

PHYTOINTELLIGENCE 3.4

Multivariate R&D; Framework | Forensic Pharmacology Specification | Version 3.4.0

Owner	Marie-Soleil Seshat Landry	Model	AI-Assisted (LLM Verification Layer)
Protocol	LHFP Compliant (Hallucination-Free)	Epistemic Standard	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 $p = 1 + \ln(1 + R \times C)$; always ≥ 1
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 relation
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
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
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 ≥ 0.2
F-08	Node mass range (250–300mg) has no selection algorithm; no rule linking CES to mass allocation	MEDIUM	CES-Weighted Mass Allocation (CWMA) algorithm introduced; mass $\propto$ normalised CES
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

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	
02	Intel Requirement	Define specific enzymatic, genomic, or metabolic targets. Targets must be cited from peer-reviewed PubMed / Scopus). Mini	PASS (Pass)
02a	Confidence Tier Pre-Screen ★NEW	Assign each candidate compound to Confidence Tier (T1–T4) per Section V. Exclude all T4-only compounds from the primary stack u	Confidence Tier
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 di	
04	Experimental Design	Set 750 mg volumetric/stoichiometric constraints. Assign provisional node roles (Primary, Secondary, Synergy, Epigenetic, Kinetic). A	
05	Collection	Extract verified IC50 and PK data (Tmax, t½, Cmax, OBC, MSI) from PubMed/Scopus. LHFP applies: IC50 may be inferred from st	IC50 Gate
06	DSV Analysis	Deconvolve candidate compounds through the 6-Dimensional DSV. Score each compound per dimension. Rank all candidates by DS	
07	Logic-Gating	Reject pathways lacking: (a) ≥2 independent replications, (b) n≥30 or in vivo study, (c) effect size ≥ 1.5 (Cohen's d) (or eq	IC50 Gate
08	Node Selection	Select the 6 primary nodes from surviving candidates. Apply CWMA to assign final mass per node. Verify total ≤ 740 mg (reserve ≥ 10	
09	Synergy Simulation	Compute full 6×6 Synergy Matrix (Section III-B). Calculate aggregate Network SI. Flag any antagonistic pair (SI < 0.8) for substitution	SI Gate
10	PK Alignment	Compute PKAS for all 6 nodes (Section III-C). All nodes must satisfy $ \Delta T_{max} \leq 2h$ relative to Node 1. Nodes exceeding threshold req	PKAS Gate
10a	Safety Interaction Gate ★NEW	Compute Safety Interaction Index (SII) for all nodes (Section III-D). Screen all CYP/P-gp interactions. Flag contraindicated pairs. Node	SII Gate
11	Conclusion & Formulation	Finalise the 6+1 Node stack. Document final mass allocation, Confidence Tiers, SI values, PKAS, and SII for all nodes. Produce the F	
12	Reporting	Generate final LaTeX proposal, formulation recipe, and decision log. Archive to Zenodo under LHFP protocol. All claims must be t	Final Review

III. COMPUTATIONAL MODELS (REVISED & EXTENDED)

III-A | Compound Efficacy Score (CES) — Corrected Formula

PI 3.3 fault F-01 / F-02 / F-03 corrected. The original formula contained a logarithmic singularity and a pharmacological redundancy. PI 3.4 introduces a bounded Risk Penalty Factor and separates bioavailability from the ADME composite.

$$CES = [W_M \cdot (\text{Mechanistic Score}) + W_V \cdot (\text{Validation Score})] \times \text{Plausibility}$$
$$\rho(R, TCI) \times [OBC + MSI]$$

Term	Definition	Range / Units
W_M	Mechanistic weight coefficient	0 – 1 (sum W_M + W_V = 1)
W_V	Validation weight coefficient	0 – 1 (sum W_M + W_V = 1)
Mechanistic Score	Number of independently validated MoA pathways for the target	1 – 10
Validation Score	Confidence Tier multiplier × effect size (Cohen's d or equivalent)	0 – 10
Plausibility	Expert consensus score on clinical translatability	0.0 – 1.0
ρ(R, TCI)	Risk Penalty Factor = 1 + ln(1 + R × TCI) [always ≥ 1, no singularity]	1.0
R	Risk score: adverse effect profile (0 = none, 1 = severe)	0.0 – 1.0
TCI	Translational Cost Index = log10(IC50_human / IC50_cell) — dose burden proxy	0.0 – 1.0
OBC	Oral Bioavailability Coefficient: fraction absorbed (0–1)	0.0 – 1.0
MSI	Metabolic Stability Index: fraction surviving first-pass (0–1)	0.0 – 1.0

III-B | 6×6 Synergy Matrix — Network Synergy Index

PI 3.3 fault F-04 corrected. The original Bliss formula was shown for N=2 only. A 6-node stack contains C(6,2) = 15 pairwise interactions. PI 3.4 computes a full pairwise Bliss matrix and aggregates into a Network SI.

