HiroPharmaConsulting® Co., Ltd.

HPC_HPVM Whitepaper v2.0（English）

AI-PV HiroPharma Validation Method (HPVM)

— Regulatory-Ready Human-Based Validation Framework for AI-Enabled PV Systems —

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(Reflecting Registered Patent No. 7778327 and PCT/JP2025/042095)

Executive Summary

Artificial intelligence transforms pharmacovigilance (PV), particularly in ICSR intake, triage, and medical evaluation. As pharmaceutical companies adopt AI-driven decision-making, regulators increasingly expect transparency, explainability, and continuous oversight. The AI-PV HiroPharma Validation Method (HPVM), now formally **patented in Japan as Patent No. 7778327** and **internationally filed under PCT/JP2025/042095**, establishes a rigorous, human-based validation and governance framework to ensure the trustworthiness of AI functions used in PV operations.

HPVM is built on a foundational principle: **AI must not validate itself**. Instead, AI output must always be benchmarked against human-based medical judgments by qualified physicians (M.D.) and PV specialists. This principle forms the basis of a structured lifecycle validation method that regulators can audit and trust.

With the patent officially published on **J-PlatPat** and globally protected through PCT filing, HPVM is now positioned as a practical, regulator-aligned standard for AI validation in drug safety.

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1. HPVM Patent Framework

- **Japanese Patent:** 特許第 7778327 号 (Patent No. 7778327)
- **Title:** AI 機能を搭載した適正基準対応バリデーションシステム及び方法
- **Registration Date:** 21-Nov-2025
- **Publication Date:** 02-Dec-2025
- **International Application:** PCT/JP2025/042095 (Filed 03-Dec-2025)

The granted patent protects the process architecture of HPVM—specifically, a **non-self-validating, human-based evaluation system**, continuous re-validation logic, template case methodology, sampling method (√N+1), alert mechanisms, and full lifecycle traceability.

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2. Core Principle: AI Must Not Validate Itself

HPVM requires that AI outputs be compared to a **human-based gold standard**, eliminating circular logic where the AI system "confirms its own correctness."

This aligns with emerging global expectations from **FDA, EMA, PMDA**, and ISPE GAMP AI Guide (2025), which emphasize:

- Transparency and explainability
- Traceability and audit readiness
- Separation of development vs. verification roles
- Continuous monitoring across the model lifecycle

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3. The Seven Elements of HPVM

1. **Expert-Confirmed Gold-Standard Template Cases**
   – ICSR cases with confirmed medical assessments (seriousness, causality, severity).
   – Serve as the constant reference set for evaluation.
2. **√N+1 Population-Proportional Sampling**
   – Scales with operational volume; practical and defensible.
3. **Production-Frozen Validation Environment**
   – Identical model, parameters, dictionaries, and data structure as production; isolated for testing.
4. **Performance Criteria (100% Match or Confidence Interval)**
   – Predefined acceptance criteria include simple agreement, CI-based thresholds (e.g., 99%).
5. **Continuous Re-Validation Cycle**
   – Weekly / Monthly / Quarterly / Semiannual / Annual cycles depending on AI function and risk level.
6. **Alert Mechanism**
   – Automated notifications before re-validation deadlines to prevent compliance gaps.
7. **Difference Evaluation & Full Traceability**
   – Version-to-version performance comparison after updates or retraining.
   – Complete historical evidence for regulatory inspection.

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4. HPVM Validation Methodology

4.1 Template Case Construction

Expert-confirmed judgments create a reproducible, medical gold standard for AI comparison.

4.2 Sampling Logic (√N+1)

Ensures proportional evaluation relative to actual case volume (N).

4.3 Execution in Frozen Environment

Guarantees reproducibility and regulator-traceable evidence.

4.4 Performance Metrics

- Agreement rate (%)
- Cohen’s Kappa (κ)

- CI-based acceptance thresholds

4.5 Continuous Re-Validation

AI drift and model evolution are continuously monitored and controlled.

4.6 Alerts

Pre-deadline notifications ensure operational compliance.

4.7 Traceability and Difference Evaluation

Every cycle is archived with audit-ready documentation.

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5. Regulatory Alignment

HPVM matches the direction of latest global regulatory trends:

- **FDA (2025 AI Guidance):** lifecycle monitoring, change control, human oversight
- **EMA GVP Module I / Annex I:** quality system, documentation, auditability
- **PMDA:** explainability, transparency, independence of validation
- **ISPE GAMP AI Guide (2025):** AI lifecycle governance, separation of duties

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6. Example Scenario

For an AI system determining seriousness criteria for **12,000 annual ICSRs**, monthly validation requires:

- N ≈ 1,000
- √N+1 ≈ 32 cases per month
  (or scaled to operational load, e.g., 110 cases depending on frequency and distribution)

This ensures statistically sound, regulator-ready validation evidence.

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7. Conclusion

HPVM provides:

- Human-based evaluation ensuring medical reliability
- Scalable sampling with √N+1
- Documented, audit-ready lifecycle evidence
- Continuous oversight and drift management
- Global regulatory alignment
- A patented, internationally protected framework for AI-enabled PV validation

HPVM establishes a practical standard for ensuring the safety, reliability, and compliance of AI in pharmacovigilance.
