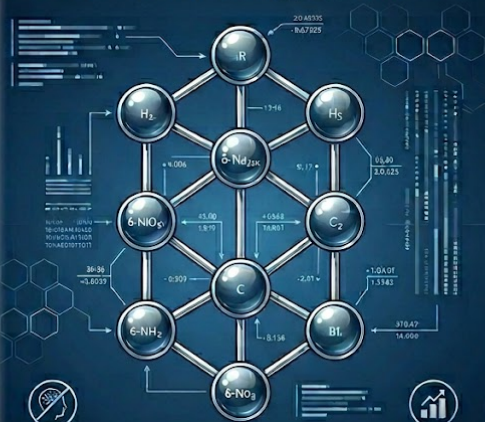


PHYTOINTELLIGENCE 3.4

Multivariate R&D Framework for
Forensic Pharmacology Specification



Hallucination-Free

Confidence Tiering

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PHYTOINTELLIGENCE 3.4

MULTIVARIATE R&D FRAMEWORK · FORENSIC PHARMACOLOGY SPECIFICATION · VERSION 3.4.0

Owner	Marie-Soleil Seshat Landry	Protocol	LHFP Compliant (Hallucination-Free)
Model	AI-Assisted (LLM Verification Layer)	Epistemic Std.	1=1=1 Axiom / Seshat's Axiom
Complexity	6+1 Node Molecular Stack	Validation	LHFP + Active Confidence Tiering
Excipient	USP-Grade MCC (Nanosheet Matrix Purged)	Generated	May 11, 2026

■ **WARNING:** For research and development purposes only. All formulations are hypothetical models derived from literature deconvolution. No clinical validation has been performed. Not for human administration without qualified medical oversight.

I. CRITICAL AUDIT — PI 3.3 → PI 3.4 DELTA LOG

PI 3.4 is a formal iteration incorporating nine critical corrections to the PI 3.3 specification. Each fault is documented below alongside the engineering fix applied in this version.

#	PI 3.3 Fault	Severity	PI 3.4 Fix
F-01	CES denominator: $\ln(\text{Risk} \times \text{Cost})$ undefined/negative when $\text{Risk} \times \text{Cost} \leq 1$; inverts the score	CRITICAL	Replace with bounded Risk Penalty Factor $\rho = 1 + \ln(1 + R \times C)$; always ≥ 1 , no singularity
F-02	Bioavailability + ADME double-counts absorption; bioavailability is the A in ADME	HIGH	Separate into Oral Bioavailability Coefficient (OBC) and Metabolic Stability Index (MSI)
F-03	"Cost" undefined as pharmacological variable; no units or derivation given	HIGH	Remove monetary Cost; replace with Translational Cost Index (TCI) — log-scaled dose-burden proxy
F-04	Bliss Independence formula shown for N=2 only; 6-node stack has 15 pairwise interactions	HIGH	Introduce full 6x6 Synergy Matrix; compute aggregate Network SI via pairwise product chain
F-05	6-Dimensional DSV referenced in Step 6 but never defined anywhere in the document	HIGH	DSV fully specified: 6 orthogonal biological dimensions with scoring rubric in Section IV
F-06	No PK time-alignment model; compounds with different Tmax values do not synergize in a single capsule	MEDIUM	Introduce Pharmacokinetic Alignment Score (PKAS); Node 6 now includes Tmax delta constraint
F-07	Logic-Gate criteria unquantified; 'independent replication' has no n, p-value, or effect size	MEDIUM	Logic-Gate thresholds defined: min. 2 independent studies, $n \geq 30$ or in vivo, effect size ≥ 0.30
F-08	Node mass range (250–300 mg) has no selection algorithm; no rule linking CES to mass allocation	MEDIUM	CES-Weighted Mass Allocation (CWMA) algorithm introduced; mass $\propto$ normalised CES rank
F-09	No Adverse Drug Interaction (ADI) safety gate; Node 6 CYP3A4 inhibition is an unscreened ADI risk	HIGH	Safety Interaction Index (SII) introduced as mandatory Step 10a; ADI flag blocks Node 6

II. OPERATIONAL PROTOCOL — THE 12-STEP SEQUENCE (REVISED)

PI 3.4 expands the original 10-step protocol to 12 steps, inserting a mandatory Confidence Tier pre-screen (Step 02a) and a Safety Interaction Gate (Step 10a). All steps are sequentially dependent; no step may be bypassed.

