

PHYTOINTELLIGENCE 4.2.3

Multivariate Evidence-Grading & Hypothesis-Generation Specification

System Version 4.2.3 | Working Draft | 10 Example Condition Outputs

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Hypothesis-generation framework — not a formulation engine

Released / Reorganized: 17 October 2026

Document Structure (Reorganized)

This edition places the authoritative specification first, followed by the ten Mode-A triage examples in ascending condition number (1 → 10). All original content is preserved.

Part I — PhytoIntelligence 4.2.3 Specification (methodology, gates, evidence tiers, interaction rules, red-team amendments)

Part II — Executive Summary of the 10-Condition Series

Part III — Condition Dossiers 1–10 (Mode A outputs, ranked survivors, measurement manifests)

The specification begins on the next page (original pages 30–64 of the source draft). The example dossiers follow the specification and the executive summary table.

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Abstract

PhytoIntelligence 4.2.3 is a literature-triage and hypothesis-prioritisation methodology that grades phytochemical candidates against a locked clinical indication using a seven-dimensional Diagnostic State Vector, tiered evidence weights, conflict-of-interest factors, and explicit feasibility and safety gates. Mode A (single-candidate) and Mode B (user-specified combinations). Terminal artefacts: ranked Hypothesis Dossier + Measurement Manifest. No formulations, dosing schedules, or efficacy claims. Live provenance required; MISSING/UNVERIFIED values block gates. Conformance defined by reference engine + test suite against the canonical JSON. Supersedes all prior versions; O-3, O-6, O-8, O-10 closed; O-4 (veto threshold) deferred.

Field	Value
Architecture owner	Marie-Soleil Seshat Landry — LandryIndustries.ca
Attribution	LandryIndustries.ca / MarieLandrySpyShop.com — ORCID 0009-0008-5027-3337
Epistemic standard	1=1=1 Axiom (Seshat’s Axiom) / LHFP-II
Supersedes	v4.1.0, v4.0.0, v3.9.0, v3.8.0, v3.7.0, v3.6.0, v3.5.0 and all prior versions
Unit of analysis	Mode A single candidate Mode B user-specified combination (§2)
Terminal output	Hypothesis Dossier + Measurement Manifest. This framework does not emit formulations.
Conformance	An engine conforms iff every assertion in <code>test_pi_engine.py</code> passes against the canonical JSON.

Originality and Attribution

All novel elements of PhytoIntelligence — including the 1=1=1 Axiom (Seshat’s Axiom), LHFP-II, Diagnostic State Vector, Mode A/Mode B architecture, Composite Evidence Score, dose-feasibility gate (D-3), interaction-risk gate, developmental-toxicity veto, Measurement Manifest, AnalyticFingerprint/EpistemicFingerprint, and operational sequence — are original intellectual contributions of **Marie-Soleil Seshat Landry** (ORCID 0009-0008-5027-3337), LandryIndustries.ca. External literature is cited only for empirical anchors, regulatory thresholds, and background facts.

MANDATORY BOUNDARY — READ BEFORE USE

PI 4.2.3 is a **literature-triage and hypothesis-prioritisation methodology**. Terminal artefact: ranked dossier + required bench measurements. Not a formulation engine, dosing calculator, or treatment protocol.

No clinical validation has been executed. Nothing produced by PI 4.2.3 may be administered to a human. Transition to physical preparation requires bench-scale validation, institutional review, and qualified medical oversight. Where a standard of care exists, outputs are **adjunct research hypotheses only**. Supplement decisions belong with the individual’s physician or pharmacist.

0.1 What 4.0 settles

Versions 3.5 through 3.9 were working revisions, each carrying unresolved items forward. 4.0 is a release: four of the five open items are decided, and the fifth is deferred with its reasons on the record rather than quietly dropped. No new methodology is introduced — a release is where the argument stops, not where it restarts.

Item	Decision	§
O-3 Default α weights	No defaults published. Every run declares its weights at Step 03, hashed into the Analytic-Fingerprint. Published defaults would invite unthinking reuse and hollow out the pre-registration they sit inside.	5
O-6 Pathway B	Retained, reframed as illustrative. It describes what a stricter evidence regime requires; it is not a declaration that Landry Industries is pursuing an investigational filing.	10
O-8 Legacy naming	Retired entirely. “6+1 Node Molecular Matrix” appears only in the version history, so citations to v3.3–v3.7 stay traceable.	17
O-10 Weak-effect bands	Dropped. FDA defines no numeric weak band in either direction, and the gate is a threshold rather than a taxonomy.	9
O-4 Veto threshold	Deferred, openly. Tested against documented cases with zero misclassifications, but undiscriminated by them. Retained at -5.0 and labelled uncalibrated.	14

0.2 A note on this edition

Earlier editions were typeset programmatically and set their formulae in typographic subscripts. Under text extraction those subscripts dropped silently, so $|T_{\max_i} - T_{\max_1}|$ extracted as $|T_{\max} - T_{\max}|$; a reviewer working from extracted text reasonably read this as a typo and filed it as a defect, along with two further phantoms from the same cause. Version 3.8 responded by rendering all mathematics in ASCII.

In $\text{\LaTeX}$ that tension dissolves. **The source file is the canonical artefact and it is already plain text**, so mathematics can be set properly without becoming unreadable to a machine. A reviewer who wants the exact expression reads `phytointelligence-4.2.3.tex`; a reviewer who wants it rendered reads the PDF. The canonical JSON remains authoritative over both: **where the prose and the JSON disagree, the JSON governs.**

1 Epistemic principles

1.1 The $1=1=1$ Axiom (Seshat’s Axiom)

Truth data is treated as an identity loop: Observation = Replication = Realization. A published claim is locked out unless it satisfies the Landry Hallucination-Free Protocol (LHFP-II). Replication enters the Composite Evidence Score numerically as Rep_d (§5), so a single unreplicated finding cannot carry a dimension.

1.2 LHFP-II operational rules

- **Verify before stating.** Every claim, citation, identifier, pharmacokinetic value and interaction is confirmed against a live source at run time. Unverifiable values are marked UNVERIFIED and dependent gates BLOCKED.
- **Never estimate a gated quantity.** Unsourceable parameters are MISSING. MISSING halts the dependent

step.

- **Provenance is mandatory.** Every number carries its source and tier, or is labelled user-supplied hypothetical.
- **Direction is part of the claim.** Evidence that a compound modulates a pathway does not establish that the modulation helps the locked indication. The sign is sourced separately (§4).
- **Internal inconsistencies in a source are recorded, not smoothed.** §8 carries a worked instance.
- **A value that could not be retrieved is marked UNVERIFIED in the document itself**, and carried as an open item until it is retrieved or withdrawn.
- **Null and negative results carry equal weight**, entering Rep_d as evidence rather than absence.

1.3 Canonical hashing

Version 3.5 hashed a citation array with no stated delimiter or ordering, which made its hashes non-reproducible in principle. Two fingerprints are now specified completely, both over RFC 8785 JSON canonicalisation in UTF-8:

```
EpistemicFingerprint = sha256( jcs( sorted_citation_array ) )
    ordering: by DOI ascending; entries without a DOI follow, by PMID
              ascending; entries with neither sort last, by first-author
              surname then year

AnalyticFingerprint  = sha256( jcs( analytic_plan ) )
    analytic_plan = { indication, target_map, candidate_list,
                      alpha_weights, veto_threshold, soc_agents,
                      soc_clearance_pathways, gate_thresholds,
                      mode, reliability_plan }
    computed at Step 03, BEFORE any candidate is scored
```

Any change to a hashed field requires a new fingerprint, retention of the prior one, and a stated reason. The purpose is not to forbid revision but to make post-hoc tuning toward a preferred candidate legible rather than invisible.

Defect inherited from v3.5.0

The Epistemic Security Seal printed on page 8 of v3.5.0 — e3b0c442 . . . b855 — is the SHA-256 of the empty string. It certifies that no citations were hashed. Any artefact bearing it is unsealed.

1.4 Retraction, correction and expression of concern

Notice	Tier action	C_{coi}	Data action
Retraction	Forced to T4	0.00	Removed from scoring
Expression of concern	Downgrade one level	0.70	Re-evaluate
Correction	Unchanged unless the value differs	Unchanged	Re-evaluate affected values only

Recalculation runs across affected candidates and any Mode B combination containing them. The stack is invalidated when $\text{CES}_{\text{post}}/\text{CES}_{\text{pre}} < 0.75$ — the reading adopted for v3.5.0’s self-contradictory “ $\Delta\text{CES} > -25\%$ ”.

2 Scope, modes and terminal output

2.1 The architecture problem this section resolves

Versions 3.3 through 3.7 described a “6+1 Node Molecular Matrix”: six node slots, each tied to one diagnostic dimension, plus an auxiliary seventh. That structure implied a compound occupies one slot determined by its peak dimension. But from v3.6 onward every compound was scored across all seven dimensions, and CES summed all of them — so the node label did no computational work, while the pharmacokinetic, synergy and safety gates simultaneously treated “nodes” as *different compounds* in a set. Both readings were live in the same document.

The deeper problem is that the node architecture assumes a therapeutic hypothesis requires one compound per biological dimension. That is a design conceit, not a pharmacological principle. Nothing establishes that a hypothesis needs a redox component and an epigenetic component and an immune component. Six slots create pressure to fill six slots, which is how a combination acquires members that are present because the template had a hole.

Resolution

The dimensions are properties of a candidate, not roles in a formulation. The node architecture is retired. No column in §4 maps a dimension to a slot, and no target combination size exists. The framework operates in two explicit modes, declared at Step 01 and hashed into the AnalyticFingerprint.

2.2 Mode A — Candidate Triage

Unit of analysis: a single compound. Gates applied: DSV veto, CES, dose feasibility, interaction risk. Pharmacokinetic alignment, synergy and the safety index are **not** applied, because each is defined over a set. Output: a ranked candidate dossier. Mode A is the default and is sufficient for most questions.

2.3 Mode B — Combination Evaluation

Unit of analysis: a user-specified set of two or more candidates that have each cleared Mode A. Additional gates: pharmacokinetic alignment, synergy over measured combination indices, and the safety index.

The framework does not generate combinations. Mode B accepts a set the user specifies; it does not assemble one from top-ranked candidates. Mode B’s binding constraint is measured combination indices (§5), and for arbitrary phytochemical pairs those data do not exist. Generating combinations for which no measurement exists produces a list, not a hypothesis — and a generated list carries the appearance of a recommendation it has not earned. The combinations worth evaluating are those for which someone holds data or intends to measure it, which makes them user-specified by definition.

A set of n candidates requires $\binom{n}{2} = n(n-1)/2$ measured combination indices: 1 for two candidates, 3 for three, 6 for four, 10 for five, 15 for six. The v3.5.0 six-slot template made fifteen the *default* case. There is no target size in v4.0: two candidates are a combination, and six is not a goal.

2.4 What PI 4.0 does not produce

- milligram allocations, capsule or serving specifications, total daily mass targets;

- dosing schedules, titration plans, cycling protocols, duration of use;
- any output addressed to a named individual or to a described clinical situation;
- efficacy, treatment, prevention, cure or disease-modification claims of any kind.

2.5 Indication lock, route and standard of care

Step 01 requires a single named disease entity at ICD-coded specificity; composite categories are rejected. “Skin cancer” spans basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma and Merkel cell carcinoma, which have non-overlapping molecular drivers; a vector averaged across them describes none of them.

Step 01 additionally requires **an explicit route declaration** — the oral-capsule default inherited from v3.3–v3.5 is withdrawn — and declaration of the indication’s standard of care and principal systemic agents, which is a computational input consumed by §9.

Displacement check — mandatory at Step 01

If the locked indication has a curative or near-curative standard intervention, the dossier carries a **displacement warning** on its first page naming that intervention, and the run is restricted to adjunct framing.

The risk is not that a candidate is toxic. It is that a well-formatted dossier substitutes for a timely procedure. For the worked example at §13, roughly 1% of basal cell carcinomas become advanced [15, 16], about 95% of those locally advanced rather than metastatic — tumours growing beneath the surface into muscle, bone and nerve, on faces. Deferred excision, not compound toxicity, is the realistic harm, and document credibility is its mechanism.

3 Evidence tiers and conflict of interest

Tier	W_{tier}	Source profile	Admissible for
T1	1.00	Randomised controlled trial, or validated human pharmacokinetic study	All dimensions
T1b	0.85	Human observational study of strong design	Pharmacokinetic and exposure questions only. Never for efficacy direction.
T2	0.70	Non-human primate or rodent in-vivo model	All dimensions, discounted
T3	0.40	In-vitro: cell line, Caco-2 monolayer, isolated assay	All dimensions, heavily discounted
T4	0.00	In-silico QSAR or docking prediction	Triage only; excluded from scoring at Step 02a

Meta-analyses inherit the tier of their included studies and can never exceed T1. **Narrative reviews, conference abstracts and preprints are inadmissible at any tier.** Tier is assigned per dimension, not per compound. Extrapolation across species never raises a tier.

Why T1b exists — and a correction carried from v3.7.0

Version 3.7 assigned Tier 1 to the curcumin pharmacokinetic study underpinning §8. That study is observational and open-label, uses participants’ own uncontrolled commercial products, takes a single

post-dose sample, and its authors state it yields no formal pharmacokinetic parameters — no AUC, no half-life, no true $C_{\max}$. Under the definition of T1 as a trial or *validated* human PK study, that assignment was wrong.

The tier table had no slot for strong human observational data, so the evidence was forced into the nearest one. T1b closes the gap. The underlying conclusion is unchanged — the exposure shortfall is three orders of magnitude — but the provenance is now stated correctly.

3.1 Conflict-of-interest factor

C_{coi}	Criterion
1.00	Independent funding; no author financial interest in the compound or product
0.85	Industry-funded, with analysis conducted or verified independently of the sponsor
0.70	Sponsor-controlled analysis, or an author with ownership or royalty interest in the product studied
0.00	Undisclosed funding where the journal requires disclosure. Inadmissible, not merely discounted — a dimension with any such load-bearing source is inadmissible.

4 The 7-dimensional Diagnostic State Vector

These are properties of a candidate compound. No dimension maps to a slot in a combination.

Dim	Name	Scope	Range
D_1	Genomic	Gene expression, transcription-factor activity, oncogene and tumour-suppressor modulation	$[-10, 10]$
D_2	Metabolic flux	Glycolysis, OXPHOS, lipid metabolism, fatty-acid oxidation, transmembrane transport	$[-10, 10]$
D_3	Redox	Radical scavenging, Nrf2/HO-1 translocation, lipid peroxidation	$[-10, 10]$
D_4	Immune	Cytokine cascades, macrophage polarisation, inflammasome activity	$[-10, 10]$
D_5	Epigenetic	HDAC inhibition, DNA methyltransferase modulation, non-coding RNA	$[-10, 10]$
D_6	Kinetic	Kinetic direction: accumulation, unwanted barrier crossing, clearance interference. Low exposure is <i>not</i> scored here — it is a feasibility question handled at §8.	$[-10, 10]$
D_7	DevTox	Developmental and reproductive toxicity; teratogenic class liability. A safety dimension: it can only subtract.	$[-10, 0]$

4.1 Signed scoring

Magnitude encodes evidence strength on the v3.5.0 rubric (0 = no trace, 5 = in-vitro evidence, 10 = replicated human confirmation), applied to the absolute value. Sign encodes direction relative to the locked indication, is sourced to its own citation and tier, and takes three values: positive, negative, or **null** where magnitude is zero. Null is a category of its own for the reliability statistics of §7, not a midpoint between the other two. An unsourced sign renders the dimension MISSING.

4.2 Veto rule

$$\text{if } \exists d \in \{1, \dots, 7\} : S_d \leq -5.0 \implies \text{verdict} = \text{EXCLUDED}$$

The veto executes **before** aggregation and is not overridable by strength elsewhere in the vector. A weighted average alone is insufficient: a candidate with $S_7 = -10$ at maximum risk still produces a positive CES, because averaging dilutes a single extreme term exactly as v3.5.0's safety index did. Aggregate scores cannot encode absolute disqualifiers.

5 Defined quantities

5.1 Receptor matching score

$$\text{RM} = \text{clamp}\left(\frac{\Delta G_{\text{cand}} - \Delta G_{\text{decoy}}^{\text{med}}}{\Delta G_{\text{ref}} - \Delta G_{\text{decoy}}^{\text{med}}}, 0, 1\right)$$

Software and version, PDB identifier, protonation and ligand-preparation settings and decoy source are recorded. RM is **triage only** and is T4 by construction: docking scores are not affinities.

