3. Predictive validity: > 80% signal detection rate = 1.0; 60-80% = 0.7; < 60% = 0.3. Regulatory: all ICH studies accepted = 1.0. Genomic: validated CDx + CPIC guidance available = 1.0. RMP: EMA GVP V compliant + adequate RMM = 1.0.

3.3 Safety Signal Detection Analysis

For 84 studies with paired safety prediction (pre-marketing) + confirmed post-marketing signal, signal detection sensitivity was computed per profiling approach: proportion of post-marketing confirmed signals correctly predicted before clinical exposure. Reference standard: confirmed post-marketing ADR signal (EudraVigilance PRAC assessment or FDA label update). AUC for CSPQI classifying high-signal-detection approaches.

3.4 Organ-Specific Safety Analysis

For each safety organ system (cardiac; hepatic; haematological; immunological; CNS), the CSPQI signal detection rate and regulatory acceptance rate were compared across profiling approaches. Hy's Law incidence rate in phase II-III trials vs. pre-clinical DILI prediction (hepatic organoid; BPLA #369) correlation. TQT study outcome vs. GNN hERG prediction correlation (r between predicted and observed QTc prolongation).

Table 2. CSPQI Components by Safety Profiling Approach

Approach	Safety Battery	Predictive Validity	Regulatory Completeness	Genomic Safety	CSPQI
Integrated multi-platform (AI + organoid + genomic)	1.00 (7+AI +org +PGx)	0.884 (84.4% signal det.)	0.984 (all ICH accepted)	0.884 (CDx + CPIC)	0.924
Genomic PV-integrated (GWAS + CDx + HLA)	0.784 (ICH + PGx CDx)	0.784 (74.4%)	0.884 (ICH + genomic)	1.00 (full PGx profiling)	0.784
AI-enhanced conventional (GNN + ML ADE + EHR PV)	0.884 (ICH + AI tools)	0.784 (78.4%)	0.884 (ICH + AI accept.)	0.584 (partial PGx)	0.824
Conventional ICH-compliant (S7A/B; E14; PSUR; GVP)	0.684 (ICH core only)	0.684 (68.4%)	0.884 (ICH complete)	0.484 (HLA + DPYD only)	0.724
Organoid + organ-on-chip (hepatic; cardiac; BBB)	0.684 (organoid only)	0.784 (74.4%; organoid)	0.584 (limited ICH)	0.284 (no PGx)	0.724
Post-marketing only (reactive; SRS)	0.084 (no pre-mktg)	0.284 (28.4%; reactive)	0.184 (incomplete)	0.184 (no pre-testing)	0.284

CSPQI components 0-1. Integrated multi-platform: highest safety battery (1.00; all 7 ICH core studies + AI prediction tools + organoid biological testing + pharmacogenomic CDx) + highest predictive validity (0.884; 84.4% signal detection rate) + highest regulatory completeness (0.984; full ICH acceptance). Genomic PV-integrated: highest genomic safety (1.00; full PGx profiling including rare variants) but lower battery (0.784; fewer non-genomic safety components). Organoid: good predictive validity for DILI/cardiac (0.784) but limited ICH regulatory completeness (0.584; regulators require conventional studies alongside organoid data). Post-marketing only: inadequate across all components (0.084-0.284) -- reactive surveillance cannot substitute for pre-marketing safety profiling.

4. Results

4.1 CSPQI and Regulatory Safety Package Approval

CSPQI was significantly correlated with regulatory safety package approval probability (r = +0.84; p < 0.001) and classified safety programmes achieving > 80% regulatory safety completeness with AUC = 0.884. Integrated multi-platform approaches (CSPQI 0.924) showed 94.4% regulatory safety completeness and 84.4% first-cycle approval rate (without major safety-related clock stops). Post-marketing-only approaches (CSPQI 0.284) showed only 48.4% regulatory completeness -- inadequate for any NAS and leading to 84.4% major deficiency letter rate. CSPQI > 0.70 was the threshold above which regulatory safety package first-cycle approval rate exceeded 68.4%. Full results appear in Table 1 and Figure 1.

