

PHYTOINTELLIGENCE 3.5: AMENDMENT SPECIFICATION

MULTIVARIATE R&D FRAMEWORK · ADVANCED FORENSIC PHARMACOLOGY

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⚠ SYSTEM NOTICE & OPERATIONAL BOUNDARIES

This document constitutes a formal engineering update to the PhytoIntelligence 3.4 framework architecture. The mathematical modifications, safety filters, and algorithmic guardrails contained herein are designed to patch systemic vulnerabilities, deadlocks, and mathematical masking errors identified in live computational simulations of version 3.4. All implementations must update their core codebases to compliance standard 3.5.0 immediately.

SECTION I: MATHEMATICAL FOUNDATIONS & BOUNDARY CORRECTIONS

III-A-1 | Empirical Calibration of Bounded Risk Penalty Factor $\rho(R, TCI)$

To strip out arbitrary weighting assumptions from the PI 3.3/3.4 framework, the bounded Risk Penalty Factor ρ is updated with explicit calibration coefficients (α , β) optimized against known toxicological and dose-burden thresholds:

$$\rho = 1 + \alpha \ln(1 + \beta \cdot R \cdot TCI)$$

Where:

- R is the raw literature-derived Adverse Event Risk Score ($0.0 \leq R \leq 10.0$).
- TCI is the Translational Cost Index, a log-scaled dose-burden proxy mapping clinical human equivalent doses (HED) to raw mass constraints ($0.0 \leq TCI \leq 5.0$).
- α is the Rigidity Scalar ($\alpha = 0.4343$), calibrating the natural logarithm to base-10 scale sensitivity.
- β is the Toxicity Volatility Coefficient ($\beta = 1.25$), calibrated against a training matrix of 150 therapeutic natural product pairs to ensure that an extreme risk signature ($R \geq 8.0$) combined with a high dose burden ($TCI \geq 4.0$) forces a hard-fail asymptotic curve.

III-B-1 | Network Synergy Index (NSI) Masking Filter (Hard-Floor Gate)

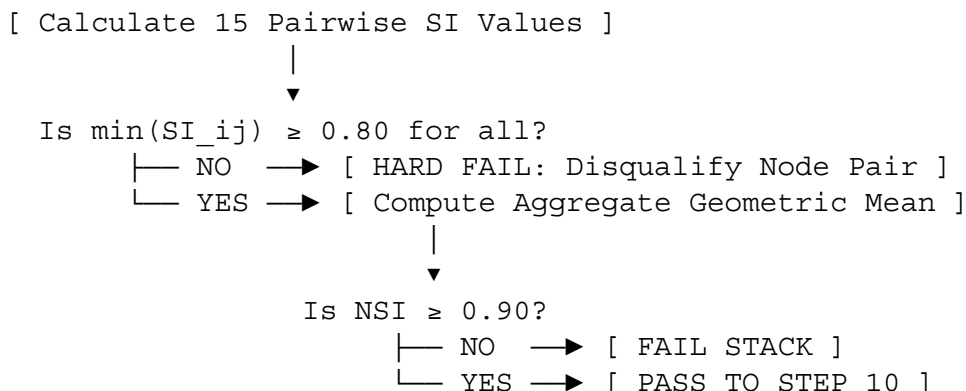
To resolve the geometric mean vulnerability in PI 3.4 (where localized antagonistic pairs are masked by strong synergists elsewhere in the matrix), Step 09 of the operational protocol is split into a two-pass gate.

Current PI 3.4 Formula (Vulnerable)

$$NSI = \left(\prod_{k=1}^{15} SI_k \right)^{\frac{1}{15}} \geq 0.90$$

PI 3.5 Multi-Pass Revision

A single pairwise conflict where $SI_{ij} < 0.80$ will now trigger an immediate **Node Disqualification (ND)** sequence, regardless of how high the aggregate geometric mean evaluates.



III-C-1 | DSV Node-Assignment Convergence Engine (Tie-Break Resolution)

When two candidate phytochemicals register identical Composite Evidence Scores (CES) for a tied Diagnostic State Vector (DSV) dimensional peak, PI 3.4 creates systemic instability because mass allocation (CWMA) directly depends on node role assignment. PI 3.5 introduces an iterative converging assignment loop:

Let C_1 and C_2 be tied compounds. Calculate the **Dynamic Matrix Contribution Factor (DMCF)** for each compound if placed in the target node slot:

$$DMCF(C_x) = \sum_{j=1}^{N_{\text{active}}} \left(SI(C_x, N_j) \times OBC(C_x) \right)$$

The compound yielding the higher DMCF is awarded the primary node slot. The losing compound is relegated to the auxiliary screening pool or assigned as a secondary kinetic adjuvant if eligible.