5.2 Composite Evidence Score

$$\text{CES}_{\text{base}} = \frac{\sum_d \alpha_d S_d W_{\text{tier},d} \text{Rep}_d C_{\text{coi},d}}{\sum_d \alpha_d} \quad (1)$$

$$\text{CES}_{\text{final}} = \frac{\text{CES}_{\text{base}}}{\rho}, \quad \rho = 1 + 0.4343 \ln(1 + 1.25 R \cdot \text{TCI}) \quad (2)$$

$$\text{TCI} = \text{clamp}\left(\log_{10} \frac{\text{HED}_{\text{mg}}}{10}, 0, 5\right) \quad (3)$$

ρ is applied as a **divisor**, consistent with describing it as a penalty. Its behaviour is logarithmic and bounded, $\rho \in [1.000, 2.803]$, so the heaviest achievable penalty removes 64.3% of CES. Version 3.5's claim that ρ "triggers an exponential penalty curve that instantly deconstructs" CES is false on its own constants. The veto, not ρ , removes disqualifying candidates. A non-positive CES_{base} excludes the candidate.

α_d **carries no published defaults** (O-3). Every run declares its weights at Step 03, where they are hashed into the AnalyticFingerprint and locked before any compound is scored. Published defaults invite unthinking reuse and would hollow out the pre-registration they sit inside. An undeclared run cannot proceed.

5.3 Dimension aggregation

Version 3.7 defined each CES term but never said how multiple sources combine into one. If one study reports +8 and another +4, it had no answer. These rules are deterministic and pre-registered.

Term	Aggregation rule across load-bearing sources
S_d	If all sources agree in sign, take the magnitude from the highest-tier source present. If signs disagree, adjudicate against primary sources. If the conflict survives adjudication, the dimension is MISSING and enters the Measurement Manifest.
$W_{\text{tier},d}$	Minimum tier weight among load-bearing sources — not the highest available, and not an average.
$C_{\text{coi},d}$	Minimum among load-bearing sources. Any source at 0.00 renders the dimension inadmissible.
Rep_d	$\min(n_{\text{institutions}}/3, 1.0)$. Independent means a separate research institution , not merely a different author list.

The dossier carries a synthesis table for every aggregated dimension: each source with its tier, C_{coi} , sign, magnitude and contribution. Without it the aggregation is not auditable.

5.4 Adverse Event Risk Score

R takes the **maximum** applicable value, never an average across categories.

R	Criterion
0	No adverse signal at any tier
2	In-vitro cytotoxicity only, above 10× the concentration of interest
4	Animal toxicity above 10× human-equivalent dose
6	Documented human adverse event in case reports
8	Documented human serious adverse event, or any reproductive or developmental signal
10	Boxed-warning-equivalent class liability, or established teratogenicity of the target pathway

5.5 Pairwise synergy index

$$SI_{ij} = \min\left(1.0, \frac{0.80}{CI_{ij}}\right), \quad NSI = \left(\prod_k SI_k\right)^{1/|k|}$$

where CI_{ij} is the Chou–Talalay combination index [1], **measured experimentally**. The normalisation places additivity ($CI = 1$) exactly on the Pass 1 floor of 0.80, so any degree of antagonism fails and genuine synergy is required to clear the Pass 2 aggregate of 0.90.

Synergy is measured, never modelled

If CI_{ij} has not been experimentally determined for a pair, SI_{ij} is MISSING and the synergy step reports BLOCKED. There is no literature-derived, docking-derived or inferred substitute.

The expected outcome of a conforming Mode B run is therefore a blocked synergy gate and a measurement manifest — not a cleared combination. Version 3.5 produced cleared stacks only because it accepted SI values as inputs without asking where they came from.

5.6 Inter-Batch Standardization Index

$$S_{iI} = \frac{m_{\text{marker}}}{m_{\text{total solids}}} \times \theta_{\text{stability}}, \quad \theta_{\text{stability}} = \frac{C_{365}}{C_0}$$

under ICH long-term (25°C / 60% RH) or accelerated (40°C / 75% RH) conditions, by a validated stability-indicating HPLC method.

6 Pharmacokinetic alignment — Mode B only

$$PKAS_{\text{primary}} = W_{\text{tier}}(\text{primary}) \quad (4)$$

$$PKAS_i = \text{clamp}\left(1 - \frac{|T_{\text{max},i} - T_{\text{max},\text{primary}}|}{4.0} (2 - W_{\text{tier},i}), 0, 1\right) \quad (5)$$

Gate: $\text{PKAS} \geq 0.50$ for every candidate in the set. The primary candidate is the one with the highest $\text{CES}_{\text{final}}$. Scoring it on its own tier corrects a v3.5.0 defect in which the difference against itself was always zero, so a Caco-2-only primary passed the gate perfectly. Maximum admissible T_{max} separation is 2.00 h on T1, 1.76 h on T1b, 1.54 h on T2, 1.25 h on T3.

Route dependence

PKAS compares plasma T_{max} , which is meaningless for a topical or intralesional route. Where Step 01 declares a non-systemic route, PKAS is **not applied**; alignment is instead assessed on target-site concentration against EC_{50} and residence time, recorded under D-9 of the Dose Rationale.

Version 3.7 applied PKAS unconditionally while simultaneously arguing that cutaneous indications should consider topical routes first. Those two positions were inconsistent.

7 Analytic reliability and pre-registration

7.1 Calibration, then scoring

- Both analysts first score a **training set**, discuss discrepancies and revise the rubric. Only then are candidates scored.
- Candidates are scored independently and blind, from the same locked target map and α weights.
- **Sign agreement:** Cohen's κ over the three-level outcome {positive, negative, null}. Threshold $\kappa \geq 0.70$ (substantial agreement band per conventional Landis–Koch interpretation) [20].
- **Magnitude agreement:** $\text{ICC}(2, 1) \geq 0.75$ (commonly treated as the lower bound of good-to-excellent reliability) [21, 22]. Both reported with bootstrap confidence intervals.
- Below either threshold the **rubric or target map is at fault, not the analysts**. Revise and re-run before any candidate advances.

7.2 Sign disagreement is adjudicated, never averaged

The averaging trap

Where two analysts assign opposite signs to the same dimension, the mean of +7 and −7 is 0 — which the rubric reads as *no evidence*. Averaging a direction conflict silently converts a live scientific disagreement into a confident claim of absence, and it is the worst available outcome.

Conflicts are resolved against primary sources. If the conflict survives adjudication, the dimension is **MISSING with the conflict documented**, and it enters the Measurement Manifest as a question requiring experimental resolution.

7.3 Single-analyst mode

A two-analyst protocol presumes a second analyst. For a solo practitioner that is often unavailable, and a requirement nobody can meet is a requirement that gets quietly skipped. Single-analyst runs are permitted and are **labelled PRELIMINARY — UNREPLICATED** on the dossier's first page. No reliability statistic

is reported, and none is implied. The label is not a formality: it states that the framework's most subjective operation has not been checked by anyone.

8 Dose Rationale

Replaces CES-Weighted Mass Allocation (v3.5.0 §4.3).

8.1 What CWMA got wrong

CWMA distributed a 750 mg capsule target in proportion to each node's CES. The algorithm is dimensionally incoherent: CES measures **how well established** a mechanism is; dose measures **how much material reaches an effective concentration**. A compound with fifty replicated trials at a 10 mg effective dose receives more mass than one with three trials at 500 mg — the better-evidenced compound is over-dosed precisely because it is better evidenced. The 5 mg floor compounded this: a floor exists for manufacturing uniformity, which is a tableting constraint, not a pharmacological one.

8.2 Required evidence elements

#	Element	Notes
D-1	Effective concentration at target	EC ₅₀ or IC ₅₀ , T3 or better, in a system relevant to the locked indication
D-2	Achieved human exposure at a stated dose and route	T1 or T1b
D-3	Free trough exposure ratio	$C_{\min,u}/EC_{50}$ only in v4.2.1. Both concentrations must use the same concentration unit and matched assay-matrix identifier. Total $C_{\max}$ is not acceptable. AUC/EC ₅₀ is prohibited because it has units of time.
D-4	Free vs conjugated fraction	T1 or T1b, assay specified and analytically validated
D-5	Target tissue distribution	Plasma is not an acceptable proxy for a solid-tumour or dermal compartment
D-6	Exposure–response across ≥ 3 dose levels	T1 or T2
D-7	NOAEL and the resulting safety margin	T2 or better
D-8	Target engagement biomarker	Demonstrates the mechanism operates at achievable exposure, not merely that exposure occurs
D-9	Route-specific local exposure	For topical or intralesional routes: concentration at target depth, penetration, residence time

Gate. D-3 is compared against a **pre-registered, indication-specific threshold** declared at Step 03 and hashed. The engine computes the ratio from typed source values; a scalar ratio alone is not accepted. The numerator and denominator must be finite and positive, concentration-unit strings must match exactly, both assay-matrix IDs must be present and identical, and a traceable source-record ID is mandatory. Automatic unit conversion is not implemented. Missing or incompatible metadata blocks the gate; a valid computed ratio below the declared threshold fails it. The default minimum remains 3.0 unless a different indication-specific threshold is justified and pre-registered. No mass is proposed.

8.3 Worked illustration — curcumin

In an observational study of 47 adults taking their own commercial products (140–2100 mg curcumin across 34 formulations), plasma drawn 1.5 h post-dose showed unhydrolysed curcumin at a mean of 1.0 ng/mL, detectable in only 2 of 47 participants. After β -glucuronidase treatment, capturing conjugated plus free drug, the mean was 25.4 ng/mL. The authors estimate concentrations effective in vitro are roughly **1000-fold higher** than what circulates [2]. Curcumin's half-life at neutral pH and 37°C is short (classically reported on the order of minutes to tens of minutes under buffer conditions) [14, 23].

The study is **T1b**, not T1: observational, open-label, uncontrolled products, a single post-dose sample, and no formal pharmacokinetic parameters. It is admissible for the exposure question and for nothing else. D-3 is of order 10^{-3} against any plausible threshold, and the gate terminates. **No capsule mass for curcumin is defensible from this evidence base, at any CES.**

Source-quality note

This study carries two internal inconsistencies a conforming run must record: the discussion states free curcumin never exceeds 0.74 ng/mL, conflicting with hydrolysed values up to 130.8 ng/mL in the same paper's table; and the in-vitro benchmark is expressed in μ M in the introduction and μ g/mL in the discussion [2].

The headline finding is unaffected, but D-3 cannot be computed until the units and assay-matrix context are reconciled against primary in-vitro sources. This enters the Measurement Manifest as M-1 and blocks the dependent gate.

9 Bioavailability limitation and interaction risk

Replaces Node 7 (v3.5.0 §5.2).

9.1 The excluded approach

Version 3.5 addressed poor oral exposure by recruiting a metabolic inhibitor — piperine, naringin — with CYP inhibition locked at 0.85 or above *by design*. Two objections, in order of weight.

First, it is an uncontrolled dose change to every co-administered substrate. Inhibiting a clearance pathway raises exposure of everything cleared by it. Where the standard of care includes a narrow-therapeutic-index agent, this is the dominant hazard of the whole framework. For basal cell carcinoma, sonidegib is primarily CYP3A-metabolised and its label directs prescribers to avoid both strong and moderate CYP3A inhibitors; erythromycin, a *moderate* inhibitor, raised steady-state exposure 1.8-fold at 14 days and 2.8-fold at four months [3, 6]. Piperine is documented to inhibit human P-glycoprotein and CYP3A4 [2].

Second objection — the one v3.5.0 never tested: it does not appear to work

In the 47-adult curcumin study above, **piperine did not raise curcumin plasma levels** [2].

The flagship pairing of the entire Node 7 concept failed in humans. The mechanism that justified accepting the interaction risk did not deliver the benefit meant to offset it, so the approach is excluded on efficacy grounds before the safety argument is reached.

9.2 Legitimate approaches

Approach	What must be demonstrated
Particle engineering (micronisation, nanocrystals)	Measured dissolution profile and a repeat human PK study
Lipid-based systems (SEDDS, SMEDDS, liposomes)	Comparative PK against the unformulated reference
Amorphous solid dispersion	Physical stability across the stated shelf life
Structural analogue or prodrug	This is a new chemical entity — the regulatory path changes entirely
Alternate route (topical, intralesional)	Local tolerability; penetration to target depth (D-9)

For a lesion on the skin, topical and intralesional routes deserve first consideration rather than last. A compound failing D-3 orally may clear it comfortably at the site of application, and most of the interaction problem dissolves along with the systemic exposure.

9.3 Interaction Risk Gate

```
if interaction_magnitude(candidate, pathway) >= 0.30
    and pathway in clearance_pathways(standard_of_care):
        verdict = EXCLUDED      # reason: interaction liability
```

Version 3.7 screened CYP *inhibition* only. That omits induction — a CYP3A4 inducer lowers standard-of-care exposure and reduces efficacy, St John's wort being the canonical case — and omits transporters and pharmacodynamic interactions entirely. The gate screens all of them, in **both directions**.

Mechanism	Static criterion	Source
CYP inhibition, reversible	$R_1 = 1 + I_{\max,u}/K_{i,u} \geq 1.02$	[4]
CYP inhibition, oral gut CYP3A4	$R_{1,\text{gut}} \geq 11$	[4]
CYP inhibition (EMA equivalent)	$[I]/K_i \geq 0.02$, unbound $C_{\max}$ at highest dose	[5]
Time-dependent inhibition	$R_2 \geq 1.25$	[4, 5]
CYP induction, in vitro	$R_3 \leq 0.8$, or mRNA fold change ≥ 2 concentration-dependent, or $> 20\%$ of positive control	[4]
Transporters	P-gp, BCRP, OATP1B1, OATP1B3, screened for inhibition and induction	[3]
Pharmacodynamic	Anticoagulant, antiplatelet, QT prolongation, immunosuppression, serotonergic	—

Exclusion rule. A candidate is excluded if it is predicted to alter standard-of-care exposure beyond the pre-registered band in **either direction**, or if a severe pharmacodynamic interaction exists. The residual interaction profile is reported for every surviving candidate whether or not interactions formed part of the question asked.

9.4 Effect classification — strong and moderate only

Band	Criterion	Source
Strong inhibitor	AUC increase ≥ 5 -fold	[3]
Moderate inhibitor	AUC increase ≥ 2 -fold and < 5 -fold	[3]
Strong inducer	AUC decrease $\geq 80\%$ (ratio ≤ 0.20)	[3]
Moderate inducer	AUC decrease $\geq 50\%$ and $< 80\%$ (ratio 0.20–0.50)	[3]

O-10 resolved: weak-effect classification is dropped

Verification against the FDA table of substrates, inhibitors and inducers confirmed the strong and moderate bands in both directions, and established that **FDA defines no numeric threshold for either weak band** — the agency labels particular drugs weak inhibitors or weak inducers in footnotes without stating a cutoff.

Version 3.8 asserted a weak-inducer band of 0.5 to 0.8 and marked a weak-inhibitor band as verified. Neither was supportable; both were withdrawn in v3.9 and are not reinstated here under another name.

The gate is a threshold, not a taxonomy. A candidate either crosses the pre-registered exclusion threshold or it does not, and nothing in the pipeline consumes a weak/moderate/strong label.

An external review of v3.7 proposed an inhibition threshold of $[I]/K_i \geq 0.1$; the EMA static threshold is 0.02, five times stricter, and the proposed figure was not adopted.

10 Safety Interaction Index — Mode B only

$$\text{term}_i = m_i \cdot \text{ADI}_i \cdot C_{p,i}, \quad \text{Pass 1: } \max_i(\text{term}_i) \leq 0.35, \quad \text{Pass 2: } \frac{1}{N} \sum_i \text{term}_i \leq 0.25$$

where m_i is the interaction magnitude across every mechanism of §9, not CYP inhibition alone, and N is the number of active candidates. The per-candidate ceiling exists because v3.5.0's arithmetic mean reproduced exactly the masking vulnerability its own synergy gate was written to eliminate: six benign terms at 0.02 dilute a worst-case term of 0.425 to an aggregate of 0.078, a comfortable pass. A single severe interaction is sufficient reason to stop.

ADI	Criterion
0.00	No known interaction
0.25	Theoretical or in-vitro signal only
0.50	Documented pharmacokinetic change below 2-fold
0.75	Documented pharmacokinetic change of 2-fold or greater
1.00	Documented clinical harm, or a labelled contraindication

C_p derives from a named population prescription dataset mapped to the indication's demographic, citing file and survey cycle. Absent demographic-specific data, the conservative default $C_p = 0.50$ applies and is labelled as the default in the dossier. The psoriasis values in v3.5.0 §5.2 (statins 0.342, NSAIDs 0.512) have no source in that document and must be re-derived or struck before reuse.

10.1 Regulatory pathways

Pathway	Framing	SII
A — Dietary supplement	Structure-function language only. Zero disease, treatment or prevention claims.	≤ 0.10
B — Investigational botanical (illustrative)	Investigational hypothesis requiring IND-level oversight. Never framed as treatment or cure. Describes what a stricter evidence regime demands; not a declaration of regulatory intent.	≤ 0.50
Default	Pathway undeclared	≤ 0.25

O-6 resolved: Pathway B is illustrative

Pathway B sets out what a disease-intervention evidence regime would require — Tier 1 mandatory for core drivers, a wider but monitored safety envelope. That standard is worth stating as a benchmark.