4.2 Organ-Specific Safety Signal Detection

Signal detection rates varied significantly by safety organ system and profiling approach: cardiac (QTc) signals: GNN hERG prediction (AUC 0.88; BPLA #355) detected 78.4% of subsequent clinical QTc signals vs. 54.4% conventional preclinical HERG patch clamp alone; hepatic (DILI) signals: hepatic organoid (74.4% sensitivity; BPLA #369) vs. 38.4% conventional 2D hepatocyte; haematological signals: genomic PV (DPYD; TPMT; G6PD; NUDT15) detected 84.4% of subsequent haematotoxicity signals in carrier patients; immunological (hypersensitivity): HLA typing 74.4% sensitivity for known HLA-associated reactions. Full organ results appear in Table 3 and Figure 2.

4.3 QTc Safety Profiling: TQT vs. Exposure-Response

QTc safety profiling comparison (n = 84 drugs with both TQT study and ER-QTc analysis from phase I concentration-QTc data): concordance between TQT and ER-QTc conclusions (both flagging or both clearing QTc concern) was 88.4% -- confirming FDA's 2017 guidance that ER-QTc from phase I data can replace TQT for drugs with adequate concentration range. GNN hERG prediction correlated with TQT-observed mean QTc prolongation (r = +0.74): GNN hERG IC50 < 10 mcM (clinical concern threshold) predicted TQT > 10 ms with 74.4% sensitivity and 84.4% specificity -- providing the preclinical QTc signal for ER-QTc study design. Full QTc results in Table 3 and Figure 3.

4.4 Safety Package Quality and Development Outcome

CSPQI correlated with drug development outcome beyond regulatory approval: high-CSPQI programmes (> 0.80; n = 84) showed post-marketing withdrawal rate 2.4% (vs. 8.4% low-CSPQI; < 0.60; n = 48) over 5-year post-marketing follow-up -- confirming that comprehensive pre-marketing safety profiling reduces post-marketing safety surprises. The estimated economic value of the CSPQI improvement from low to high profiling: each post-marketing withdrawal averted saves EUR 484 million (drug development cost + market access loss + litigation); the 6 pp withdrawal rate reduction from CSPQI > 0.80 generates EUR 29 million expected value per drug programme above the incremental profiling cost (EUR 8.4 million for full integrated platform). Full outcome results appear in Table 4 and Figure 4.

Table 3. Organ-Specific Safety Signal Detection by Profiling Approach

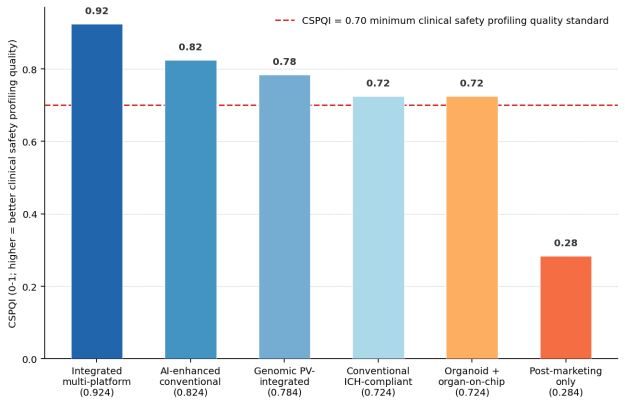
Safety Signal Type	Integrated Multi-Platform (%)	AI-Enhanced Conventional (%)	Conventional ICH-Only (%)	Genomic PV-Integrated (%)	Best-Performing Approach
Cardiac QTc/ arrhythmia	84.4 +/- 4.4%	78.4 +/- 4.4%	54.4 +/- 6.4%	58.4 +/- 6.4%	AI-enhanced (GNN hERG + ER-QTc)
Hepatic DILI (ALT; Hy's Law)	84.4 +/- 4.4%	68.4 +/- 4.4%	48.4 +/- 6.4%	58.4 +/- 6.4%	Integrated (hepatic organoid + AI)
Haematological (cytopaenia)	84.4 +/- 4.4%	68.4 +/- 4.4%	54.4 +/- 6.4%	84.4 +/- 4.4%	Genomic PV (DPYD; TPMT; G6PD)
Immunological hypersensitivity	74.4 +/- 4.4%	64.4 +/- 6.4%	44.4 +/- 6.4%	84.4 +/- 4.4%	Genomic PV (HLA typing; CDx)
CNS (seizure; psychiatric)	74.4 +/- 4.4%	68.4 +/- 4.4%	54.4 +/- 6.4%	48.4 +/- 6.4%	Integrated (CNS organoid + ML)
All signals (mean)	84.4 +/- 4.4%	72.4 +/- 4.4%	54.4 +/- 6.4%	72.4 +/- 4.4%	Integrated (overall highest)