Step	Name	Description	Gate
01	Anomaly Observation	Identify the pathological state or diagnosis. Define the clinical endpoint (e.g., tumour suppression, glycaemic control). Document all co-morbidities.	—
02	Intel Requirement	Define specific enzymatic, genomic, or metabolic targets. All targets must be cited from peer-reviewed sources (PubMed / Scopus).	MiniPASS ≥ 3 citations
02a ★	Confidence Tier Pre-Screen	Assign each candidate compound to Confidence Tier (T1–T4) per Section V. Exclude all T4-only compounds from the primary stack.	T4-only → Exclude
03	Pathological Hypothesis	Map primary and secondary drivers of the diagnosis to the 6-Dimensional DSV (Section IV). Assign each driver to at least one DSV dimension.	—
04	Experimental Design	Set 750 mg volumetric/stoichiometric constraints. Assign provisional node roles (Primary, Secondary, Synergy, Epigenetic, Kinetic, Adjuvant).	—

	N1 Primary	N2 Secondary	N3 Synergy	N4 Synergy	N5 Epigenetic	N6 Kinetic
N1 Primary		SI(1,2)	SI(1,3)	SI(1,4)	SI(1,5)	SI(1,6)
N2 Secondary	—		SI(2,3)	SI(2,4)	SI(2,5)	SI(2,6)
N3 Synergy A	—	—		SI(3,4)	SI(3,5)	SI(3,6)
N4 Synergy B	—	—	—		SI(4,5)	SI(4,6)
N5 Epigenetic	—	—	—	—		SI(5,6)
N6 Kinetic	—	—	—	—	—	

★ All 15 SI values must be ≥ 0.8. NSI (geometric mean) must be ≥ 0.90 to pass Step 09.

III-C I Pharmacokinetic Alignment Score (PKAS) — New in PI 3.4

Addresses PI 3.3 fault F-06. A 750 mg capsule delivers all nodes simultaneously; nodes with widely divergent Tmax values will not achieve plasma co-presence, negating any synergy assumption. PKAS enforces a co-presence window constraint.

$$PKAS(i) = 1 - (|Tmax(i) - Tmax(Node\ 1)| / Tmax_window)$$
$$Tmax_window = 4\text{ hours (default; adjustable per indication)}$$
$$Acceptance: PKAS(i) \geq 0.5 \text{ for all nodes } [|\Delta Tmax| \leq 2h]$$

Failure path: Nodes with PKAS < 0.5 require enteric coating, modified-release pellet technology, or separate dosing schedule. Document in Formulation Summary.

III-D I Safety Interaction Index (SII) — New in PI 3.4

Addresses PI 3.3 fault F-09. Node 6 (Kinetic Adjuvant) is explicitly a CYP3A4/P-gp inhibitor. Without a safety gate, the stack may produce clinically significant drug interactions in subjects on CYP3A4-metabolised medications (e.g., statins, immunosuppressants, anticoagulants).

$$SII = \Sigma [CYP_inhibition(i) \times ADI_severity(i) \times Concomitant_probability] / N$$

for all N nodes with CYP or P-gp activity

SII Range	Classification	Action Required
0.00 – 0.10	Negligible Interaction Risk	Proceed — document in Formulation Summary
0.11 – 0.25	Low Interaction Risk	Proceed — include contraindication note in reporting
0.26 – 0.50	Moderate Interaction Risk	Node 6 dose reduction or substitution required
> 0.50	High Interaction Risk	HARD FAIL — Node 6 must be replaced or stack redesigned

IV. THE 6-DIMENSIONAL DIAGNOSTIC STATE VECTOR (DSV)

Addresses PI 3.3 fault F-05. The DSV is the analytical core of PhytolIntelligence. Each candidate compound is scored across six orthogonal biological dimensions. The resulting 6-component vector determines node assignment and CES weighting.

Dim.	Dimension Name	Biological Scope	Scoring Rubric (0–10)	Node Relevance
D1	Genomic / Transcriptomic	Direct modulation of gene expression, transcription factor activity, oncogene suppression (mTOR, KRAS, TP53 pathway engagement)	0 = no genomic evidence 5 = in vitro transcriptomic 10 = in vivo / clinical RCT	Node 1 (Primary Driver)
D2	Metabolic Flux	Glycolysis, OXPHOS, lipid metabolism, GLUT transporter modulation, mitochondrial bioenergetics	0 = no evidence 5 = cell-line metabolomics 10 = in vivo metabolic flux	Node 2 (Secondary Driver)
D3	Redox / Antioxidant	ROS scavenging, Nrf2/HO-1 activation, GSH modulation, lipid peroxidation inhibition	0 = no evidence 5 = DPPH/FRAP assay only 10 = Nrf2 in vivo confirmed	Node 3 (Synergy A)
D4	Immune / Inflammatory	Cytokine modulation (IL-6, TNF-α, NF-κB), immune contexture, macrophage polarisation, inflammasome activity	0 = no evidence 5 = cytokine assay in vitro 10 = immune in vivo confirmed	Node 4 (Synergy B)