It is not a statement that Landry Industries is pursuing an investigational filing. An IND is a sponsor-scale undertaking — IND-enabling toxicology, GMP manufacturing, a clinical site — and claiming intent the organisation is not resourced to act on would undermine the document’s credibility on everything else. Any run invoking Pathway B records this status in its dossier.

If that intent ever becomes real, this is a label change, not a methodology change.

11 The operational sequence

Twelve steps in order. No step is bypassed, deferred or computed asynchronously. Every gate reports PASS, FAIL or BLOCKED with the numbers that decided it. A failed gate halts the run; inputs are never adjusted to force a pass.

Step	Name	Gate	Mode
01	Indication lock	Single ICD-coded entity; route declared ; standard of care declared; displacement check	A, B
02	Target mapping	≥ 3 independent peer-reviewed citations per target	A, B
02a	Tier and COI pre-screen	Hard fail on T4-only; $C_{\text{coi}} = 0.00$ sources inadmissible	A, B
03	Weighting and pre-registration	AnalyticFingerprint recorded before any scoring	A, B
04	Convergence mapping	$RM \geq 0.75$, triage only	A, B
05	Signed DSV scoring with aggregation	$\kappa \geq 0.70$ and $ICC \geq 0.75$, or PRELIMINARY label; veto if any $S_d \leq -5.0$	A, B
06	CES computation	$CES_{\text{final}} > 0$	A, B
07	Dose feasibility	$D-3 \geq$ pre-registered threshold	A, B
08	Interaction risk	Inhibition, induction, transporters and PD against declared standard of care	A, B
09	PK alignment	$PKAS \geq 0.50$; not applied for non-systemic routes	B
10	Synergy verification	Measured CI only; MISSING CI reports BLOCKED	B
11	Safety index	$\max(\text{term}) \leq 0.35$ and $\text{mean} \leq 0.25$	B
12	Dossier compilation	Terminal. No formulation is emitted	A, B

12 The Measurement Manifest

The manifest converts a blocked run from a dead end into a research programme, and it is the framework’s primary deliverable whenever gates block — which, per §5, is the expected case.

$$\text{priority} = \frac{\text{gates unblocked}}{\text{effort units}}$$

Entries are ordered by priority, highest first. Effort is a declared relative scale, not a cost estimate: 1 for a literature reconciliation or existing-assay run, 2 for a new in-vitro experiment, 4 for an in-vivo study. The scale and its rationale are stated, so a reader can disagree with the ordering.

Required fields: id, question, experiment, readout, system, sample_size, controls, expected_outcome, gates_unblocked, effort_units, priority_score.

13 Worked example — basal cell carcinoma (Mode A)

Step 01 parameter	Value
Indication	Basal cell carcinoma, Hedgehog-driven (ICD-O 8090/3)
Primary targets	SMO, PTCH1, GLI1/GLI2
Route declared	Oral systemic (for contrast; §9 argues topical merits first consideration here)
Standard of care	Mohs micrographic surgery (high-risk / facial sites) [17]; sonidegib / vismodegib for advanced disease
SOC clearance pathways	CYP3A4 / CYP3A, P-glycoprotein
Displacement warning	ACTIVE — a curative standard intervention exists
α weights $D_1 \dots D_7$	[2, 1, 1, 2, 1, 1, 3], declared and hashed at Step 03

Candidate	Outcome	CES	Basis
Cyclopamine	EXCLUDED Step 05	—	$S_7 = -10$. The <i>Veratrum</i> alkaloid is the parent chemotype of the approved Hedgehog-inhibitor class and the best mechanistic match in the set ; it is also a potent teratogen. Both approved inhibitors carry embryo-fetal boxed warnings [6, 18, 19, 27].
Curcumin	EXCLUDED Step 07	0.681	Free exposure ratio of order 10^{-3} . Evidence tiered T1b. Clears DSV and CES; fails feasibility.
Piperine	EXCLUDED Step 08	0.570	CYP3A4 and P-gp inhibition against declared sonidegib clearance. This is the v3.5.0 Node 7 exemplar.
Sulforaphane	Ranked — sole survivor	0.436	S_3 sign inverted : Nrf2 activation reads as a positive redox finding conventionally, but Nrf2 overexpression increases cancer-cell resistance to cisplatin, doxorubicin and etoposide, while Keap1 overexpression or Nrf2 knockdown increases sensitivity [11–13, 24, 25]. Sign is T3 and borrowed from non-Hedgehog models.

Terminal state

Mode A ranks one surviving candidate. **Mode B is not entered**: it requires a user-specified set of two or more candidates that have each cleared Mode A, and only one exists.

Output: Hypothesis Dossier plus Measurement Manifest. No combination, no formulation, no mass. Three candidates were removed by three different gates, each for a sourced reason — which is the framework functioning, not failing.

14 O-4 calibration — a negative result

Versions 3.7 and 3.8 both recorded the veto threshold of -5.0 as “a reasoned midpoint, not an empirical one”. It has been tested against compounds whose reproductive status is documented.

Compound	S_7	Veto	Basis
Cyclopamine	-10	fires	Causes cyclopia in lambs [7, 8]; parent chemotype of the Hedgehog-inhibitor class, both approved members of which carry embryo-fetal boxed warnings [6, 18, 19, 27]. Teratogenicity is a property of the target pathway.
Blue cohosh	-8	fires	Anagyrine, a known livestock teratogen, at roughly 290 ppm in the rhizome [9, 10]; N-methylcytisine caused malformations in cultured rat embryos at 20 ppm; infant congestive heart failure and myocardial infarction reported after maternal use.
Curcumin	0	—	No reproductive or developmental signal; extensive dietary exposure.
Sulforaphane	0	—	Dietary isothiocyanate; no reproductive signal identified.
EGCG	0	—	Dietary catechin. High-dose hepatotoxicity enters R , not S_7 .

The threshold is adequate, and it is not calibrated

Zero misclassifications. But the nearest must-veto case sits at -8 and the nearest must-not-veto case at 0 , a separation of eight points. **Any threshold in the open interval $(-8, 0]$ classifies this set identically**, so the set cannot distinguish -5.0 from -1.0 or from -7.0 .

What the exercise establishes is that -5.0 does not misfire on clear cases. What it does not establish is that -5.0 is the right value, and no amount of adding further clear-cut compounds would change that.

Calibration requires borderline cases — compounds whose reproductive signal is equivocal, species-limited or dose-restricted, populating the region $S_7 \in [-7, -3]$. Assembling that set is primary research, not a specification decision. O-4 therefore remains open, with its status upgraded from untested to tested-and-undiscriminated.

15 Reference implementation and conformance

Every version before 3.9 asserted that a non-conforming engine would produce different numbers, while providing no way to check. The engine and conformance suite ship with the specification as embedded PDF attachments.

File	Role
<code>pi_engine.py</code>	Loads the canonical JSON and executes Mode A and Mode B. Gate thresholds are loaded from the canonical JSON. Formula definitions are documented there and implemented in the reference engine; formula parity must be established by the conformance suite and is not a claim of biological or clinical validity.
<code>test_pi_engine.py</code>	63 assertions covering the primitive formulas, the three repaired PKAS defects, the aggregation rules, the veto, the validation set, the worked example, and fingerprint reproducibility.
<code>PI_4.2.2_machine_readable.json</code>	The v4.2.3 specification as data. Authoritative over this prose.

Definition. An engine is conforming if and only if every assertion in the conformance suite passes against the canonical JSON. A specification that cannot be failed is not a specification.

Result at release

63 assertions, 62 passed. The suite pins down deterministic aggregation and fingerprint behaviour, the serious-risk hard gate, and typed D-3 rejection for unit mismatch, assay-matrix mismatch, invalid

concentrations, missing provenance, and legacy scalar-only inputs.

Running the suite requires only a Python interpreter and the specification file; there are no dependencies.

16 The one open item

#	Item	Status
O-4	Veto threshold of -5.0	DEFERRED — tested, not settled. Zero misclassifications across documented cases (§14), but the separation margin is eight points, so the value is indiscriminated by that evidence. Settling it requires a borderline set populating $S_7 \in [-7, -3]$. Assembling that set is primary research, not a specification decision. The threshold is retained at -5.0 and labelled uncalibrated rather than silently promoted to settled.

Closed in 4.0: O-3, O-6, O-8, O-10. Closed in 3.9: O-9. Closed in 3.8: O-1, O-2, O-5, O-7.

17 Versioning and provenance

17.1 Version scheme

Component	Meaning
MAJOR	A change that alters what the framework computes or what it emits. A conforming 4.x engine is not expected to reproduce 3.x outputs.
MINOR	A new section, gate or rule that leaves existing outputs unchanged.
PATCH	Corrections, clarifications and provenance fixes that change no computed value.

17.2 Version history

Version	What it was	Principal change
3.5.0	Standalone release	Gate thresholds specified for quantities the document never defined a way to compute. Nine of fourteen required inputs, including CES and the pairwise synergy index, appeared only as given values in the validation appendix.
3.6.0	Working revision	CES, SI, receptor match and $\theta_{\text{stability}}$ defined. Signed dimensions and a developmental-toxicity veto added. CWMA and the Node 7 enhancer removed without replacement.
3.7.0	Working revision	Dose Rationale and Bioavailability Limitation written as reasoned replacements. Analytic reliability, COI weighting, measurement manifest and a worked example added.
3.8.0	Working revision	Unit of analysis resolved into Mode A and Mode B; node architecture retired. Aggregation rules, interaction gate expanded, canonical hashing. Mathematics moved to ASCII after subscripts were found to drop under text extraction.
3.9.0	Working revision	Reference implementation and conformance suite. Inducer bands verified; two weak bands withdrawn. Veto threshold tested, with a negative result.
4.0.0	Release	Open items O-3, O-6, O-8 and O-10 decided; O-4 deferred on the record. No new methodology.

17.3 Retired terminology

6+1 Node Molecular Matrix. Used in v3.3 through v3.7 for an architecture of six dimension-keyed slots plus an auxiliary seventh. The architecture was replaced in v3.8 by Mode A and Mode B (§2); the name is withdrawn entirely in v4.0 and appears here only so that citations to the earlier documents remain traceable. Nothing in v4.0 should be described using it.

17.4 What a reader should take from the history

Every substantive change between 3.5 and 4.0 came from finding that something the specification asserted was not true, or not checkable: a formula that was never defined, a gate that could be satisfied by averaging away the hazard it existed to catch, a seal that was the hash of an empty string, a citation used in the direction opposite to its finding, a tier assigned above what the study design supported. None came from adding capability.

That pattern is the argument for the framework rather than against it. A scoring system that cannot report its own defects produces confident numbers indefinitely; this one has a record of changing its mind, and the conformance suite exists so the next change is forced to be visible.

A Canonical machine-readable specification

This PDF carries everything required to reproduce itself. Four files are embedded as attachments: the $\text{\LaTeX}$ source of this document, the canonical specification, the reference implementation and the conformance suite. Most readers list attachments in a sidebar; from Python:

```
from pypdf import PdfReader
r = PdfReader("phytointelligence-4.2.3.pdf")
for name in r.attachments:          # 4 files
    open(name, "wb").write(r.attachments[name][0])
```

Attachment	Role
phytointelligence-4.2.3.tex	The source of this document. Recompiling it with the other three files present reproduces this PDF, including the attachments themselves.
PI_4.2.2_machine_readable.json	The canonical specification. Authoritative over this prose.
pi_engine.py	Reference implementation; reads the JSON, hard-codes nothing.
test_pi_engine.py	Conformance suite; 50 assertions.

Extracted into an empty directory, `latexmk -pdf phytointelligence-4.2.3.tex` rebuilds the document and `python3 test_pi_engine.py` verifies the engine. Neither step needs any file that is not inside this PDF, so a reader who has the PDF has the whole artefact — prose, specification, implementation and proof that the implementation matches the specification.

Where this prose and the JSON disagree, the JSON governs. It is reproduced below for reading; the attachment, not this rendering, is what a parser should consume.

```
{
  "specification": "PhytoIntelligence",
  "version": "4.2.3",
  "released": "2026-10-17",
  "author": "Marie-Soleil Seshat Landry, LandryIndustries.ca",
  "orcid": "0009-0008-5027-3337",
  "supersedes": "4.2.2",
  "purpose": "Literature-triage and hypothesis-prioritisation methodology. Terminal artefact is a Hypothesis Dossier plus
```

```

Measurement Manifest.",
"does_not_emit": [
  "milligram allocations, capsule or serving specifications, total daily mass",
  "dosing schedules, titration plans, cycling protocols, duration of use",
  "output addressed to a named individual or described clinical situation",
  "efficacy, treatment, prevention, cure or disease-modification claims"
],
"modes": {
  "A": {
    "name": "Candidate Triage",
    "unit_of_analysis": "single compound",
    "gates": [
      "dsv_veto",
      "serious_adverse_event_risk",
      "ces_positive",
      "dose_feasibility",
      "interaction_risk"
    ],
    "not_applied": [
      "pk_alignment",
      "synergy",
      "sii"
    ],
    "output": "ranked candidate dossier"
  },
  "B": {
    "name": "Combination Evaluation",
    "unit_of_analysis": "user-specified set of 2 or more candidates that have cleared Mode A",
    "gates": [
      "pk_alignment",
      "synergy",
      "sii"
    ],
    "assembly": "user-specified only; the framework does not generate combinations",
    "assembly_rationale": "Mode B's binding constraint is measured combination indices. Generating combinations for which no CI data exists produces a list, not a hypothesis.",
    "target_size": null,
    "ci_measurements_required": "n * (n - 1) / 2"
  }
},
"dimensions": {
  "note": "Dimensions are properties of a CANDIDATE, not roles in a formulation. The 6+1 node architecture of v3.3-v3.7 is retired (see spec section 4.1).",
  "D1": {
    "name": "Genomic",
    "scope": "gene expression, transcription-factor activity, oncogene and tumour-suppressor modulation",
    "range": [
      -10,
      10
    ],
    "veto": true
  },
  "D2": {
    "name": "Metabolic flux",
    "scope": "glycolysis, OXPHOS, lipid metabolism, fatty-acid oxidation, transmembrane transport",
    "range": [
      -10,
      10
    ],
    "veto": true
  },
  "D3": {
    "name": "Redox",
    "scope": "radical scavenging, Nrf2/HO-1 translocation, lipid peroxidation",
    "range": [
      -10,
      10
    ],
    "veto": true
  },
  "D4": {
    "name": "Immune",
    "scope": "cytokine cascades, macrophage polarisation, inflammasome activity",
    "range": [
      -10,
      10
    ],
    "veto": true
  },
  "D5": {
    "name": "Epigenetic",
    "scope": "HDAC inhibition, DNA methyltransferase modulation, non-coding RNA",
    "range": [
      -10,
      10
    ],
    "veto": true
  },
  "D6": {
    "name": "Kinetic",
    "scope": "kinetic DIRECTION: accumulation, unwanted barrier crossing, clearance interference. Low exposure is NOT scored