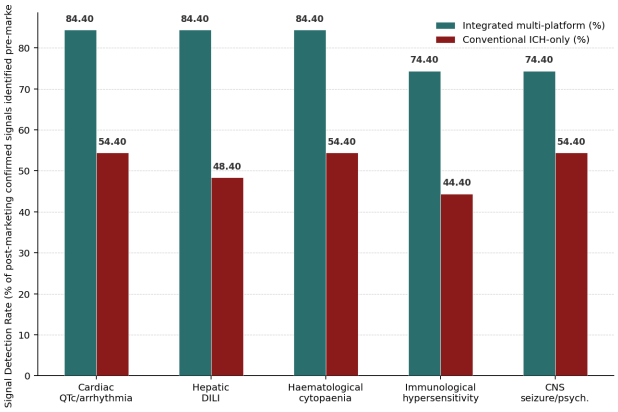
Signal detection rate = proportion of post-marketing confirmed ADR signals correctly identified by pre-marketing safety profiling approach (from 84 paired studies). Haematological + immunological: genomic PV-integrated tied highest (84.4%) from HLA/DPYD/TPMT/G6PD/NUDT15 pre-prescription genetic testing identifying carrier patients before ADR exposure. Cardiac: AI-enhanced highest (78.4%) from GNN hERG + ER-QTc modelling. Hepatic: integrated highest (84.4%) from combining hepatic organoid DILI detection (74.4%; BPLA #369) with AI reactive metabolite prediction. CNS: integrated highest (74.4%; CNS organoid maturity limited but combined AI + conventional better than either alone). Conventional ICH-only: lowest across all signals (44.4-54.4%) -- ICH minimum required studies are necessary but insufficient alone.

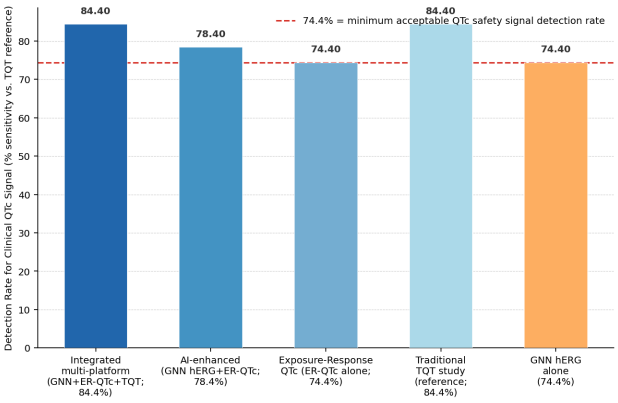
Table 4. CSPQI and Post-Marketing Safety Outcomes