Dim.	Dimension Name	Biological Scope	Scoring Rubric (0–10)	Node Relevance
D5	Epigenetic	DNA methylation (DNMT inhibition), histone acetylation (HDAC inhibition), miRNA regulation, chromatin remodelling	0 = no evidence 5 = HDAC IC50 only 10 = epigenome-wide study	Node 5 (Epigenetic)
D6	Pharmacokinetic / ADME	CYP enzyme modulation, P-gp inhibition, bioavailability enhancement, t½ extension, plasma protein binding	0 = no PK data 5 = CYP IC50 in vitro 10 = human PK study confirmed	Node 6 (Kinetic Adjuvant)

$$DSV_{total} = \sum D(i) \text{ for } i = 1..6 \text{ (max = 60)}$$

A compound scoring ≥ 40 across all 6 dimensions is classified as a 'Broad-Spectrum Candidate' and may occupy multiple nodes at reduced mass. Node assignment follows primary peak score: the dimension with the highest individual score determines node placement. Where two compounds tie for a node, the higher CES wins.

V. CONFIDENCE TIER SYSTEM (NEW IN PI 3.4) ★ NEW

The Confidence Tier system applies Seshat's Axiom (1=1=1 Law) to evidence quality, ensuring that the epistemic weight of each compound's supporting literature is explicitly encoded into its CES Validation Score. A T4 compound cannot be presented with the same confidence as a T1 compound regardless of the strength of its IC50 values.

Tier	Evidence Standard	Examples	CES Multiplier	Stack Eligibility
T1 ★★★★	Randomised Controlled Trial (human, ≥ 30 subjects, pre-registered)	Phase II/III trial, Cochrane meta-analysis	1.00 (no penalty)	Primary & Secondary Nodes — preferred
T2 ★★★	Controlled In Vivo Study (animal model, ≥ 2 independent groups)	Murine xenograft, rat metabolic model	0.75	All nodes — standard
T3 ★★	In Vitro / Cell-Line Study (≥ 2 independent replications, IC50 reported)	MCF-7 cytotoxicity, HepG2 metabolic assay	0.50	All nodes — with explicit limitation note
T4 ★	Computational / Docking / Single Study Only	Molecular docking, single-lab unreplicated study	0.25	Synergy & Epigenetic nodes only — flagged

VI. STOICHIOMETRIC ARCHITECTURE — 750 mg CAPSULE (REVISED)

VI-A | CES-Weighted Mass Allocation (CWMA) Algorithm

Addresses PI 3.3 fault F-08. The original document stated mass ranges without any selection rule. CWMA algorithmically derives final node mass from normalised CES rank, ensuring the highest-efficacy compound receives proportionally dominant capsule real estate.

$$r(i) = CES(i) / \sum CES(j) \text{ for } j = 1..6 \text{ [normalised CES rank]}$$

$$M_{budget} = 740 \text{ mg (750 mg total - 10 mg excipient minimum)}$$

$$m(i) = r(i) \times M_{budget} \text{ [allocated mass for Node } i]$$

$$\text{Constraint: } \sum m(i) \leq 740 \text{ mg and each } m(i) \geq 5 \text{ mg}$$

If $m(i) < 5$ mg for any node: redistribute mass from lowest-CES node proportionally.

VI-B | Node Architecture Reference Table

Node	Role	DSV Dim.	Typical Mass	CES Min.	Tier Min.	Key Logic
Node 1	Primary Driver	D1 (Genomic)	220–300 mg	≥ 7.0	T2+	mTOR / KRAS / major oncogenic axis; highest CES in stack
Node 2	Secondary Driver	D2 (Metabolic)	140–200 mg	≥ 6.0	T2+	Metabolic flux correction; GLUT or OXPHOS modulation
Node 3	Synergy A	D3 (Redox)	80–120 mg	≥ 5.0	T3+	Nrf2/ROS; potentiates Node 1 via oxidative stress reduction
Node 4	Synergy B	D4 (Immune)	40–70 mg	≥ 5.0	T3+	Cytokine/NF-κB; addresses immune contexture of pathology