```

```

here; it is a feasibility question handled by dose_rationale.",
  "range": [
    -10,
    10
  ],
  "veto": true
},
"D7": {
  "name": "Developmental and reproductive toxicity",
  "scope": "teratogenic class liability",
  "range": [
    -10,
    0
  ],
  "veto": true,
  "safety_dimension": true
}
},
"sign_convention": {
  "positive": "sourced evidence indicates modulation moves the locked indication toward the therapeutic objective",
  "negative": "sourced evidence indicates modulation moves away from it",
  "null": "magnitude 0; sign is 0, a category of its own for reliability statistics",
  "unsourced_sign": "dimension is MISSING"
},
"aggregation": {
  "applies_when": "a dimension draws on more than one source",
  "S_d": "if all load-bearing sources agree in sign, take the magnitude from the highest-tier source present; if signs disagree, adjudicate against primary sources; if conflict survives adjudication, dimension is MISSING",
  "W_tier_d": "minimum tier weight among load-bearing sources",
  "C_coi_d": "minimum C_coi among load-bearing sources",
  "Rep_d": "min(n_independent_institutions / 3, 1.0); independent means separate research institution, not merely a different author list",
  "inadmissible": "any load-bearing source with C_coi = 0.00 renders the dimension inadmissible",
  "dossier_requirement": "a synthesis table listing each source with tier, C_coi, sign, magnitude and contribution",
  "missing_semantics": "MISSING dimensions contribute zero to the numerator while retaining their alpha in the denominator; this is conservative evidence-coverage penalization, not evidence of inactivity.",
  "coverage": "coverage = sum(alpha_d for dimensions with status OK) / sum(alpha_d for all declared dimensions); report in every dossier.",
  "mechanism_dedup": "In v4.2.2, Mode A reports exact versioned mechanism ontology ID reuse across dimensions, annotation coverage, and source citations. This is diagnostic only: no score discount is applied, ontology ancestry is not inferred, and no detected overlap does not prove independence. Unannotated load-bearing records are explicitly counted; incomplete annotations prevent a clean no-overlap conclusion."
},
"evidence_tiers": {
  "T1": {
    "w": 1.0,
    "definition": "randomised controlled trial, or validated human pharmacokinetic study"
  },
  "T1b": {
    "w": 0.85,
    "definition": "human observational study of strong design; admissible for pharmacokinetic and exposure questions only, never for efficacy direction"
  },
  "T2": {
    "w": 0.7,
    "definition": "non-human primate or rodent in-vivo model"
  },
  "T3": {
    "w": 0.4,
    "definition": "in-vitro: cell line, Caco-2 monolayer, isolated assay"
  },
  "T4": {
    "w": 0.0,
    "definition": "in-silico QSAR or docking prediction; triage only, excluded from all scoring at step 02a"
  },
  "meta_analysis": "inherits the tier of its included studies and can never exceed T1",
  "narrative_review": "inadmissible",
  "preprint_or_abstract": "inadmissible"
},
"coi_factor": {
  "1.00": "independent funding; no author financial interest in the compound or product",
  "0.85": "industry-funded, analysis conducted or verified independently of the sponsor",
  "0.70": "sponsor-controlled analysis, or author ownership or royalty interest in the product studied",
  "0.00": "undisclosed funding where the journal requires disclosure; inadmissible, not merely discounted"
},
"formulas": {
  "CES_base": "sum_d( alpha_d * S_d * W_tier_d * Rep_d * C_coi_d ) / sum_d( alpha_d )",
  "CES_final": "CES_base / rho",
  "rho": "1 + log10(e) * ln(1 + 1.25 * R * TCI)",
  "rho_range": [
    1.0,
    2.803
  ],
  "rho_application": "divisor",
  "TCI": "clamp( log10( HED_mg / 10 ), 0, 5 ); HED conversion method, species Km and source must be declared at Step 01; otherwise TCI and CES_final are BLOCKED.",
  "PKAS_primary": "W_tier(primary)",
  "PKAS_other": "clamp( 1 - ( abs(Tmax_i - Tmax_primary) / 4.0 ) * ( 2 - W_tier_i ), 0, 1 )",
  "SI_ij": "Chou-Talalay CI at pre-registered effect level fa=0.5 and pre-registered dose ratio; report confidence interval and model. Cross-model sensitivity (Loewe/Bliss/HSA) is reported when data permit.",
  "NSI": "geometric_mean( all SI_ij )",

```

```

    "SII_term": "interaction_magnitude_i * ADI_severity_i * Cp_i",
    "Sii": "reported stability/standardization fields: marker_fraction = m_marker/m_total_solids; theta_stability=C365/C0;
marker_relative_retention=(marker/total_actives at day 365)/(marker/total_actives at day 0). Do not collapse these distinct
quantities into one score.",
    "theta_stability": "C_365 / C_0 under ICH long-term 25C/60RH or accelerated 40C/75RH, validated stability-indicating HPLC",
    "manifest_priority": "gates_unblocked / effort_units",
    "rho_constant_explanation": "0.4343 approximates log10(e); rho remains a secondary penalty and is not a safety gate.",
    "coverage": "sum(alpha_d for scored dimensions) / sum(alpha_d for all declared dimensions)",
    "HED": "HED_mg = animal_dose_mg_per_kg * (Km_animal / Km_human) * human_body_mass_kg; species, Km values, body-mass
assumption and authoritative source are mandatory. No default Km values are implicit.",
    "PKAS_secondary": "Report unbound AUC ratio and half-life ratio as secondary alignment measures when measured; Tmax-only pass
must be labelled LIMITED.",
    "D-3": "dimensionless free trough exposure ratio = Cmin,u / EC50; computed internally from typed source values. Optional
paired bounds yield conservative interval [Cmin_low/EC50_high, Cmin_high/EC50_low]. If any bound is supplied, all four must be
finite, positive, ordered, contain the point estimates, and have matching units/matrix/provenance. Interval PASS only if lower
bound >= threshold; FAIL only if upper bound < threshold; threshold-straddling interval is BLOCKED. With no bounds, preserve
point-estimate result but explicitly mark uncertainty NOT PROVIDED.",
    "dose_feasibility_gate": "With paired D-3 bounds: PASS only if lower ratio bound >= pre-registered threshold; FAIL only if
upper bound < threshold; otherwise BLOCKED. With no bounds, point-estimate behavior is preserved for compatibility and output
must state uncertainty NOT PROVIDED. No mass or dose is proposed."
),
" Gates": {
  "receptor_match": {
    "threshold": 0.75,
    "operator": ">=",
    "note": "triage only; T4 by construction; never evidence of target engagement"
  },
  "dsV_veto": {
    "threshold": -5.0,
    "operator": "<=",
    "note": "any single dimension; executes PRE-aggregation and is not overridable"
  },
  "ces_positive": {
    "threshold": 0.0,
    "operator": ">"
  },
  "dose_feasibility": {
    "threshold": "indication-specific, pre-registered",
    "default_minimum": 3.0,
    "operator": ">=",
    "quantity": "Cmin_unbound / EC50 in a matched assay matrix",
    "threshold_units": "dimensionless",
    "note": "If optional D-3 bounds are provided, use conservative interval gate: lower bound >= threshold to PASS; upper bound
< threshold to FAIL; threshold overlap BLOCKED. Point-only legacy v4.2.0 records preserve point-estimate outcome but
uncertainty must be labelled NOT PROVIDED."
  },
  "pk_alignment": {
    "threshold": 0.5,
    "operator": ">=",
    "applies_to": "Mode B only",
    "tmax_window_h": 4.0
  },
  "synergy_pass1": {
    "threshold": 0.8,
    "operator": ">=",
    "quantity": "min(SI_ij)"
  },
  "synergy_pass2": {
    "threshold": 0.9,
    "operator": ">=",
    "quantity": "NSI"
  },
  "sii_pass1": {
    "threshold": 0.35,
    "operator": "<=",
    "quantity": "max(term_i)"
  },
  "sii_pass2": {
    "threshold": 0.25,
    "operator": "<=",
    "quantity": "mean(term_i)",
    "N": "active candidates"
  },
  "sii_pathway_A": {
    "threshold": 0.1,
    "operator": "<="
  },
  "sii_pathway_B": {
    "threshold": 0.5,
    "operator": "<="
  },
  "missing_input": "any MISSING input reports the dependent gate as BLOCKED; it is never estimated",
  "serious_adverse_event_risk": {
    "threshold": 8,
    "operator": ">=",
    "action": "EXCLUDED by default. v4.1.0 engine has no exception pathway; a future exception mechanism requires a versioned
adjudication record schema and tests.",
    "note": "Mode A hard gate; R cannot be neutralized by TCI or rho",
    "exception_status": "not implemented; fail-closed exclusion"
  }
},
),

```

```

"interaction_risk_gate": {
  "replaces": "v3.7.0 section 9.4, which screened CYP inhibition only",
  "mechanisms": [
    "cyp_inhibition",
    "cyp_induction",
    "transporter_inhibition",
    "transporter_induction",
    "pharmacodynamic"
  ],
  "transporters": [
    "P-gp",
    "BCRP",
    "OATP1B1",
    "OATP1B3"
  ],
  "static_criteria": {
    "fda_R1": {
      "formula": "1 + (Imax_u / Ki_u)",
      "flag_at": 1.02,
      "source": "FDA 2020"
    },
    "fda_R1_gut_cyp3a4": {
      "flag_at": 11,
      "source": "FDA 2020"
    },
    "ema_I_over_Ki": {
      "flag_at": 0.02,
      "basis": "mean unbound Cmax at highest dose",
      "source": "EMA 2012"
    },
    "time_dependent_inhibition": {
      "flag_at": 1.25,
      "quantity": "R2"
    },
    "fda_induction_R3": {
      "flag_at": 0.8,
      "operator": "<=",
      "source": "FDA 2020"
    }
  },
  "clinical_bands": {
    "strong_inhibitor": {
      "auc_ratio": ">= 5",
      "verified": true,
      "source": "FDA table of substrates, inhibitors and inducers"
    },
    "moderate_inhibitor": {
      "auc_ratio": ">= 2 and < 5",
      "verified": true,
      "source": "FDA table of substrates, inhibitors and inducers"
    },
    "strong_inducer": {
      "auc_decrease": ">= 80%",
      "auc_ratio": "<= 0.20",
      "verified": true,
      "source": "FDA table of substrates, inhibitors and inducers"
    },
    "moderate_inducer": {
      "auc_decrease": ">= 50% and < 80%",
      "auc_ratio": "> 0.20 and <= 0.50",
      "verified": true,
      "source": "FDA table of substrates, inhibitors and inducers"
    },
    "weak": {
      "status": "not used",
      "note": "FDA defines no numeric weak band in either direction. v4.0 does not classify weak effects. The gate is a threshold, not a taxonomy: a candidate either crosses the pre-registered exclusion threshold or it does not."
    }
  },
  "exclusion_rule": "EXCLUDE if the candidate is predicted to alter standard-of-care exposure beyond the pre-registered band in EITHER direction, or if a severe pharmacodynamic interaction exists",
  "pd_interactions_screened": [
    "anticoagulant",
    "antiplatelet",
    "QT prolongation",
    "immunosuppression",
    "serotonergic"
  ],
  "disclosure": "residual interaction profile is reported for every surviving candidate whether or not interactions were part of the question asked"
},
"dose_rationale": {
  "D-1": "effective concentration at target (EC50/IC50), T3 or better, in a system relevant to the locked indication",
  "D-2": "achieved human exposure at a stated dose and route, T1 or T1b",
  "D-3": "dimensionless free trough exposure ratio = Cmin,u / EC50; numerator and denominator must be in the same concentration units and assay-matrix context. AUC/EC50 is prohibited in v4.1.0.",
  "D-4": "free vs conjugated fraction, assay specified AND analytically validated",
  "D-5": "target tissue distribution; plasma is not an acceptable proxy for a solid-tumour or dermal compartment",
  "D-6": "exposure-response across at least three dose levels",
  "D-7": "NOAEL and the resulting safety margin",
  "D-8": "target engagement biomarker demonstrating the mechanism operates at achievable exposure",

```

```

    "D-9": "for topical or intralesional routes: local concentration at target depth, penetration and residence time",
    "gate": "if D-3 is below the pre-registered threshold the hypothesis is not dose-feasible by that route as formulated;
    recorded as a terminal finding; no mass is proposed"
  },
  "reliability": {
    "calibration_phase": "both analysts score a training set, discuss discrepancies, revise the rubric, then score candidates",
    "sign_agreement": {
      "statistic": "Cohen kappa over {positive, negative, null}",
      "threshold": 0.7,
      "supplement": "Report Gwet AC1 alongside Cohen kappa; interpret prevalence-sensitive statistics jointly."
    },
    "magnitude_agreement": {
      "statistic": "ICC(2,1)",
      "threshold": 0.75
    },
    "confidence_intervals": "bootstrap",
    "below_threshold": "do not proceed; the rubric or target map is at fault, not the analysts; revise and re-run",
    "sign_conflict_resolution": "adjudicate against primary sources; NEVER average. The mean of +7 and -7 is 0, which the rubric
    reads as no evidence, converting a live disagreement into a confident claim of absence.",
    "single_analyst_mode": "permitted; the dossier is labelled PRELIMINARY - UNREPLICATED and no reliability statistic is
    reported",
    "pre_registration": "the reliability plan is included in the AnalyticFingerprint",
    "minimum_training_set": "At least 20 compounds x 7 dimensions, or label reliability calibration UNDERPOWERED and do not claim
    calibrated reliability.",
    "gate_rule": "Use lower bootstrap confidence bound for reliability thresholds; if below threshold, BLOCKED."
  },
  "hashing": {
    "algorithm": "SHA-256",
    "encoding": "UTF-8",
    "canonical_form": "RFC 8785 JSON Canonicalization Scheme",
    "epistemic_fingerprint": {
      "input": "sorted extraction records, not citation list alone",
      "required_fields": [
        "doi_or_pmid",
        "dimension",
        "sign",
        "magnitude",
        "tier",
        "coi",
        "institution",
        "load_bearing",
        "mechanism_ontology_ids"
      ],
      "ordering": "canonical JSON sorting; each record includes extracted claim attributes",
      "pseudocode": "sha256(jcs(sorted_extraction_records).encode(utf-8)).hexdigest()",
      "compatibility": "legacy citation-only fingerprints are retained as legacy seals and are not equivalent to v4.1.0 claim-
      level seals"
    },
    "analytic_fingerprint": {
      "input_fields": [
        "indication",
        "target_map",
        "candidate_list",
        "alpha_weights",
        "veto_threshold",
        "soc_agents",
        "soc_clearance_pathways",
        "all_gate_thresholds",
        "mode",
        "reliability_plan"
      ],
      "computed_at": "step 03, before any candidate is scored",
      "pseudocode": "sha256(jcs(analytic_plan_object).encode('utf-8')).hexdigest()"
    },
    "revision_rule": "any change to a hashed field requires a new fingerprint, retention of the prior one, and a stated reason",
    "warning": "the seal e3b0c44298fc1c149afb4c8996fb92427ae41e4649b934ca495991b7852b855 printed in v3.5.0 is the SHA-256 of the
    empty string; any artefact bearing it is unsealed"
  },
  "retraction_cascade": {
    "retraction": {
      "tier": "T4",
      "C_coi": 0.0,
      "action": "data removed"
    },
    "expression_of_concern": {
      "tier": "downgrade one level",
      "C_coi": 0.7,
      "action": "re-evaluate"
    },
    "correction": {
      "action": "re-evaluate affected values only"
    },
    "invalidation_threshold": "CES_post / CES_pre < 0.75",
    "scope": "recalculates affected candidates and any Mode B combination containing them"
  },
  "operational_sequence": [
    {
      "step": "01",
      "name": "Indication lock",
      "gate": "single ICD-coded entity; route declared; standard-of-care declared; displacement check"
    },
  ],

```

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{
  "step": "02",
  "name": "Target mapping",
  "gate": ">= 3 independent peer-reviewed citations per target"
},
{
  "step": "02a",
  "name": "Tier and COI pre-screen",
  "gate": "hard fail on T4-only; C_coi = 0.00 sources inadmissible"
},
{
  "step": "03",
  "name": "Weighting and pre-registration",
  "gate": "AnalyticFingerprint recorded before any scoring"
},
{
  "step": "04",
  "name": "Convergence mapping",
  "gate": "receptor_match >= 0.75, triage only"
},
{
  "step": "05",
  "name": "Signed DSV scoring with aggregation",
  "gate": "kappa >= 0.70 and ICC >= 0.75, or PRELIMINARY label; veto if any S_d <= -5.0"
},
{
  "step": "06",
  "name": "CES computation",
  "gate": "CES_final > 0"
},
{
  "step": "07",
  "name": "Dose feasibility",
  "gate": "D-3 >= pre-registered threshold"
},
{
  "step": "08",
  "name": "Interaction risk",
  "gate": "inhibition, induction, transporters and PD against declared standard of care"
},
{
  "step": "09",
  "name": "PK alignment",
  "gate": "PKAS >= 0.50",
  "mode": "B only"
},
{
  "step": "10",
  "name": "Synergy verification",
  "gate": "measured CI only; MISSING CI reports BLOCKED",
  "mode": "B only"
},
{
  "step": "11",
  "name": "Safety index",
  "gate": "max(term) <= 0.35 and mean <= 0.25",
  "mode": "B only"
},
{
  "step": "12",
  "name": "Dossier compilation",
  "gate": "terminal; no formulation emitted"
}
},
"measurement_manifest_fields": [
  "id",
  "question",
  "experiment",
  "readout",
  "system",
  "sample_size",
  "controls",
  "expected_outcome",
  "gates_unblocked",
  "effort_units",
  "priority_score"
],
"open_items": {
  "O-4": {
    "item": "veto threshold of -5.0",
    "status": "DEFERRED - tested, not settled",
    "finding": "Zero misclassifications across documented must-veto and must-not-veto compounds, but the separation margin is 8 points, so any threshold in (-8, 0] classifies the same set identically.",
    "what_would_settle_it": "A borderline set populating D7 = -3 to -7: compounds whose reproductive signal is equivocal, species-limited or dose-restricted.",
    "why_deferred": "Assembling that set is primary research, not a specification decision. The threshold is retained at -5.0 and labelled uncalibrated rather than silently promoted."
  },
  "v4.1_followups": [
    "Validate cross-dimensional mechanism discount before using it as a numerical adjustment.",
    "Validate seeded bootstrap propagation to candidate gate probabilities before gate-probability estimates are used"
  ]
}

```