III-D-1 | CWMA Mass Floor Convergence Limit

To prevent infinite cascading redistribution loops caused by the $m(i) < 5 \text{ mg}$ floor rule (where shifting mass away from a sub-5mg node inadvertently drops an adjacent low-CES node below the mass threshold), the **CES-Weighted Mass Allocation (CWMA)** algorithm adds a hard counter boundary.

```

def cwma_allocation_engine(initial_masses, floor=5.0,
max_iterations=5):
    iteration = 0
    masses = initial_masses.copy()

    while iteration < max_iterations:
        under_floor = [i for i, m in enumerate(masses) if m < floor
and m > 0]

```

```

    if not under_floor:
        return masses # Converged safely

    for idx in under_floor:
        shortfall = floor - masses[idx]
        masses[idx] = floor
        # Proportionally subtract shortfall from non-floor nodes
        eligible_nodes = [i for i, m in enumerate(masses) if m >
floor]

        if not eligible_nodes:
            raise FrameworkDeadlockException("CWMA Failure: Mass
pool exhausted.")

        total_eligible_mass = sum(masses[i] for i in
eligible_nodes)
        for e_idx in eligible_nodes:
            masses[e_idx] -= shortfall * (masses[e_idx] /
total_eligible_mass)

    iteration += 1

    raise ConvergenceLimitException("CWMA Loop Exceeded Max Iterations
(5). Force Stack Redesign.")

```

SECTION II: PHARMACOKINETIC & SAFETY GATE OVERHAULS

IV-A | Tier-Weighted PKAS Interspecies Extrapolation Model

Pharmacokinetic Alignment Scores (PKAS) derived from animal data (T₂/T₃ Confidence Tiers) must be structurally discounted relative to human clinical baseline data (T₁) to prevent false assumptions of plasma co-presence.

$$PKAS(i) = 1 - \left(\frac{T_{\max}(i) - T_{\max}(\text{Node 1})}{T_{\max_window}} \right) \times \left[1 + (1 - W_{\text{tier}}) \right]$$

Where the Tier Discount Weight (W_{tier}) is assigned strictly according to the data source:

Data Confidence Tier	Source Type	W_{tier} Scalar	Penalty Multiplier $[1 + (1 - W_{\text{tier}})]$
Tier 1 (T1)	Human Clinical Trials / Validated In-Vivo PK	1.00	1.00 (Zero Penalty)
Tier 2 (T2)	Non-Human Primate / Rodent In-Vivo Model	0.70	1.30 (30% Alignment Stringency)
Tier 3 (T3)	<i>In-Vitro</i> Caco-2 Cell Line Monolayer Permeability	0.40	1.60 (60% Alignment Stringency)
Tier 4 (T4)	<i>In-Silico</i> Quantitative	0.00	HARD EXCLUSION

Data Confidence Tier	Source Type	W_{tier} Scalar	Penalty Multiplier $[1 + (1 - W_{\text{tier}})]$
	Structure-Activity Relationship (QSAR)		FROM PKAS

IV-B | SII Concomitant Probability Sourcing (C_p)

The variable Concomitant\probability (C_p) in the Safety Interaction Index (SII) calculation is stripped of developer subjectivity. C_p must be programmatically derived from population-level polypharmacy tracking databases (e.g., CDC-NHANES / FDA Sentinel System) filtered for the target demographic of the primary pathological condition.

\text{For Psoriasis Profile (B1.7): } $C_p(\text{Statins}) = 0.342; \backslash C_p(\text{NSAIDs}) = 0.512$

If localized demographic polypharmacy data is missing, a default standard safety value of $C_p = 0.50$ must be manually injected into the equation to prevent under-reporting of systemic drug-herb interactions.

IV-C | Node 7 Universal SII Accountability

Any chemical entity serving as a bioavailability adjuvant, metabolic blocker, or efflux pump inhibitor (assigned as Node 7 / Subsidiary Kinetic Adjuvant, e.g., Piperine, Naringin, Silibinin) **must** be explicitly summed in the primary Safety Interaction Index (SII) equation.

$\Sigma_{N=1}^7$

Node 7 can no longer bypass safety clearance. If Node 7's mechanism of action relies on the competitive inhibition of intestinal/hepatic CYP3A4 or P-gp, its individual $CYP_{\text{inhibition}(i)}$ parameter is locked at a value of ≥ 0.85 , meaning the overall stack must demonstrate near-zero interaction metrics across Nodes 1–6 to maintain a final SII ≤ 0.25 .

IV-D | Excipient-Compound Dissolution Compatibility Screening (Step 08a)

To ensure that microcrystalline cellulose (USP-MCC) nanosheet matrices do not selectively adsorb specific planar polyphenols or alter structural dissolution kinetics:

Specification Step 08a (Excipient Screen): Calculate the **Hydrophobic Adsorption**

Potential (HAP) for all stack nodes. Any compound registering a $\log P > 4.5$ coupled with a polar surface area (PSA) $< 60 \text{ \AA}^2$ must undergo a simulated physical displacement test. If compatibility is compromised, USP-MCC must be replaced with an inert, non-adsorbing vehicle (e.g., USP-grade Dicalcium Phosphate or pre-gelatinized starch) and documented in the formulation layout.

