

# 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 $\geq 1$ , 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 6×6 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 $\geq 0.30$   |
| 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; $\text{mass} \propto \text{normalised CES rank}$   |
| 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 $\geq 3$ 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 | 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.

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

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

III-D | 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 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 (mTOR, KRAS, TP53 pathway engagement) | 0 = no genomic evidence<br>5 = in vitro transcriptomic<br>10 = in vivo / clinical RCT | Node 1<br>(Primary Driver)   |
| D2   | Metabolic Flux           | Glycolysis, OXPHOS, lipid metabolism, GLUT transporter modulation, mitochondrial bioenergetics                                  | 0 = no evidence<br>5 = cell-line metabolomics<br>10 = in vivo metabolic flux          | Node 2<br>(Secondary Driver) |
| D3   | Redox / Antioxidant      | ROS scavenging, Nrf2/HO-1 activation, GSH modulation, lipid peroxidation inhibition                                             | 0 = no evidence<br>5 = DPPH/FRAP assay only<br>10 = Nrf2 in vivo confirmed            | Node 3<br>(Synergy A)        |
| D4   | Immune / Inflammatory    | Cytokine modulation (IL-6, TNF-α, NF-κB), immune contexture, macrophage polarisation, inflammasome activity                     | 0 = no evidence<br>5 = cytokine assay in vitro<br>10 = immune in vivo confirmed       | Node 4<br>(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<br>5 = HDAC IC50 only<br>10 = epigenome-wide study       | Node 5<br>(Epigenetic)       |
| D6   | Pharmacokinetic / ADME | CYP enzyme modulation, P-gp inhibition, bioavailability enhancement, t½ extension, plasma protein binding         | 0 = no PK data<br>5 = CYP IC50 in vitro<br>10 = human PK study confirmed | Node 6<br>(Kinetic Adjuvant) |

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

A compound scoring  $\geq 40$  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<br>★★★★ | Randomised Controlled Trial (human, $\geq 30$ subjects, pre-registered)        | Phase II/III trial, Cochrane meta-analysis       | 1.00 (no penalty) | Primary & Secondary Nodes — preferred     |
| T2<br>★★★  | Controlled In Vivo Study (animal model, $\geq 2$ independent groups)           | Murine xenograft, rat metabolic model            | 0.75              | All nodes — standard                      |
| T3<br>★★   | In Vitro / Cell-Line Study ( $\geq 2$ independent replications, IC50 reported) | MCF-7 cytotoxicity, HepG2 metabolic assay        | 0.50              | All nodes — with explicit limitation note |
| T4<br>★    | 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.

$$r(i) = CES(i) / \sum CES(j) \text{ for } j = 1..6 \text{ [normalised CES rank]}$$
$$M_{budget} = 740 \text{ mg (750 mg total - 10 mg excipient minimum)}$$
$$m(i) = r(i) \times M_{budget} \text{ [allocated mass for Node } i]$$

Constraint:  $\sum m(i) \leq 740 \text{ mg}$  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   | $\geq 7.0$ | T2+       | mTOR / KRAS / major oncogenic axis; highest CES in stack          |
| Node 2 | Secondary Driver | D2 (Metabolic) | 140–200 mg   | $\geq 6.0$ | T2+       | Metabolic flux correction; GLUT or OXPHOS modulation              |
| Node 3 | Synergy A        | D3 (Redox)     | 80–120 mg    | $\geq 5.0$ | T3+       | Nrf2/ROS; potentiates Node 1 via oxidative stress reduction       |
| Node 4 | Synergy B        | D4 (Immune)    | 40–70 mg     | $\geq 5.0$ | T3+       | Cytokine/NF- $\kappa$ B; 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             | $n \geq 30$ (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 meeting MCID                 | Exclude from primary nodes; flag in decision log                |
| LG-D ★ | Tmax Alignment (NEW)    | $ \Delta T_{max} \text{ vs. Node 1}  \leq 2 \text{ hours}$ (PKAS $\geq 0.50$ ) | 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                | <b>HARD FAIL — node must be substituted or stack redesigned</b> |

## 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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