```

operationally.",
  "Publish source-backed empirical references and complete extraction tables for the worked example.",
  "Define validated marker-relative stability thresholds before making SiI a gating score.",
  "Specify PKAS rerun ordering when the highest-CES primary fails downstream Mode B gates."
]
},
"reference_implementation": {
  "module": "pi_engine.py",
  "conformance_suite": "test_pi_engine.py",
  "definition": "An engine is conforming if and only if every assertion in the conformance suite passes against this file.",
  "conformance_assertions": 47,
  "version_assertion": "spec.version must equal 4.1.0",
  "negative_tests": "Mode A R>=8 exclusion; dimensionless D-3 metadata; claim-level fingerprint sensitivity; stale-version rejection; mutation tests for threshold constants."
},
"status": "4.2.0 development draft: enforces typed D-3 concentration evidence, unit and assay-matrix compatibility, and source-record provenance; not a final release. Uncertainty propagation and several model-validation items remain open.",
"alpha_weights": {
  "defaults": null,
  "rule": "Every run declares alpha_d at Step 03. No default sets are published. Declaration is hashed into the AnalyticFingerprint; an undeclared run cannot proceed.",
  "rationale": "Published defaults invite unthinking reuse and would hollow out the pre-registration they are hashed into."
},
"pathways": {
  "A": {
    "name": "Dietary supplement",
    "framing": "structure-function language only; zero disease, treatment or prevention claims",
    "evidence_floor": "T1-T3 permitted",
    "sii_ceiling": 0.1,
    "status": "operative"
  },
  "B": {
    "name": "Investigational botanical",
    "framing": "investigational hypothesis requiring IND-level oversight; never framed as treatment or cure",
    "evidence_floor": "T1 mandatory for core drivers",
    "sii_ceiling": 0.5,
    "status": "illustrative",
    "note": "Pathway B describes what a stricter evidence regime would require. It is NOT a declaration that Landry Industries is pursuing an investigational filing. Any run invoking Pathway B states this in its dossier."
  },
  "default": {
    "sii_ceiling": 0.25,
    "status": "operative"
  }
},
"retired_terminology": {
  "6+1 Node Molecular Matrix": "Used in v3.3 through v3.7 for an architecture of six dimension-keyed slots plus an auxiliary. Retired in v3.8 when the architecture was replaced by Mode A / Mode B, and the name withdrawn entirely in v4.0. Retained here only so citations to older versions remain traceable."
},
"versioning": {
  "scheme": "MAJOR.MINOR.PATCH",
  "major": "a change that alters what the framework computes or what it emits; a conforming 4.x engine is not expected to reproduce 3.x outputs",
  "minor": "a new section, gate or rule that does not change existing outputs",
  "patch": "corrections, provenance fixes, and additive optional input/output metadata that preserve results for existing valid inputs; behavior for newly supplied optional data may be added if existing inputs remain unchanged.",
  "conformance": "An engine is conforming if and only if every assertion in test_pi_engine.py passes against this file."
},
"release_notes": [
  {
    "version": "4.2.3",
    "title": "CES uncertainty interval and ranking robustness patch"
  }
],
"dose_feasibility_schema": {
  "required_fields": [
    "cmin_unbound",
    "cmin_unit",
    "ec50",
    "ec50_unit",
    "exposure_assay_matrix_id",
    "ec50_assay_matrix_id",
    "source_record_id"
  ],
  "constraints": {
    "cmin_unbound": "finite numeric value > 0; measured unbound trough concentration",
    "ec50": "finite numeric value > 0; concentration from the assay used for the matched target hypothesis",
    "units": "cmin_unit must exactly match ec50_unit in v4.2.0; automatic conversion is not implemented",
    "assay_matrix": "exposure_assay_matrix_id must exactly match ec50_assay_matrix_id; missing identifiers block the gate",
    "provenance": "source_record_id must be non-empty and resolve to a traceable source record",
    "ratio": "computed internally as cmin_unbound / ec50; caller-supplied ratio is not accepted",
    "legacy": "free_exposure_ratio-only records are invalid and cannot pass D-3",
    "uncertainty_bounds": "Optional. If any bound is supplied, all four are required, finite, positive, ordered, and must contain the corresponding point estimate. Ratio bounds are conservative arithmetic bounds, not automatically a statistical confidence interval.",
    "interval_ratio": "lower = cmin_unbound_lower / ec50_upper; upper = cmin_unbound_upper / ec50_lower. PASS only if lower bound reaches threshold; FAIL only if upper bound is below threshold; otherwise BLOCKED.",
    "point_only": "If no uncertainty bounds are supplied, preserve point-estimate behavior and explicitly report uncertainty NOT PROVIDED."
  }
},

```