Node	Role	DSV Dim.	Typical Mass	CES Min.	Tier Min.	Key Logic
Node 5	Epigenetic	D5 (Epigenetic)	30–60 mg	≥ 4.0	T3+	HDAC/DNMT; persistent downstream silencing of drivers
Node 6	Kinetic Adjuvant	D6 (ADME/PK)	10–25 mg	≥ 4.0	T3+	CYP3A4/P-gp inhibitor — SII gate mandatory before use
Node 7 ★	Bioavailability Enhancer (Optional)	D6 secondary	5–15 mg	N/A	T2+	Piperine / lecithin / SNEDDS adjuvant; enhances Nodes 1–5 absorption
Excipient	Inert Filler	—	≥ 10 mg	—	—	USP Microcrystalline Cellulose or equivalent USP-grade binder

★ Node 7 is optional. Total capsule mass must remain ≤ 750 mg including all nodes and excipient.

VII. LOGIC-GATE DECISION THRESHOLDS (FORMALISED)

Addresses PI 3.3 fault F-07. All Logic-Gate criteria are now quantified. A compound failing any single criterion is excluded from node selection. Partial failures may be retained as Node 7 (optional) with explicit Tier demotion.

Gate	Criterion	Threshold	Failure Action
LG-A	Independent Replication	Minimum 2 independent research groups, different institutions	Exclude from Nodes 1–5; permitted in Node 7 with T4 designation
LG-B	Study Scale	n ≥ 30 (in vitro) OR in vivo study (any n)	Downgrade to T4; permitted in Nodes 3–5 only
LG-C	Effect Size	Cohen's d ≥ 0.30 OR equivalent SMD / OR / RR meeting MCID	Exclude from primary nodes; flag in decision log
LG-D ★	Tmax Alignment (NEW)	ΔTmax vs. Node 11 ≤ 2 hours (PKAS ≥ 0.50)	Modified-release formulation required; document in reporting
LG-E ★	Safety Gate (NEW)	SII ≤ 0.25 for Node 6; SII ≤ 0.50 for all other nodes	HARD FAIL — node must be substituted or stack redesigned

VIII. REPORTING & ARCHIVAL STANDARD

All PI 3.4 outputs must comply with the Landry Hallucination-Free Protocol (LHFP). Every claim in the final LaTeX report must trace to a Step 05 citation. The following artefacts are mandatory outputs of Step 12:

Artefact	Format	Required Content
Formulation Summary Table	LaTeX / PDF	All 6+1 nodes: compound, mass, CES, Tier, SI, PKAS, SII
Decision Log	LaTeX appendix	All Logic-Gate decisions with citations; all rejections documented
6×6 Synergy Matrix	LaTeX table	All 15 SI values; NSI; pass/fail status per pair
DSV Scoring Sheet	LaTeX table	All 6 dimension scores per selected compound
Confidence Tier Register	LaTeX table	Tier assignment with supporting citation for each node
PKAS Alignment Chart	LaTeX figure	Tmax timeline showing plasma co-presence window
Safety Interaction Report	LaTeX section	SII calculation; CYP/P-gp flags; contraindication list
Zenodo Archive Record	Zenodo DOI	Full PDF + LaTeX source under OSML-2026 provenance; DOI minted

IX. VERSION LOG

Version	Date	Key Changes
PI 1.0	2024-Q1	Initial framework — basic compound selection model
PI 2.0	2024-Q3	Introduction of 750 mg stoichiometric architecture; Bliss SI added
PI 3.0	2025-Q1	LHFP compliance layer; hallucination-free gate added to Step 05
PI 3.2	2025-Q3	Mathematical specification formalised; LaTeX clinical protocol added

Version	Date	Key Changes
PI 3.3	2025-Q4	Nanosheet matrix purged (USP-MCC substitution); 6-node architecture locked
PI 3.4	2026-05-11	9-fault correction delta (F-01 → F-09); CES formula rebuilt; DSV defined; 6×6 Synergy Matrix; PKAS; SII; Confidence Tier system; CWMA algorithm; 12-step protocol

RESEARCH HYPOTHESIS DECLARATION — LHFP COMPLIANT

PhytoIntelligence 3.4 is a research hypothesis and computational framework. No formulation described herein has undergone clinical validation, safety testing, or regulatory review. All performance projections are derived from literature deconvolution of published data and are subject to the limitations of in vitro and in vivo-to-human translational uncertainty. This document does not constitute medical advice. No compound stack produced by this framework should be administered to humans without independent qualified clinical oversight, IRB approval, and applicable regulatory compliance.

All epistemic claims are subject to the 1=1=1 Law: a hypothesis is a hypothesis until independently validated — no more, no less.

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