Pairwise Bliss (unchanged): $E(a,b) = E(a) + E(b) - E(a) \cdot E(b)$

Synergy Index for pair (i,j): $SI(i,j) = E(\text{observed}) / E(a,b)$

$SI > 1.0 \rightarrow$ synergistic

$0.8 \leq SI \leq 1.0 \rightarrow$ additive (acceptable)

$SI < 0.8 \rightarrow$ antagonistic (FAIL – substitute Node)

Network SI: $NSI = (\prod SI(i,j) \text{ for all 15 pairs }) ^ { (1/15)}$

Acceptance threshold: $NSI \geq 0.90$ (geometric mean across all pairs)

The 6×6 matrix is computed as a lower-triangular table during Step 09. Each cell SI(i,j) is populated from literature co-administration studies where available, or estimated via Bliss Independence from individual efficacy data. Any cell with SI < 0.8 triggers a Node substitution loop (→ Step 08).

Node	N1 Primary	N2 Secondary	N3 Synergy	N4 Synergy	N5 Epigenetic	N6 Kinetic
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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			—	SI(3,4)	SI(3,5)	SI(3,6)
N4 Synergy				—	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 | 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.

$$PKAS(i) = 1 - (|Tmax(i) - Tmax(Node1)| / Tmax_window)$$

Tmax_window = 4 hours (default; adjustable per indication)

Acceptance: PKAS(i) ≥ 0.5 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 | 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
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 PhytoIntelligence. 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 (Primary Driver)	0 = no data 5 = in vitro transcriptomic 10 = in vivo / clinical RCT	Node 1 (Primary Driver)
D2	Metabolic Flux	Glycolysis, OXPHOS, lipid metabolism, GLUT transporter modulation, mitochondrial biogenesis (Secondary Driver)	0 = no data 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 (Node 3 Synergy)	0 = no data 5 = DPPH/FRAP assay only 10 = Nrf2 in vivo confirmed	Node 3 (Synergy)
D4	Immune / Inflammatory	Cytokine modulation (IL-6, TNF-α, NF-κB), immune evasion, macrophage polarization (Node 4 Synergy)	0 = no data 5 = cytokine assay in vitro 10 = immune in vivo confirmed	Node 4 (Synergy)
D5	Epigenetic	DNA methylation (DNMT inhibition), histone acetylation (HDAC inhibition), miRNA regulation, chromatin remodelling (Node 5 Synergy)	0 = no data 5 = HDAC IC50 only 10 = epigenome-wide study	Node 5 (Synergy)
D6	Pharmacokinetic / ADME	CYP enzyme modulation, P-gp inhibition, bioavailability enhancement, t½ extension, plasma protein binding (Node 6 Synergy)	0 = no data 5 = CYP IC50 in vitro 10 = human PK study confirmed	Node 6 (Synergy)

DSV Aggregate Score: $DSV_total = \sum D(i)$ for $i=1..6$ (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)

The Confidence Tier system applies Seshat's Axiom (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, in vivo PK study	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
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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 (e.g., Node 1: 250–300 mg) 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.

Normalised CES rank for Node *i*: $r(i) = \text{CES}(i) / \sum \text{CES}(j)$ for $j=1..6$

Available mass budget: $M_{\text{budget}} = 740 \text{ mg}$ (750 mg total – 10 mg excipient minimum)

Allocated mass for Node *i*: $m(i) = r(i) \times M_{\text{budget}}$

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

If $m(i) < 5 \text{ mg}$ 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 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 three 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	$n \geq 30$ (in vitro) OR in vivo study (any n)	Downgrade to T4; permitted in Nodes 3–5 only
LG-C	Effect Size	Cohen's $d \geq 0.30$ OR equivalent SMD / OR / RR	Exclude from Primary nodes; flag in decision log
LG-D	Tmax Alignment (NEW)	$ \Delta T_{\text{max vs. Node 1}} \leq 2 \text{ hours}$ (PKAS ≥ 0.50)	Modified-release formulation required; document in reporting
LG-E	Safety Gate (NEW)	$SII \leq 0.25$ for Node 6; $SII \leq 0.50$ for all other nodes	NRBS 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; 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; 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; LHFP hallucination-free gate added to Step 05
PI 3.2	2025-Q3	Mathematical specification formalized; LaTeX clinical protocol added
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 through F-09); CES formula rebuilt; DSV defined; 6×6 Synergy Matrix; PKAS; SII; Confidence

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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