```

    "optional_uncertainty_fields": [
      "cmin_unbound_lower",
      "cmin_unbound_upper",
      "ec50_lower",
      "ec50_upper"
    ]
  },
  "mechanism_overlap": {
    "version": "4.2.2",
    "scope": "Mode A candidate dimensions",
    "included_records": "load-bearing extraction sources only",
    "match_rule": "exact string equality after trimming surrounding whitespace on versioned mechanism ontology IDs",
    "output_fields": [
      "status",
      "load_bearing_source_records",
      "annotated_source_records",
      "annotation_coverage",
      "unannotated_source_records",
      "invalid_records",
      "overlaps",
      "score_adjustment_applied",
      "limitation"
    ],
    "overlap_definition": "one exact mechanism ID appears in at least two distinct dimensions",
    "score_adjustment_applied": false,
    "not_implemented": [
      "ontology ancestor/descendant inference",
      "causal dependence estimation",
      "correlation discount",
      "automatic score adjustment"
    ],
    "interpretation": "potential double counting review flag only; absence of exact matches is not proof of independent mechanisms"
  },
  "source_record_uncertainty": {
    "magnitude_bounds": {
      "fields": [
        "magnitude_lower",
        "magnitude_upper"
      ],
      "optional": true,
      "range": [
        0,
        10
      ],
      "requirements": "Both bounds supplied together; lower <= point magnitude <= upper; all load-bearing sources at the selected highest evidence tier must have valid bounds to compute a dimension interval.",
      "semantics": "Declared compatibility/uncertainty bounds only. They are not automatically confidence or credible intervals."
    },
    "ces_interval": {
      "method": "Conservative interval arithmetic across signed dimension intervals; tier weight, replication, COI, alpha, and rho remain point-valued constants.",
      "requires": "Every dimension contributing to the point CES must have a valid magnitude interval.",
      "missing_behavior": "CES point estimate may remain available for compatibility, but ces_uncertainty.status is UNKNOWN and no interval ranking claim is made.",
      "correlation": "No independence assumption is needed for the worst-case interval enclosure, but bounds may be conservative and their validity depends on source provenance.",
      "limits": "Does not propagate uncertainty in tier, alpha, COI, replication, adverse-event risk, HED/TCI, rho, or model structure; does not estimate probability of a rank ordering."
    },
    "pairwise_ranking": {
      "statuses": [
        "A_ROBUSTLY_ABOVE_B",
        "B_ROBUSTLY_ABOVE_A",
        "OVERLAP_INDETERMINATE",
        "UNKNOWN_UNCERTAINTY"
      ],
      "rule": "A robustly above B only if lower(A) > upper(B); B robustly above A only if lower(B) > upper(A); touching or overlapping intervals are indeterminate."
    }
  }
}

```

PhytoIntelligence 4.2.3 — Marie-Soleil Seshat Landry, LandryIndustries.ca LandryIndustries.ca / MarieLandrySpyShop.com — ORCID 0009-0008-5027-3337. Released October 17, 2026.

This document carries no epistemic seal. A seal is issued only over a populated citation array at run time; a seal printed on a specification would certify nothing.

4.1.0 Red-Team Amendment and Implementation Record

Development draft dated October 17, 2026. Supersedes v4.1.0 when formally released.

This patch incorporates the highest-priority findings from an independent static review and replication. It does not claim that all sixteen findings are closed. The canonical JSON and reference engine are authoritative for the implemented rules; the items below distinguish implemented controls from work that remains open.

Implemented in 4.1.0

1. **Mode A serious-adverse-event hard gate.** A candidate with $R \geq 8$ is excluded before ranking. The bounded ρ penalty cannot substitute for a safety gate. An exception requires documented dose-dependence below the pre-registered exposure threshold and independent adjudication; absent those records, exclusion stands.
2. **D-3 dimensional correction.** D-3 is restricted to the dimensionless ratio $C_{\min,u}/EC_{50}$, with matching concentration units and assay-matrix context. The expression AUC_u/EC_{50} is prohibited because it has units of time. A future AUC-based definition must normalize by the dosing interval and be versioned transparently.
3. **Claim-level EpistemicFingerprint.** The new seal covers extraction records including citation identity, dimension, sign, magnitude, tier, conflict-of-interest factor, institution, load-bearing status, and mechanism ontology identifiers. Legacy citation-only hashes are not equivalent to v4.1.0 seals.
4. **Conformance negative tests.** The suite asserts the active spec version, rejects stale-version specifications, verifies the $R \geq 8$ gate, and checks that changing an extracted claim changes the epistemic fingerprint. The release suite reports 42 passing assertions.
5. **Declared missingness and exposure context.** The canonical specification now states how MISSING dimensions affect CES and requires a reported evidence-coverage metric. HED conversion inputs must be declared rather than silently assumed.

Additional controls specified; validation remains open

Mechanism overlap across dimensions must be flagged pending validation of a numerical correlation discount. Gwet's AC1 is added as a supplement to Cohen's κ ; reliability calibration must disclose training-set adequacy and use lower bootstrap confidence bounds. Mode B must report measured secondary exposure alignment where available, pre-register the combination-index model/effect level/dose ratio, and report uncertainty. The inter-batch standardization index is separated into standardization, total stability, and marker-relative retention fields. Full source-backed extraction tables and references for every empirical anchor in the worked example remain required before that example can be treated as independently reproducible.

Scientific and operational boundary

These changes improve software conformance and risk handling; they do not validate any compound, dose, combination, or clinical hypothesis. PI remains a literature-triage and hypothesis-prioritisation framework, not a treatment, formulation, or dosing system. A gate passing means only that the specified evidence checks passed; it is not evidence of clinical efficacy or safety.

Version classification

The hard gate and claim-level fingerprint change computed outcomes and the meaning of a seal. They are therefore disclosed as behaviour-changing 4.1.0 changes under the project's stated versioning scheme, despite the patch-style release label. Prior v4.0.0 outputs and fingerprints must be retained for audit and must not be silently relabelled.

4.2.1 D-3 Uncertainty Patch and Implementation Record

Implemented in 4.2.1

- **Optional paired bounds.** Four optional fields can represent lower and upper bounds for unbound trough concentration and EC50. If any is supplied, all four are required.
- **Conservative interval propagation.** For positive values, the engine computes $[C_{\min,u}^{low}/EC_{50}^{high}, C_{\min,u}^{high}/EC_{50}^{low}]$.
- **Robust classification.** The interval passes only if its lower bound meets the pre-registered threshold; fails only if its upper bound is below the threshold; otherwise the dependent gate is BLOCKED.
- **Input validation.** Bounds must be finite, positive, ordered, and contain the corresponding point estimate. Partial or malformed intervals are blocked.
- **Compatibility.** Point-only v4.2.0 inputs retain their prior numerical outcome and now explicitly report uncertainty NOT PROVIDED.

Test results

The v4.2.1 reference suite contained 63 assertions. It tests interval arithmetic, incomplete/reversed/point-excluding bounds, and end-to-end gate outcomes as well as the prior aggregation, hard-gate, fingerprint, and typed-evidence behavior. These are software conformance tests, not biological or clinical validation.

Interpretation and limitations

The computed interval is a conservative arithmetic interval derived from supplied bounds. It is not automatically a confidence interval or credible interval. Source records must explain how each bound was obtained, its population and assay context, and its statistical meaning if any. A PASS means only that the supplied interval lies above the pre-registered D-3 threshold; it does not establish bioavailability, target engagement, safety, efficacy, or a clinically useful exposure.

This patch does not propagate uncertainty through CES or final ranking, model dependence between evidence sources, validate the coverage of statistical intervals, calibrate reliability, correct mechanism double-counting, or resolve Mode B model uncertainty and measured secondary PK alignment. These remain open research and validation tasks.

Versioning and compatibility

This is a patch-level, additive optional input feature: valid existing point-only inputs preserve their prior numerical outcomes. v4.1.0 scalar-only `free_exposure_ratio` inputs remain retired and are rejected. Prior results must not be silently relabelled; preserve the original specification digest and dossier for audit.

4.2.2 Mechanism-Overlap Diagnostic Patch and Implementation Record

Implemented in 4.2.2

- **Exact cross-dimension mechanism-ID matching.** Load-bearing source records may carry versioned mechanism ontology identifiers. Reuse of the same identifier in two or more dimensions is reported with the affected dimensions and source citations.
- **Annotation coverage.** The report counts load-bearing source records, annotated records, missing annotations, invalid annotations, and annotation coverage. Missing annotation prevents a clean no-overlap conclusion.
- **Report-only behavior.** The diagnostic is attached to Mode A output but does not modify CES, gate outcomes, or candidate ranking.
- **Non-load-bearing evidence excluded.** Sources marked non-load-bearing do not contribute to overlap flags or annotation coverage.

Interpretation rules

An exact repeated ontology identifier is a *potential double-counting flag*, not proof that two dimensions are statistically dependent or biologically redundant. The current implementation does not traverse ontology parent/child relationships, estimate causal dependence, apply correlation discounts, or alter scores. Likewise, failure to find an exact identifier match does not prove mechanism independence. IDs must be versioned and consistently normalized by the evidence-curation process.

Verification

The conformance suite includes synthetic tests for exact ID reuse, affected dimension reporting, exclusion of non-load-bearing records, missing-annotation coverage, invalid IDs, and the invariant that no score adjustment is applied. Synthetic fixtures test software behavior only; they are not biological evidence. The release test count is printed by the test runner and must be preserved in the build record rather than inferred from historical counts.

Remaining work

Ontology ancestor/descendant matching, evidence-source correlation estimation, uncertainty propagation beyond source-magnitude bounds, Mode B uncertainty and measured secondary pharmacokinetic alignment, reliability calibration, and fully reproducible source-backed worked examples remain open. A numerical dependence correction must not be introduced until its method, assumptions, validation dataset, and failure behavior are pre-registered and tested.

Versioning

This release adds a report-only diagnostic to Mode A outputs. Prior dossiers must retain their original version and specification digest; v4.2.2 reports must not be retroactively substituted for older results.

4.2.3 CES Uncertainty and Ranking-Robustness Patch

Purpose

Version 4.2.3 adds conservative interval propagation from declared source-magnitude bounds through dimension aggregation and the Composite Evidence Score (CES). The goal is to distinguish a point-score ordering from an ordering that remains separated across the declared bounds. This remains literature triage and hypothesis prioritisation, not a treatment-selection or clinical decision system.

Input schema

Each `Source` may optionally include `magnitude_lower` and `magnitude_upper`. Bounds must be supplied together and satisfy

$$0 \leq m_{\text{lower}} \leq m_{\text{point}} \leq m_{\text{upper}} \leq 10.$$

For the highest evidence tier that determines a dimension's magnitude, every selected-tier source must have valid bounds to compute that dimension's interval. Bounds from lower tiers do not change the point-score aggregation rule. If any selected-tier source lacks bounds, the dimension interval is unknown; malformed bounds are invalid and block interval reporting.

Propagation rule

For a positive signed dimension, the magnitude interval is the maximum of the selected-tier lower bounds through the maximum of their upper bounds. For a negative signed dimension, endpoints are reversed when applying the sign. The engine then propagates the signed dimension intervals through the CES numerator using the declared point values of α_d , $W_{\text{tier},d}$, Rep_d , and $C_{\text{coi},d}$, divides by the existing denominator, and divides by point-valued ρ :

$$\text{CES}_{\text{interval}} = [\text{CES}_{\text{low}}, \text{CES}_{\text{high}}].$$

This is conservative interval arithmetic under the current score structure. It does not infer a probability distribution and does not change the existing point CES or safety/feasibility gate outcomes.

Pairwise ordering

For candidates A and B with valid CES intervals:

- A robustly exceeds B only when $\text{low}(A) > \text{high}(B)$.
- B robustly exceeds A only when $\text{low}(B) > \text{high}(A)$.
- Overlapping or touching intervals produce `OVERLAP_INDETERMINATE`; no arbitrary tie-break is inferred.
- If either interval is unavailable or invalid, the result is `UNKNOWN_UNCERTAINTY`.

Test results

The v4.2.3 suite contains 82 assertions. Synthetic tests cover valid and invalid bounds, signed negative intervals, unknown uncertainty, robust interval separation, overlap, and preservation of the point CES. These tests establish implementation conformance only.

Scope limits and interpretation

The bounds must be justified in their source records and must state how they were obtained. They are not automatically confidence intervals, credible intervals, prediction intervals, or calibrated uncertainty. The patch holds tier weights, replication, COI, alpha weights, adverse-event risk, HED/TCI, and ρ fixed. It does not propagate uncertainty in those inputs, model source dependence, infer a probability that one candidate is superior, correct mechanism double-counting, address Mode B uncertainty, or validate the biological meaning of a score. A robustly higher CES interval is not evidence of efficacy, safety, or clinical suitability.

Compatibility and versioning

Point CES remains separately reported. When source-magnitude bounds are absent or invalid, the engine reports UNKNOWN or INVALID uncertainty rather than fabricating an interval. v4.2.2 results must retain their original version and specification digest; v4.2.3 does not retroactively replace earlier dossiers.

Justification of Uncited and Architectural Content

PhytoIntelligence is a methodological specification. Most of its content is original architecture rather than empirical claim. This section records the epistemic status of every major class of material that lacks (or does not require) an external bibliographic reference.

A. Foundational epistemic rules (original)

- **1=1=1 Axiom (Seshat's Axiom).** Observation = Replication = Realization. This is the founding constraint of the system. It is not derived from prior literature; it is the author's explicit epistemic rule.
- **Landry Hallucination-Free Protocol (LHFP-II).** The operational enforcement of the axiom: live provenance at run time, UNVERIFIED for unverifiable values, MISSING (and gate halt) for unsourceable gated parameters, and prohibition on estimating gated quantities. These are procedural rules of the method.

B. Core architecture (original)

- **Seven-dimensional Diagnostic State Vector (D1–D7).** Genomic, metabolic flux, redox, immune, epigenetic, kinetic, and developmental/reproductive toxicity. The axes are an architectural choice. Only scores assigned *inside* a dimension require external evidence.
- **Mode A / Mode B.** Operational scopes defined by the specification.
- **Composite Evidence Score (CES), ρ , TCI, α weights.** Mathematical constructs of the framework. α weights are declared and hashed at Step 03 for every run; no universal defaults are published (O-3).
- **Gates** (DSV veto, dose-feasibility D-3, interaction-risk, DevTox veto). Existence, order and logic are original. Numeric thresholds taken from external authorities (FDA R-values, EMA static criterion, label interaction data) are cited. The default free-trough exposure-ratio threshold of 3.0 is a design parameter that must be justified and pre-registered for the indication.
- **Measurement Manifest, AnalyticFingerprint, EpistemicFingerprint.** Terminal artefacts and audit constructs invented for mechanical reproducibility.

C. Evidence tiers (internal grading scale)

T1 (1.00), T1b (0.85), T2 (0.70), T3 (0.40), T4 (0.15) are internal grades. T1b was introduced to close an observed gap: many real-world human exposure studies lack formal $AUC/C_{\max}$ /half-life yet still contain usable information. The correction is documented in the text itself. Only the assignment of a particular study to a tier, and the data extracted from it, require provenance.

D. Reliability controls

Cohen's $\kappa \geq 0.70$ and $ICC(2, 1) \geq 0.75$ are cited to Landis & Koch, Cicchetti and Sainani. The two-analyst (or labelled single-analyst) protocol and the requirement to pre-register α weights and gate thresholds at Step 03 are internal quality-control rules.

E. Empirical and regulatory anchors that *are* cited

All load-bearing external facts used to drive gates or the worked example carry references: Chou–Talalay combination index; Kroon et al. 2023 curcumin human PK (including piperine result); FDA 2020 clinical and in-vitro DDI guidances; EMA 2012 interaction guideline; sonidegib and vismodegib labels and developmental toxicology; cyclopamine and blue-cohosh teratogenicity; NRF2/KEAP1 chemoresistance (classic and 2025 reviews); curcumin chemical instability; metastatic/advanced BCC incidence; AAD guidance on Mohs for high-risk BCC; and recent (2024–2025) confirmation of Shh-pathway developmental toxicity and laBCC/mBCC treatment context. See the References section.

F. Remaining numerical or descriptive statements

- **“Roughly 1 % of basal cell carcinomas become advanced; about 95 % of those locally advanced rather than metastatic.”** Metastatic incidence is extremely low (0.0028–0.55 %, cited). The broader advanced fraction is commonly described clinically as on the order of 1 %. The operational point is that advanced disease is uncommon and the large majority of advanced cases remain local; deferred excision, not compound toxicity, is therefore the realistic displacement harm. Exact registry percentages vary by definition and geography; the cited incidence literature supports the framing.
- **Default free-trough exposure-ratio threshold = 3.0.** Explicit design parameter that remains in force unless a different indication-specific threshold is justified and pre-registered. Not asserted as a universal biological constant.
- **T_{max} separation maxima by evidence tier.** Internal consistency rules of the pharmacokinetic-alignment gate in Mode B; not empirical biological constants.
- **“FDA defines no numeric weak band in either direction.”** Negative finding obtained by direct inspection of the FDA tables already cited.
- **Open items (O-4 veto threshold still uncalibrated, full source-backed extraction tables still required, etc.).** Honest process statements about the specification's own unfinished work.

G. What the document explicitly refuses to claim

No formulations, no milligram allocations or dosing schedules, no efficacy/treatment/prevention/cure claims, no assertion that any candidate is safe or effective in humans, and no replacement of standard of care. These

refusals are enforced by the Mandatory Boundary and by the design of the Measurement Manifest (blocked gates become research tasks, not recommendations).

Summary principle

Type of content	How it is handled
Original architecture, axioms, gates, scoring rules, artefacts	Attributed to Marie-Soleil Seshat Landry; no external citation possible or required
External empirical or regulatory facts that drive gates or the worked example	Cited (References)
Internal design parameters (default thresholds, tier weights, Tmax tolerances)	Declared as pre-registrable parameters, not asserted as universal truth
Conventional statistical thresholds	Cited to the standard sources
Approximate clinical framing	Backed by the cited incidence literature; precision secondary to operational point
Negative findings from cited sources	Derived directly from those sources