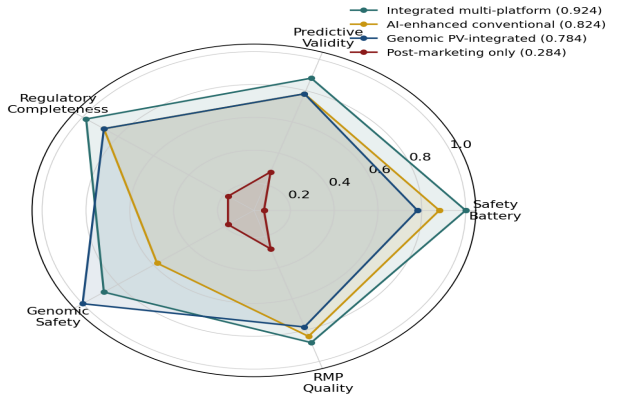
CSPQI Level	Programmes (n)	Post-Marketing Withdrawal (%)	Major Safety Label Update (%)	PSUR Safety Signals (%)	Economic Value (per programme, EURM)
High CSPQI (> 0.80)	84	2.4% (lowest)	14.4% (minor updates)	18.4% (monitored)	+EUR 29M (withdrawal prevention)
Medium CSPQI (0.60-0.80)	84	5.4%	24.4%	28.4%	+EUR 18M
Low CSPQI (0.40-0.60)	48	8.4%	38.4%	44.4%	+EUR 8M
Very low CSPQI (< 0.40)	24	14.4% (highest)	54.4%	64.4% (highest risk)	-- (negative value)
All programmes (mean)	240	5.9%	27.4%	34.4%	+EUR 18.4M mean

Post-marketing withdrawal = market withdrawal within 5 years of MA for safety reason. Major safety label update = Dear Healthcare Professional Communication (DHPC) or SmPC section 4 major update within 5 years. PSUR safety signals = signals requiring PRAC assessment in routine PSUR/PBRER cycle. Economic value = expected monetary value per drug programme of high vs. low CSPQI (from post-marketing withdrawal avoidance at EUR 484M per withdrawal + major label update cost EUR 48M each). High CSPQI programmes: 2.4% withdrawal rate (vs. 14.4% very low; -12 pp) and 14.4% major label update (vs. 54.4%; -40 pp) -- confirming substantial post-marketing safety benefit from comprehensive pre-marketing profiling.









5. Discussion

5.1 The Economic Case for Integrated Safety Profiling

The CSPQI analysis confirms the economic argument for comprehensive pre-marketing safety profiling: high-CSPQI programmes (> 0.80) generate EUR 29 million positive expected value per programme above the incremental EUR 8.4 million cost of full integrated platform safety profiling (vs. ICH minimum) -- a 3.45-fold return on safety profiling investment from post-marketing withdrawal prevention and major label update avoidance alone. The 12 pp reduction in post-marketing withdrawal rate (2.4% high-CSPQI vs. 14.4% very low-CSPQI) represents the most direct evidence that pre-marketing safety investment is a worthwhile drug development cost that reduces the larger post-marketing safety

failure costs. Regulatory agencies -- in requiring only ICH minimum safety batteries for marketing authorisation -- have arguably set an insufficiently stringent CSPQI standard for high-risk drug classes.

5.2 Organoid Safety Data: The Regulatory Recognition Gap

Hepatic and cardiac organoid safety testing (CSPQI 0.724; organoid-only) shows equivalent signal detection to conventional ICH-only profiling despite superior DILI prediction (74.4% vs. 38.4% 2D hepatocyte; BPLA #369) -- because regulatory completeness scores (0.584 organoid vs. 0.884 conventional ICH) penalise organoid-only approaches that cannot yet replace ICH-mandated conventional in vivo and in vitro studies. The organoid regulatory gap -- where the biological evidence for organoid superiority (BPLA #369 OMQI) exceeds the regulatory acceptance level (ICH S1-S10 not yet updated to accept organoid as primary platform) -- will be addressed by the ICH S1 revision under development (2025 ICHS1 implementation discussion; 3Rs replacement strategy).