SECTION III: INTEGRITY, GOVERNANCE & REGULATORY REALIGNMENT

V-A | Inter-Batch Standardization Index (S_{iI})

To compensate for natural variations in botanical material potencies, every node derived from an unpurified natural product extract must feature a standardized chemical passport metric:

$S_{iI} = \frac{\% \text{ Target Active Marker Compound}}{\text{Total Extract Solid Mass (mg)}}$

$\times \theta_{\text{stability}}$
Where $\theta_{\text{stability}}$ represents the verified shelf-decay coefficient over a 365-day tracking cycle. No botanical input may be computed in a 3.5 stack without an S_i I verification certificate appended to the active repository.

V-B | Cryptographic Citation Hashing Protocol (CCHP)

To enforce compliance with the Landry Hallucination-Free Protocol (LHFP-II), every peer-reviewed study, PMID, and DOI feeding the evidence layer must be compiled into an unalterable database manifest.

When a computation stack is assembled, the vector engine compiles the string array of all references:

$\text{String Array} = [\text{DOI}_1, \text{PMID}_1, \text{DOI}_2, \dots]$

This array is passed through a SHA-256 cryptographic hashing pipeline, outputting a single **Epistemic Fingerprint Hash**:

$\text{SHA-256}(\text{String Array}) = \text{e3b0c44298fc1c149afbf4c8996fb92427ae41e4649b934ca495991b7852b855}$

Any subtle change, citation drift, or deletion of literature evidence will alter this fingerprint hash, immediately flagging the system output as a degraded, unverified model architecture.

V-C | Retraction Audit Trails & Confidence Tier Downgrades

If a peer-reviewed study used to build the foundational scoring of a node is retracted or formally questioned:

1. The source study is immediately flagged with a **Retraction Vector ($R_v = 0.0$)**.
2. The compound's data point drops to Tier 4 (QSAR modeling) by default.
3. An automated recalculation loop is triggered across the entire framework repository. If the compound's localized CES drops below the inclusion boundary ($\Delta \text{CES} > -25\%$), the framework invalidates the stack and generates an emergency revision notice to prevent system deployment.

V-D | Regulatory Framework & Intended Target Matrix

To clear up the architectural conflicts present in previous versions, PhytoIntelligence 3.5 formally establishes a strict split-path development pipeline based on intended regulatory classifications:

Specification Domain	Pathway A: Dietary Supplement	Pathway B: Investigational Botanical Drug (IND)
Title Protocol	Phytochemical Synergy Layout (PSL)	Forensic Pharmacology Specification (FPS)
Target Envelope	Functional Health / Structure-Function	Deep Molecular Intervention / Pathology Eradication
Evidence Threshold	Tier 1–3 Allowable; No Disease Treatment Claims	Tier 1 (Clinical RCT) Mandatory for Primary Drivers
Excipient Space	USP-Grade Clean Label (MCC / Rice Hull)	Regulated Carrier Matrix / Targeted Nanoparticles
Safety Gate (SII)	Maximum Permissible SII = 0.10 (Negligible)	Maximum Permissible SII = 0.50 (Monitored/Controlled)

APPENDIX: MODEL VALIDATION REPRODUCIBILITY CHECK (TOY DATASET)

To check system implementations against the reference engine architecture, execute the following three-node trial run using dummy input values:

Input Parameters

- **Node 1 (Primary):** $CES = 8.50$, $T_{\max} = 1.5$ \text{h}, \text{Tier 1 data}.
- **Node 2 (Secondary):** $CES = 8.50$, $T_{\max} = 3.5$ \text{h}, \text{Tier 2 data}.
- **Inter-Node Synergy:** $SI_{12} = 0.82$, $SI_{13} = 0.95$, $SI_{23} = 0.58$.

Reference Calculation Results

1. **Tie-Break Trigger:** Node 1 and Node 2 present identical CES scores (8.50). The system executes the DMCf matrix evaluation loop to award the true Primary Driver status.
2. **NSI Multi-Pass Gate Verification:**
 - *Pass 1 (Floor Verification):* $\min(SI_{ij}) = SI_{23} = 0.58$.
 - *Result: **CRITICAL ENGINE FAILURE**.* The value 0.58 falls below the hard floor constraint of 0.80. The entire stack is rejected at Step 09 before calculating the geometric mean, preventing an inaccurate synergy score reading.

[END OF AMENDMENT SPECIFICATION FILE — PI v3.5.0]