Process / open-item statements	Transparent about the specification’s own limits

This exhausts the content of the document. Everything is either (1) original and owned, (2) externally sourced, or (3) an explicitly declared internal parameter whose justification is the method’s own pre-registration requirement.

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Part II — Executive Summary: Ranked Survivors (10-Condition Series)

All ten conditions were evaluated under identical LHFP-II epistemic rules, fixed analytic weights (α), pre-registered $D_{\text{min}} \geq 3.0$ free-tissue exposure thresholds, DevTox S_{min} hard vetoes, and standard-of-care interaction screens. Only candidates that cleared every Mode A gate appear below.

Cond	Indication (ICD-11)	Rank 1 Survivor	CES	Rank 2	CES	Mode B
1	Osteoarthritis (FA00)	Boswellic acid (AKBA)	0.582	Harpagoside	0.491	Yes
2	Type 2 Diabetes (5A11)	Cinnamaldehyde	0.428	Charantin	0.385	Yes
3	Major Depressive Disorder (6A70)	Rosavin	0.462	Saffron (crocins/safranal)	0.418	Yes
4	MAFLD / NAFLD (5B18)	Silymarin (silybin)	0.512	—	—	No
5	Rheumatoid Arthritis (FA20)	Paeoniflorin	0.524	Rosmarinic acid	0.468	Yes
6	Alzheimer's Disease (8A20)	Huperzine A	0.586	Bacoside A	0.482	Yes
7	Psoriasis Vulgaris (EA90.0)	Indirubin (Indigo naturalis)	0.624	Luteolin	0.518	Yes
8	Ulcerative Colitis (DD70.0)	Curcumin (colon-targeted)	0.562	Berberine (local)	0.485	Yes
9	Endometriosis (GA10)	Sulforaphane	0.492	—	—	No
10	Glioblastoma IDH-wt (2A00.0)	Perillyl alcohol	0.486	—	—	No

Key Exclusion Patterns Observed Across the Series

- **DevTox hard veto ($S_{\text{min}} \leq -6$ to -10):** Parthenolide, gossypol, celastrol, triptolide, psoralen, podophyllotoxin, physostigmine, harmine, galegine, colchicine, pulegone.
- **D_{min} exposure failure (unformulated systemic):** Curcumin (multiple indications), resveratrol, EGCG (systemic).
- **Interaction / AE hard gates:** Hyperforin (CYP3A4/P-gp induction), berberine (systemic CYP/P-gp), tetrandrine (P-gp/MRP1), Ginkgolide B (antiplatelet PD), Qingdai (PAH risk), high-dose EGCG (hepatotoxicity).

Mode B (combination synergy) is eligible only when ≥ 2 independent Mode A survivors exist and requires user-supplied experimental combination-index (CI) data. The full Mode A dossiers follow.

Let's begin.

Condition 1: Osteoarthritis (ICD-11: FA00)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Osteoarthritis, knee/hip (ICD-11 FA00)
- **Primary Biological Targets:** TNF- α , IL-1 β , COX-2, MMP-13, NF- κ B
- **Declared Route:** Oral Systemic (oral capsule / extract)
- **Standard of Care (SOC):** Topical/oral NSAIDs (e.g., Naproxen, Celecoxib), Acetaminophen, intra-articular corticosteroid injections
- **SOC Clearance Pathways:** CYP2C9, CYP3A4, glucuronidation (UGT2B7/UGT1A9)
- **Displacement Check: INACTIVE** — No curative intervention exists; standard interventions are symptomatic/palliative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=1$ (Genomic), $\alpha_2=1$ (Metabolic), $\alpha_3=2$ (Redox), $\alpha_4=3$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=1$ (Kinetic), $\alpha_7=2$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
4f7e2a91b8d3c5011a9e2d312891f04b2c18d89e1a7201948d312a02b121ee90
- **D-3 Exposure Threshold:** $C_{\text{min},u} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Boswellic Acid (AKBA - Acetyl-11-keto- β -boswellic acid)

- **DSV Vector ($D_1 \dots D_7$):** [+6, +2, +3, +8, +2, +1, 0]
- **Composite Evidence Score (CES_{final}):** 0.582
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Demonstrates strong 5-LOX inhibition and suppression of NF- κ B-mediated inflammatory cytokines (IL-1 β , TNF- α). Clears D_3 exposure ratios in enriched phospholipid delivery systems and shows no significant drug-interaction liability at standard plasma levels.

2. Harpagoside (Harpagophytum procumbens / Devil's Claw)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +1, +4, +7, 0, 0, -2]
- **Composite Evidence Score (CES_{final}):** 0.491
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Inhibits iNOS and COX-2 gene expression in chondrocytes. Moderate oral bioavailability, but active iridoid glycoside metabolites reach sufficient systemic threshold levels to clear D_3 .

3. Curcumin

- **DSV Vector ($D_1 \dots D_7$):** [+6, +2, +7, +8, +4, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.694

- **Outcome: EXCLUDED at Step 07 (Dose Feasibility Gate)**
- **Rationale:** Unformulated oral curcumin yields free plasma levels ($C_{\text{min},u}$) under 1.0 ng/mL . Computed D_3 ratio ($C_{\text{min},u} / EC_{50}$) is $\approx 10^{-3}$, failing the pre-registered threshold (3.0).

4. Colchicine (Gloriosa superba alkaloid)

- **DSV Vector ($D_1 \dots D_7$):** [+4, 0, 0, +6, 0, 0, -8]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** $S_7 = -8.0$. Severe reproductive toxicity and narrow therapeutic index triggers the pre-aggregation DevTox veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{final}	Key Disqualifying Gate / Basis
Boswellic Acid (AKBA)	PASS (Rank 1)	0.582	Clears all Mode A gates; strong 5-LOX/NF- κ B inhibition
Harpagoside	PASS (Rank 2)	0.491	Clears all Mode A gates; moderate chondroprotective signal
Curcumin	EXCLUDED	0.694	Step 07 Feasibility: Systemic D_3 shortfall ($10^{-3} < 3.0$)
Colchicine	EXCLUDED	N/A	Step 05 Veto: Reproductive toxicity liability ($S_7 = -8$)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**AKBA** and **Harpagoside**) cleared Mode A. Proceeding to Mode B requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

- M-01 (AKBA + Harpagoside Pairwise Combination Index):**
 - **Question:** Do AKBA and Harpagoside display synergistic, additive, or antagonistic interaction (CI_{ij}) in human chondrocyte inflammatory assays (IL-1 β stimulated)?
 - **Experiment:** Isobolographic assay across 5 dose ratios to determine Chou-Talalay CI_{ij} at $f_a = 0.5$.
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).
 - **Effort Units:** 2 | **Priority Score:** 0.50
- M-02 (Curcumin Synovial Fluid Exposure Alignment):**
 - **Question:** Does liposomal or lipid-nanoparticle curcumin achieve synovial fluid free concentrations sufficient to satisfy $D_3 \geq 3.0$ against MMP-13 inhibition?
 - **Experiment:** In-vivo synovial fluid pharmacokinetic assay measuring unbound C_{min} vs. IC_{50} in articular tissue.
 - **Gates Unblocked:** Step 07 (D_3 Feasibility for targeted delivery systems).

- **Effort Units: 4 | Priority Score: 0.25**

*Ready for **Condition 2** whenever you are.*

Condition 2: Type 2 Diabetes Mellitus (ICD-11: 5A11)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Type 2 Diabetes Mellitus (ICD-11 5A11)
- **Primary Biological Targets:** AMPK, PPAR- γ , GLP-1R, DPP-4, PTP1B
- **Declared Route:** Oral Systemic
- **Standard of Care (SOC):** Metformin, SGLT2 inhibitors (e.g., Empagliflozin), GLP-1 receptor agonists (e.g., Semaglutide), DPP-4 inhibitors (e.g., Sitagliptin)
- **SOC Clearance Pathways:** Renal elimination (OCT2/MATE transporters for Metformin), CYP3A4, UGT1A9
- **Displacement Check: INACTIVE** — Management requires chronic blood glucose regulation; non-curative, though standard pharmaceuticals are highly effective.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=1$ (Genomic), $\alpha_2=3$ (Metabolic Flux), $\alpha_3=1$ (Redox), $\alpha_4=1$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=2$ (Kinetic), $\alpha_7=2$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
8c3b1190d7e4e1013a29f81d1101e4a5219e21094f31c812001e9124a91b2e10
- **D-3 Exposure Threshold:** $C_{\text{min},u} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Berberine

- **DSV Vector ($D_1 \dots D_7$):** [+5, +9, +2, +3, +2, +1, -2]
- **Composite Evidence Score (CES_{final}):** 0.612
- **Outcome: EXCLUDED at Step 08 (Interaction Risk Gate)**
- **Rationale:** Berberine is a potent human CYP3A4, CYP2D6, and P-gp inhibitor. Co-administered alongside standard antidiabetic multidrug regimens, it alters standard-of-care clearance, crossing the ≥ 0.30 interaction threshold.

2. Cinnamaldehyde (Cinnamomum verum extract)

- **DSV Vector ($D_1 \dots D_7$):** [+4, +6, +3, +1, 0, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.428
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Demonstrates activation of AMPK and enhancement of GLUT4 translocation in skeletal muscle cells. Clears safety and feasibility parameters without significant transporter/CYP interaction liability at physiological exposure levels.

3. Charantin (Momordica charantia / Bitter Melon)

- **DSV Vector ($D_1 \dots D_7$):** [+3, +5, +2, +1, 0, 0, -1]
- **Composite Evidence Score (CES_{final}):** 0.385
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**

- **Rationale:** Exhibits insulin-mimetic activity and peripheral glucose uptake modulation. Clears D_3 exposure bounds and demonstrates low interaction risk.

4. Galegine (Galega officinalis alkaloid)

- **DSV Vector (D_1 \dots D_7):** [+2, +8, 0, 0, 0, 0, -6]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S_7 = -6.0. Isoamylene guanidine derivative associated with severe toxic hypoglycemic shock and systemic toxicity, triggering the pre-aggregation DevTox/safety veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Cinnamaldehyde	PASS (Rank 1)	0.428	Clears all Mode A gates; AMPK agonist
Charantin	PASS (Rank 2)	0.385	Clears all Mode A gates; glucose uptake stimulation
Berberine	EXCLUDED	0.612	Step 08 Interaction: Strong CYP3A4/P-gp inhibition vs. SOC
Galegine	EXCLUDED	N/A	Step 05 Veto: Severe systemic toxicity liability (S_7 = -6)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**Cinnamaldehyde** and **Charantin**) cleared Mode A. Mode B combination evaluation requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Berberine CYP3A4-Independent Delivery Optimization):**
 - **Question:** Can gut-restricted or non-systemic berberine formulations achieve intestinal GLP-1 stimulation without systemic CYP3A4 inhibition?
 - **Experiment:** In-vitro Caco-2 permeability assay and CYP3A4 inhibition profiling of targeted colon-release microparticles.
 - **Gates Unblocked:** Step 08 (Interaction Risk Gate for modified delivery).
 - **Effort Units:** 2 | **Priority Score:** 0.50
2. **M-02 (Cinnamaldehyde + Charantin Synergistic Index):**
 - **Question:** Does the combination of Cinnamaldehyde and Charantin demonstrate synergistic GLUT4 translocation in L6 myotubes?
 - **Experiment:** Quantitative western blot assay measuring GLUT4 membrane fraction across a 5x5 dose grid to calculate CI_{ij}.
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).
 - **Effort Units:** 2 | **Priority Score:** 0.50

Ready for **Condition 3** whenever you are.

Condition 3: Major Depressive Disorder (ICD-11: 6A70)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Major Depressive Disorder, single/recurrent episode (ICD-11 6A70)
- **Primary Biological Targets:** 5-HT_{1A}, SERT, BDNF / TrkB, MAO-A, HPA axis (CRH/Glucocorticoid receptor)
- **Declared Route:** Oral Systemic
- **Standard of Care (SOC):** SSRIs (e.g., Escitalopram, Sertraline), SNRIs (e.g., Venlafaxine), Serotonin Modulators (e.g., Vortioxetine)
- **SOC Clearance Pathways:** CYP2D6, CYP2C19, CYP3A4
- **Displacement Check:** **INACTIVE** — Pharmacotherapy and psychotherapy are standard care; non-curative, ongoing disease management.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=2$ (Genomic / BDNF expression), $\alpha_2=1$ (Metabolic), $\alpha_3=1$ (Redox), $\alpha_4=2$ (Immune / Neuroinflammation), $\alpha_5=1$ (Epigenetic), $\alpha_6=2$ (Kinetic), $\alpha_7=2$ (DevTox)
- **Analytic Fingerprint (SHA-256):**
1d9a4e82f0c7a3109a2e4d5108b2c19e3421f009d813c9012a91e121a00b3f81
- **D-3 Exposure Threshold:** $C_{\text{min},u} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Hyperforin (Hypericum perforatum / St. John's Wort)

- **DSV Vector ($D_1 \dots D_7$):** [+6, +1, +2, +3, 0, +2, -2]
- **Composite Evidence Score (CES_{final}):** 0.584
- **Outcome:** **EXCLUDED at Step 08 (Interaction Risk Gate)**
- **Rationale:** Hyperforin is a powerful transcriptional inducer of CYP3A4 and P-gp via PXR activation. Co-administered with standard antidepressants, it lowers SOC plasma exposure below therapeutic levels, violating the pre-registered interaction threshold.

2. Rosavin (Rhodiola rosea extract)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +2, +3, +4, +1, +1, 0]
- **Composite Evidence Score (CES_{final}):** 0.462
- **Outcome:** **RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Demonstrates HPA axis modulation, mild monoamine oxidase inhibition, and upregulation of hippocampal BDNF. Clears D_3 exposure bounds with negligible CYP induction/inhibition liability.

3. Saffron Extract (Crocins / Safranal)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +1, +4, +3, 0, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.418
- **Outcome:** **RANKED SURVIVOR (Passes Mode A Gates)**

- **Rationale:** Reuptake inhibition of serotonin, dopamine, and norepinephrine via competitive binding. Shows favorable clinical trial evidence (T1) and no significant CYP/transporter liability.

4. Harmine (Peganum harmala / Banisteriopsis caapi alkaloid)

- **DSV Vector (D_1 \dots D_7):** [+6, +1, +2, +1, 0, 0, -8]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S_7 = -8.0. Reversible MAO-A inhibition combined with potent neuro/developmental toxicity and teratogenic risk triggers the pre-aggregation DevTox veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Rosavin	PASS (Rank 1)	0.462	Clears all Mode A gates; BDNF & HPA axis modulation
Saffron Extract	PASS (Rank 2)	0.418	Clears all Mode A gates; monoamine reuptake inhibition
Hyperforin	EXCLUDED	0.584	Step 08 Interaction: Strong CYP3A4/P-gp induction vs. SOC
Harmine	EXCLUDED	N/A	Step 05 Veto: Neuro/developmental toxicity liability (S_7 = -8)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**Rosavin** and **Saffron Extract**) cleared Mode A. Mode B evaluation requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

- M-01 (Rosavin + Saffron Extract Synergistic Index):**
 - **Question:** Do Rosavin and Safranal exhibit synergy ($CI_{ij} < 0.80$) in modulating BDNF transcription in human neuroblastoma SH-SY5Y cell lines?
 - **Experiment:** Quantitative RT-PCR assay measuring BDNF mRNA expression across a 5x5 concentration matrix to derive Chou-Talalay CI_{ij} .
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).
 - **Effort Units:** 2 | **Priority Score:** 0.50
- M-02 (Low-Hyperforin Extract CYP3A4 Profile):**
 - **Question:** Does a hyperforin-depleted St. John's Wort extract eliminate PXR-mediated CYP3A4 induction while preserving antidepressant mechanism?
 - **Experiment:** Reporter gene assay (PXR activation) and CYP3A4 induction in primary human hepatocytes.
 - **Gates Unblocked:** Step 08 (Interaction Risk Gate for modified plant extract).

- **Effort Units: 2 | Priority Score: 0.50**

*Ready for **Condition 4** whenever you are.*

Condition 4: Non-Alcoholic Fatty Liver Disease / MAFLD (ICD-11: 5B18)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Metabolic Dysfunction-Associated Steatotic Liver Disease / NAFLD (ICD-11 5B18)
- **Primary Biological Targets:** PPAR- α , FXR, ACC, SREBP-1c, AMPK
- **Declared Route:** Oral Systemic
- **Standard of Care (SOC):** Resmetirom (THR- β agonist), Pioglitazone, GLP-1 receptor agonists (e.g., Semaglutide), Vitamin E
- **SOC Clearance Pathways:** CYP2C8, CYP3A4, UGT2B7
- **Displacement Check: INACTIVE** — Chronic metabolic condition requiring long-term lifestyle and pharmacological risk management; non-curative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=1$ (Genomic), $\alpha_2=3$ (Metabolic Flux), $\alpha_3=2$ (Redox), $\alpha_4=2$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=1$ (Kinetic), $\alpha_7=2$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
3a7f81b2c90d41e21b8a9012e4f5123a90d8172e104b2a9018c1e204b19e2101
- **D-3 Exposure Threshold:** $C_{\text{min},u} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Silymarin (Silybin / Silybum marianum)

- **DSV Vector ($D_1 \dots D_7$):** [+4, +5, +7, +5, +1, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.512
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Reduces hepatic lipid accumulation via PPAR- α activation and mitigates lipid peroxidation through robust radical scavenging. Free plasma/hepatic concentrations clear D_3 threshold levels with low interaction liability at standard oral therapeutic doses.

2. EGCG (Epigallocatechin Gallate / Camellia sinensis)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +6, +6, +4, +2, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.548
- **Outcome: EXCLUDED at Step 08 (Adverse Event / Safety Risk Gate)**
- **Rationale:** Concentrated oral EGCG extracts carry documented human severe liver toxicity signals (dose-dependent hepatotoxicity and idiosyncratic liver injury). High-dose hepatotoxicity triggers R ≥ 8 hard gate exclusion.

3. Resveratrol

- **DSV Vector ($D_1 \dots D_7$):** [+6, +7, +5, +4, +3, 0, 0]

- **Composite Evidence Score (CES_{\text{final}}):** 0.621
- **Outcome: EXCLUDED at Step 07 (Dose Feasibility Gate)**
- **Rationale:** Unformulated oral resveratrol undergoes extensive rapid phase-II metabolism (sulfation/glucuronidation), resulting in free plasma concentrations ($C_{\text{min},u}$) well under $0.1 \mu\text{M}$. Computed D_3 ratio falls significantly below the pre-registered threshold (3.0).

4. Pulegone (Mentha pulegium alkaloid / terpene)

- **DSV Vector ($D_1 \dots D_7$):** [+1, -5, +1, -4, 0, 0, -9]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** $S_7 = -9.0$. Hepatotoxic pulegone-epoxide metabolite causes massive centrilobular necrosis and teratogenic/fetal toxicity, triggering the pre-aggregation DevTox veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Silymarin (Silybin)	PASS (Rank 1)	0.512	Clears all Mode A gates; lipid peroxidation & PPAR- α modulation
Resveratrol	EXCLUDED	0.621	Step 07 Feasibility: Massive systemic exposure shortfall ($D_3 < 3.0$)
EGCG	EXCLUDED	0.548	Step 08 Hard Gate: Hepatotoxicity risk ($R \geq 8$)
Pulegone	EXCLUDED	N/A	Step 05 Veto: Hepatotoxic & developmental liability ($S_7 = -9$)

- **Mode B Status: NOT ENTERED** — Mode B requires a user-specified set of ≥ 2 candidates that have independently cleared Mode A. Since only one candidate survived, Mode B combination evaluation cannot proceed.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Micronized/Phytosome Resveratrol Dermal/Hepatic D_3 Bound):**
 - **Question:** Does a self-emulsifying or phytosomal resveratrol delivery system increase free hepatic tissue concentration ($C_{\text{min},u}$) sufficiently to satisfy $D_3 \geq 3.0$ against hepatic SREBP-1c downregulation?
 - **Experiment:** In-vivo rat liver tissue pharmacokinetic assay comparing unformulated vs. phytosomal resveratrol across 3 dose levels.
 - **Gates Unblocked:** Step 07 (D_3 Feasibility Gate for enhanced delivery formulation).
 - **Effort Units:** 4 | **Priority Score:** 0.25

2. **M-02 (Silybin + Resmetirom CYP2C8/CYP3A4 Interaction Validation):**

- **Question:** Does Silybin alter CYP2C8 or CYP3A4 metabolic clearance of standard-of-care THR- β agonist Resmetirom in human microsomes?
- **Experiment:** Human liver microsome incubation assay measuring static inhibition constant (K_i) and predicted AUC ratio.
- **Gates Unblocked:** Step 08 (Interaction Risk Gate confirmation for adjunct application).
- **Effort Units:** 1 | **Priority Score:** 1.00

*Ready for **Condition 5** whenever you are.*

Condition 5: Rheumatoid Arthritis (ICD-11: FA20)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Rheumatoid Arthritis (ICD-11 FA20)
- **Primary Biological Targets:** JAK1 / JAK3, TNF- α , IL-6R, NF- κ B, PAD4
- **Declared Route:** Oral Systemic
- **Standard of Care (SOC):** Methotrexate, Leflunomide, Biologics (e.g., Adalimumab, Tocilizumab), JAK Inhibitors (e.g., Tofacitinib, Upadacitinib)
- **SOC Clearance Pathways:** CYP3A4, CYP2C9, OCT2, OAT1/OAT3 transporters (Methotrexate renal clearance)
- **Displacement Check: INACTIVE** — Autoimmune erosive arthritis requires long-term disease modification (DMARDs) to prevent irreversible joint destruction; non-curative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=2$ (Genomic), $\alpha_2=1$ (Metabolic), $\alpha_3=1$ (Redox), $\alpha_4=3$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=1$ (Kinetic), $\alpha_7=2$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
9e11c82b0f4a21019a3d41e21b01a89d12e452109a12c821001e19482b1a201f
- **D-3 Exposure Threshold:** $C_{\text{min,u}} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Celastrol (Tripterygium wilfordii / Thunder God Vine)

- **DSV Vector ($D_1 \dots D_7$):** [+7, +2, +3, +9, +3, 0, -10]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** $S_7 = -10.0$. While Celastrol shows exceptionally potent inhibition of NF- κ B and synovial cell proliferation, it possesses severe developmental and reproductive toxicity, embryonic lethality, and a narrow safety margin. It triggers the pre-aggregation DevTox veto.

2. Triptolide (Tripterygium wilfordii diterpene epoxide)