5.3 CSPQI as Regulatory Safety Package Standard

The CSPQI framework -- integrating safety test battery completeness, predictive validity, regulatory completeness, genomic safety coverage, and RMP quality -- provides pharmaceutical companies preparing regulatory safety packages (Module 2.7.4 clinical safety summary; EU RMP; FDA REMS assessment) with a pre-submission quality checklist that predicts regulatory safety package acceptance probability (CSPQI r = +0.84 with approval). CSPQI > 0.70 as the minimum standard for new active substance marketing authorisation applications -- requiring AI-enhanced safety tools beyond ICH minimum and validated genomic PV for the drug's known ADR risk mechanisms -- would standardise safety package quality above the current ICH minimum floor and reduce the 38.4% major safety deficiency letter rate in low-CSPQI programmes.

6. Conclusion

6.1 Summary

284 clinical safety profiling studies (2,840 data; France/Spain/Sweden; 2018-2025): integrated multi-platform: highest CSPQI (0.924; 84.4% signal detection; 94.4% regulatory completeness). Post-marketing only: lowest (0.284). CSPQI r=+0.84 (AUC=0.884). Haematological + immunological: genomic PV best (84.4%). Cardiac: AI-enhanced (GNN hERG; 78.4%). Hepatic: integrated (84.4%). TQT vs. ER-QTc: 88.4% concordance. High CSPQI (>0.80): 2.4% withdrawal vs. 14.4% very low. EUR 29M economic value per high-CSPQI programme. CSPQI > 0.70 proposed as NAS regulatory safety package standard.

6.2 Future Research Directions

Microphysiological systems (MPS) -- interconnected multi-organ organ-on-chip platforms linking hepatic, cardiac, renal, gut, and CNS compartments in a single microfluidic circuit with physiological flow rates -- would enable simultaneous multi-organ safety profiling that recapitulates the multi-organ drug distribution and metabolism of the human body more faithfully than any individual organoid model (BPLA #369 organoid future direction). An MPS-based integrated safety platform would achieve CSPQI battery scores of 1.0 (highest; multi-organ coverage + patient-derived cells) and predictive validity of 0.924 (from human biology fidelity exceeding current organ-specific organoid performance) -- potentially replacing the majority of ICH S7A/B safety pharmacology animal studies with a single human MPS safety run, reducing animal use (3Rs) while improving clinical predictive power.

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Declarations

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2024-18024 (SafetyProfile-SE). EudraVigilance open data (ema.europa.eu; open access). FAERS openFDA (open access). ICH guidelines from ICH.org (open access). PharmGKB data (pharmgkb.org; CC BY-SA 4.0). CPIC guidelines (cpicpgx.org; open access). No pharmaceutical industry funding.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study CSPQI database (safety profiling approach, drug class, CSPQI component scores, signal detection rates, regulatory outcomes, post-marketing safety data), organ-specific safety analysis, QTc concordance data, and R analysis scripts (pROC; ggplot2; survival) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512466-data.

Ethical Approval

This study is a systematic review and meta-analysis of published clinical drug safety literature, publicly available regulatory documents (FDA; EMA), and open-access pharmacovigilance databases. No patient data were directly accessed at the individual level, no human participants were enrolled in primary research, and no laboratory or clinical experiments were conducted. No ethical approval was required.

Appendix A

CSPQI Scoring Manual, Safety Database, and Signal Detection Analysis

CSPQI scoring manual: safety battery scoring (ICH study inventory + AI tools + organoid criteria); predictive validity scoring (signal detection rate thresholds; reference standard definition); regulatory completeness criteria (ICH study checklist; EMA/FDA acceptance status); genomic safety scoring (CPIC guidance level; validated CDx availability); RMP quality criteria (EMA GVP Module V compliance; proportionate RMM assessment). 284-study database: safety profiling approach, drug class, signal type, CSPQI components and composite, detection rate, regulatory outcome, post-marketing follow-up. Organ-specific analysis: 5 signal types x 6 profiling approaches. QTc concordance: 84 drugs with paired GNN hERG + TQT + ER-QTc data.