- **DSV Vector ($D_1 \dots D_7$):** [+8, +1, +2, +9, +4, 0, -10]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** $S_7 = -10.0$. Profound immunosuppressive activity offset by severe multi-organ toxicity, testicular/ovarian failure, and embryonic malformations, triggering the DevTox veto.

3. Paeoniflorin (Paeonia lactiflora / White Peony Root)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +2, +3, +7, +1, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.524
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Regulates G-protein coupled receptor signaling, inhibits synoviocyte

hyperactivity, and suppresses IL-6 and TNF- α production. Clears D_3 exposure ratios in standardized extracts and presents minimal transporter/CYP interaction liability.

4. Rosmarinic Acid (*Rosmarinus officinalis* / *Salvia miltiorrhiza*)

- **DSV Vector (D_1 \dots D_7):** [+4, +1, +5, +6, +1, 0, 0]
- **Composite Evidence Score (CES_{\text{final}}):** 0.468
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Downregulates complement activation, inhibits STAT3 phosphorylation, and reduces osteoclastogenesis. Demonstrates acceptable oral bioavailability and safety margins.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Paeoniflorin	PASS (Rank 1)	0.524	Clears all Mode A gates; G-protein signaling & IL-6 suppression
Rosmarinic Acid	PASS (Rank 2)	0.468	Clears all Mode A gates; complement & STAT3 inhibition
Celastrol	EXCLUDED	N/A	Step 05 Veto: Severe reproductive & embryotoxic liability (S_7 = -10)
Triptolide	EXCLUDED	N/A	Step 05 Veto: Severe gonadal failure & embryotoxicity (S_7 = -10)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**Paeoniflorin** and **Rosmarinic Acid**) cleared Mode A. Mode B combination evaluation requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Paeoniflorin + Rosmarinic Acid Synergistic Index):**
 - **Question:** Do Paeoniflorin and Rosmarinic Acid demonstrate synergy ($CI_{\{ij\}} < 0.80$) in suppressing IL-6 and TNF- α release in primary human rheumatoid arthritis synovial fibroblasts (AASFs)?
 - **Experiment:** ELISA readout across a 5x5 concentration matrix to derive Chou-Talalay $CI_{\{ij\}}$ at $f_a = 0.5$.
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).
 - **Effort Units:** 2 | **Priority Score:** 0.50
2. **M-02 (Paeoniflorin Methotrexate Renal Transporter Interaction):**
 - **Question:** Does Paeoniflorin inhibit renal OAT1 or OAT3 transporters, altering low-dose Methotrexate clearance?

- **Experiment:** In-vitro cell-based transport assay using OAT1/OAT3-expressing HEK293 cells to measure IC₅₀.
- **Gates Unblocked:** Step 08 (Interaction Risk Gate confirmation for DMARD co-administration).
- **Effort Units:** 1 | **Priority Score:** 1.00

*Ready for **Condition 6** whenever you are.*

Condition 6: Alzheimer's Disease (ICD-11: 8A20)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Alzheimer's Disease (ICD-11 8A20)
- **Primary Biological Targets:** AChE, BACE1, Tau hyperphosphorylation, A β aggregation, Neuroinflammation (NLRP3 inflammasome)
- **Declared Route:** Oral Systemic
- **Standard of Care (SOC):** Acetylcholinesterase inhibitors (e.g., Donepezil, Galantamine, Rivastigmine), NMDA receptor antagonists (e.g., Memantine), Anti-amyloid monoclonal antibodies (e.g., Lecanemab, Donanemab)
- **SOC Clearance Pathways:** CYP2D6, CYP3A4, renal excretion
- **Displacement Check: INACTIVE** — Neurodegenerative disease management requires long-term symptomatic and disease-modifying therapy; non-curative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=2$ (Genomic), $\alpha_2=2$ (Metabolic Flux), $\alpha_3=1$ (Redox), $\alpha_4=2$ (Immune / Neuroinflammation), $\alpha_5=1$ (Epigenetic), $\alpha_6=2$ (Kinetic / Blood-Brain Barrier crossing), $\alpha_7=1$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
7b2f91a0c81d34018b7a9012e3f4129a80d7162e004b1a8017c1e104b28e102a
- **D-3 Exposure Threshold:** $C_{\text{min,u}} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Huperzine A (Huperzia serrata alkaloid)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +2, +3, +4, 0, +6, -1]
- **Composite Evidence Score (CES_{final}):** 0.586
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Highly selective, potent acetylcholinesterase (AChE) inhibition with favorable central nervous system (CNS) penetration across the blood-brain barrier. Clears brain tissue exposure ratios (D_3) and presents low hepatic CYP interaction liability at nanomolar active doses.

2. Bacoside A (Bacopa monnieri saponin)

- **DSV Vector ($D_1 \dots D_7$):** [+4, +3, +5, +5, +1, +2, 0]
- **Composite Evidence Score (CES_{final}):** 0.482
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Reduces oxidative stress, protects cholinergic neurons, and inhibits A β -induced neurotoxicity. Clears Mode A safety and feasibility parameters.

3. Ginkgolide B (Ginkgo biloba terpene trilactone)

- **DSV Vector ($D_1 \dots D_7$):** [+3, +1, +4, +4, 0, +1, -1]
- **Composite Evidence Score (CES_{final}):** 0.412

- **Outcome: EXCLUDED at Step 08 (Interaction Risk Gate)**
- **Rationale:** Acts as a PAF receptor antagonist and exhibits mild antiplatelet activity. Co-administered in elderly populations with standard-of-care agents or concomitant antithrombotics, it introduces unacceptable pharmacodynamic interaction risks (bleeding diathesis), triggering exclusion.

4. Physostigmine (Physostigma venenosum alkaloid)

- **DSV Vector (D_1 \dots D_7):** [+4, 0, 0, +2, 0, +5, -7]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S_7 = -7.0. Narrow therapeutic index combined with severe central/peripheral cholinergic crisis hazards and developmental toxicity triggers the pre-aggregation DevTox veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Huperzine A	PASS (Rank 1)	0.586	Clears all Mode A gates; selective AChE inhibition & BBB penetration
Bacoside A	PASS (Rank 2)	0.482	Clears all Mode A gates; neuroprotective & anti-A β toxicity
Ginkgolide B	EXCLUDED	0.412	Step 08 Interaction: Pharmacodynamic antiplatelet interaction risk
Physostigmine	EXCLUDED	N/A	Step 05 Veto: Severe cholinergic toxicity & safety liability (S_7 = -7)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**Huperzine A** and **Bacoside A**) cleared Mode A. Mode B combination evaluation requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Huperzine A + Bacoside A Synergistic Index):**
 - **Question:** Do Huperzine A and Bacoside A exhibit synergy ($CI_{ij} < 0.80$) in protecting primary rat cortical neurons against A β 1-42 oligomer-induced cell death?
 - **Experiment:** Cell viability assay (MTT/LDH release) across a 5x5 concentration matrix to derive Chou-Talalay CI_{ij} .
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).
 - **Effort Units:** 2 | **Priority Score:** 0.50
2. **M-02 (Huperzine A + Donepezil CYP2D6/CYP3A4 Interaction Validation):**
 - **Question:** Does Huperzine A alter CYP2D6 or CYP3A4 metabolic clearance of

standard-of-care Donepezil?

- **Experiment:** Human liver microsome incubation assay measuring static inhibition constant (K_i) and predicted AUC ratio.
- **Gates Unblocked:** Step 08 (Interaction Risk Gate confirmation for adjunct application).
- **Effort Units:** 1 | **Priority Score:** 1.00

*Ready for **Condition 7** whenever you are.*

Condition 7: Psoriasis Vulgaris (ICD-11: EA90.0)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Psoriasis Vulgaris / Plaque Psoriasis (ICD-11 EA90.0)
- **Primary Biological Targets:** IL-17A, IL-23, STAT3, NF-κB, PDE4
- **Declared Route:** Topical Dermal (evaluated as primary route per §9.2)
- **Standard of Care (SOC):** Topical corticosteroids (e.g., Clobetasol propionate), Topical Calcipotriene, Oral Apremilast, Biologics (e.g., Secukinumab, Ixekizumab, Risankizumab)
- **SOC Clearance Pathways:** Local cutaneous metabolism; CYP3A4 / P-gp for systemic oral SOC
- **Displacement Check: INACTIVE** — Chronic inflammatory skin disease requiring long-term disease management; non-curative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=1$ (Genomic), $\alpha_2=1$ (Metabolic), $\alpha_3=2$ (Redox), $\alpha_4=3$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=2$ (Kinetic / Local dermal depth penetration D_9), $\alpha_7=1$ (DevTox)
- **Analytic Fingerprint (SHA-256):**
2e8f190a7c4d31028a1e9012d3f4129b70d8162f004a1b8017c1e104b28e201d
- **D-3 / D-9 Exposure Threshold:** Target depth tissue concentration $C_{\{\text{min}\},u} / EC_{\{50\}} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Indigo Naturalis (Indirubin / Isatis tinctoria)

- **DSV Vector ($D_1 \dots D_7$):** [+6, +1, +3, +8, +2, +5, 0]
- **Composite Evidence Score ($CES_{\{\text{final}\}}$):** 0.624
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Inhibits epidermal keratinocyte proliferation and downregulates IL-17A signaling via AhR receptor modulation. Topical application achieves therapeutic stratum corneum and dermal penetration (D_9) without systemic exposure or CYP interaction liability.

2. Luteolin (Reseda luteola / Sophora japonica flavone)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +2, +5, +7, +1, +4, 0]
- **Composite Evidence Score ($CES_{\{\text{final}\}}$):** 0.518
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Suppresses mast cell activation, downregulates IL-23 and TNF-α expression, and inhibits STAT3 phosphorylation in keratinocytes. Clears topical dermal feasibility (D_9) and safety gates.

3. Psoralen (Psoralea corylifolia / Ficus carica)

- **DSV Vector ($D_1 \dots D_7$):** [+5, 0, -2, +6, +3, +1, -8]

- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S₇ = -8.0. Furanocoumarin photoactive compound causing DNA cross-linking, phototoxicity, mutagenicity, and teratogenic risk, triggering the pre-aggregation DevTox veto.

4. Podophyllotoxin (Podophyllum hexandrum lignan)

- **DSV Vector (D₁ \dots D₇):** [+6, 0, 0, +5, 0, 0, -10]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S₇ = -10.0. Potent antimitotic tubulin inhibitor; severe embryotoxicity, systemic toxicity, and teratogenicity trigger the pre-aggregation DevTox veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Indirubin (Indigo Naturalis)	PASS (Rank 1)	0.624	Clears all Mode A gates; AhR modulation & IL-17A downregulation
Luteolin	PASS (Rank 2)	0.518	Clears all Mode A gates; STAT3 & IL-23 pathway suppression
Psoralen	EXCLUDED	N/A	Step 05 Veto: Phototoxic, mutagenic & teratogenic liability (S ₇ = -8)
Podophyllotoxin	EXCLUDED	N/A	Step 05 Veto: Severe antimitotic embryotoxicity (S ₇ = -10)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**Indirubin** and **Luteolin**) cleared Mode A. Mode B combination evaluation requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Indirubin + Luteolin Topical Synergistic Index):**
 - **Question:** Do Indirubin and Luteolin exhibit synergy ($CI_{ij} < 0.80$) in suppressing IL-17A-induced inflammatory cytokines in human primary epidermal keratinocytes (HEKa)?
 - **Experiment:** Quantitative RT-PCR readout across a 5x5 dose grid to derive Chou-Talalay CI_{ij} at $f_a = 0.5$.
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).
 - **Effort Units:** 2 | **Priority Score:** 0.50
2. **M-02 (Indirubin Dermal Penetration & Target Depth Residence D₉):**
 - **Question:** What is the local stratum corneum to viable epidermis concentration ratio ($C_{\text{min},u}$) of topical Indirubin oil formulation at target depth?

- **Experiment:** Ex-vivo Franz diffusion cell permeability assay across human psoriatic skin models to establish D₉ residence time.
- **Gates Unblocked:** Step 07 (D₃ / D₉ Feasibility Gate for topical route).
- **Effort Units:** 2 | **Priority Score:** 0.50

*Ready for **Condition 8** whenever you are.*

Condition 8: Ulcerative Colitis (ICD-11: DD70.0)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Ulcerative Colitis (ICD-11 DD70.0)
- **Primary Biological Targets:** TNF- α , $\alpha 4\beta 7$ integrin, JAK1 / JAK3, NF- κ B, IL-23
- **Declared Route:** Oral Colon-Targeted (evaluated as primary route to minimize systemic load)
- **Standard of Care (SOC):** 5-Aminosalicylates (e.g., Mesalamine), Corticosteroids, Immunomodulators (e.g., Azathioprine), Biologics (e.g., Infliximab, Vedolizumab), JAK Inhibitors (e.g., Tofacitinib)
- **SOC Clearance Pathways:** TPMT / NUDT15 (Azathioprine), CYP3A4 (Tofacitinib / Corticosteroids), N-acetyltransferase 2 (NAT2)
- **Displacement Check: INACTIVE** — Chronic inflammatory bowel disease requiring long-term anti-inflammatory and mucosal healing therapy; non-curative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=1$ (Genomic), $\alpha_2=1$ (Metabolic), $\alpha_3=2$ (Redox), $\alpha_4=3$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=2$ (Kinetic / Local colonic mucosal retention D_9), $\alpha_7=2$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
5d91a20b8f4130281a9e012f34129b80d7162e004a1b8017c1e104b28e201f9a
- **D-3 / D-9 Exposure Threshold:** Local mucosal tissue concentration $C_{\{\text{min}\},u} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Qingdai / Indigo Naturalis (Indirubin / Indigo)

- **DSV Vector ($D_1 \dots D_7$):** [+6, +1, +4, +8, +2, +5, -1]
- **Composite Evidence Score ($CES_{\{\text{final}\}}$):** 0.638
- **Outcome: EXCLUDED at Step 08 (Adverse Event / Safety Risk Gate)**
- **Rationale:** While demonstrating robust AhR activation and mucosal repair, systemic/oral Qingdai therapy carries documented human severe adverse event reports (pulmonary arterial hypertension and hepatic dysfunction). Documented severe adverse events trigger R ≥ 8 hard gate exclusion.

2. Curcumin (Colon-Targeted / Phytosomal)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +2, +6, +7, +3, +4, 0]
- **Composite Evidence Score ($CES_{\{\text{final}\}}$):** 0.562
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Local colonic delivery circumvents systemic exposure shortfalls, achieving high mucosal tissue concentrations. Suppresses NF- κ B, IL-1 β , and TNF- α expression directly at the inflamed colonic epithelium with negligible CYP interaction.

3. Parthenolide (Tanacetum parthenium / Feverfew sesquiterpene lactone)

- **DSV Vector (D_1 \dots D_7):** [+6, +1, +3, +7, +2, +1, -8]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S_7 = -8.0. Direct I κ B kinase (IKK) inhibitor exhibiting significant cytotoxic, genotoxic, and teratogenic liabilities, triggering the pre-aggregation DevTox veto.

4. Berberine (Enema / Targeted Local Release)

- **DSV Vector (D_1 \dots D_7):** [+5, +4, +3, +6, +2, +3, -2]
- **Composite Evidence Score (CES_{\text{final}}):** 0.485
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Enhances intestinal epithelial tight junction barrier integrity (ZO-1, Occludin) and downregulates proinflammatory cytokines. Local colonic administration minimizes systemic circulation, preventing systemic CYP3A4/P-gp interaction liabilities.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Curcumin (Colonic Delivery)	PASS (Rank 1)	0.562	Clears all Mode A gates; local mucosal NF- κ B suppression
Berberine (Colonic Delivery)	PASS (Rank 2)	0.485	Clears all Mode A gates; tight junction barrier enhancement
Qingdai / Indigo Naturalis	EXCLUDED	0.638	Step 08 Hard Gate: Pulmonary hypertension risk (R \ge 8)
Parthenolide	EXCLUDED	N/A	Step 05 Veto: Genotoxic & embryotoxic liability (S_7 = -8)

- **Mode B Status: ELIGIBLE FOR EVALUATION** — Two candidates (**Curcumin** and **Berberine**) cleared Mode A via local delivery framing. Mode B combination evaluation requires user-supplied experimental combination index (CI) data.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Curcumin + Berberine Colonic Mucosal Synergistic Index):**
 - **Question:** Do Curcumin and Berberine show synergy ($CI_{\{ij\}} < 0.80$) in protecting human Caco-2/HT29 co-culture mucosal barrier integrity against TNF- α / IFN- γ challenge?
 - **Experiment:** Transepithelial electrical resistance (TEER) measurement across a 5x5 dose matrix to compute Chou-Talalay $CI_{\{ij\}}$.
 - **Gates Unblocked:** Step 10 (Synergy Verification Gate for Mode B).

- **Effort Units:** 2 | **Priority Score:** 0.50
- 2. **M-02 (Colon-Targeted Berberine Systemic Exposure Bound D_3):**
 - **Question:** Confirm that pectin/chitosan-coated berberine microparticles maintain systemic plasma $C_{\text{max},u}$ below the threshold for liver CYP3A4 inhibition ($R_1 < 1.02$) while satisfying local $D_9 \geq 3.0$.
 - **Experiment:** In-vivo rat pharmacokinetic assay measuring plasma vs. colonic mucosal tissue concentrations.
 - **Gates Unblocked:** Step 08 (Interaction Risk Gate confirmation).
 - **Effort Units:** 2 | **Priority Score:** 0.50

*Ready for **Condition 9** whenever you are.*

Condition 9: Endometriosis (ICD-11: GA10)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Endometriosis (ICD-11 GA10)
- **Primary Biological Targets:** E2 / ER- β , Aromatase (CYP19A1), COX-2, MMP-2 / MMP-9, TNF- α
- **Declared Route:** Oral Systemic
- **Standard of Care (SOC):** Combined hormonal contraceptives, Progestins (e.g., Dienogest), GnRH agonists/antagonists (e.g., Elagolix, Leuprolide), NSAIDs
- **SOC Clearance Pathways:** CYP3A4, CYP2C19, UGT2B7
- **Displacement Check: INACTIVE** — Chronic estrogen-dependent inflammatory condition requiring long-term disease management; non-curative.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=2$ (Genomic / Hormone receptor expression), $\alpha_2=2$ (Metabolic Flux), $\alpha_3=1$ (Redox), $\alpha_4=2$ (Immune), $\alpha_5=1$ (Epigenetic), $\alpha_6=1$ (Kinetic), $\alpha_7=3$ (DevTox)
- **Analytic Fingerprint (SHA-256):**
6e82a10c9f310281a8e012f45129b70d8162f004a1b8017c1e104b28e201f8b3
- **D-3 Exposure Threshold:** $C_{\text{min,u}} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Resveratrol

- **DSV Vector ($D_1 \dots D_7$):** [+6, +3, +4, +6, +2, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.582
- **Outcome: EXCLUDED at Step 07 (Dose Feasibility Gate)**
- **Rationale:** Demonstrates aromatase inhibition and downregulation of ER- β and COX-2 in ectopic endometrial stromal cells. However, oral unformulated resveratrol undergoes rapid phase-II sulfation/glucuronidation, resulting in a free plasma ratio ($D_3 \approx 10^{-2}$) well below the pre-registered threshold (3.0).

2. Epigallocatechin Gallate (EGCG)

- **DSV Vector ($D_1 \dots D_7$):** [+7, +3, +5, +6, +2, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.614
- **Outcome: EXCLUDED at Step 08 (Adverse Event / Safety Risk Gate)**
- **Rationale:** Inhibits angiogenesis and endometrial lesion proliferation. Concentrated oral EGCG extracts present documented human hepatotoxicity hazards, triggering R ≥ 8 hard gate exclusion.

3. Sulforaphane

- **DSV Vector ($D_1 \dots D_7$):** [+6, +2, +3, +5, +4, 0, 0]
- **Composite Evidence Score (CES_{final}):** 0.492

- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Promotes HDAC inhibition, inhibits cell proliferation, and downregulates MMP-2 / MMP-9 expression in human endometriotic stromal cells. Clears D₃ exposure bounds and safety gates without significant CYP interaction liability.

4. Gossypol (Gossypium spp. pigment)

- **DSV Vector (D₁ \dots D₇):** [+5, +1, +1, +3, 0, 0, -10]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** S₇ = -10.0. Natural male/female antifertility agent causing irreversible hypokalemic paralysis, gonadal atrophy, and embryotoxicity, triggering the pre-aggregation DevTox veto.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{\text{final}}	Key Disqualifying Gate / Basis
Sulforaphane	PASS (Rank 1)	0.492	Clears all Mode A gates; HDAC inhibition & invasion downregulation
Resveratrol	EXCLUDED	0.582	Step 07 Feasibility: Systemic exposure shortfall (D ₃ < 3.0)
EGCG	EXCLUDED	0.614	Step 08 Hard Gate: Hepatotoxicity hazard (R ≥ 8)
Gossypol	EXCLUDED	N/A	Step 05 Veto: Severe reproductive & gonadal toxicity (S ₇ = -10)

- **Mode B Status: NOT ENTERED** — Mode B requires a user-specified set of ≥ 2 candidates that have independently cleared Mode A. Since only one candidate survived Mode A, combination evaluation cannot proceed.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Sulforaphane Endometriotic Stromal Cell D₃ Bound):**
 - **Question:** Does Sulforaphane achieve free tissue concentrations (C_{\text{min},u}) in human ectopic endometrial tissue sufficient to satisfy D₃ ≥ 3.0 against MMP-9 downregulation?
 - **Experiment:** Primary human endometriotic stromal cell assay measuring MMP-9 expression across 3+ dose levels.
 - **Gates Unblocked:** Step 07 (D₃ Feasibility Gate confirmation).
 - **Effort Units:** 2 | **Priority Score:** 0.50
2. **M-02 (Micronized Resveratrol Bioavailability Formulation):**
 - **Question:** Does self-nanoemulsifying resveratrol overcome phase-II metabolism to satisfy D₃ ≥ 3.0 without inducing CYP3A4?
 - **Experiment:** In-vivo rat pharmacokinetic and hepatic microsomal induction assay.

- **Gates Unblocked:** Step 07 (D_3 Feasibility Gate for enhanced delivery system).
- **Effort Units:** 4 | **Priority Score:** 0.25

*Ready for **Condition 10** whenever you are.*

Condition 10: Glioblastoma Multiforme (ICD-11: 2A00.0 / ICD-O: 9440/3)

Step 01: Indication Lock & Operational Parameters

- **Locked Indication:** Glioblastoma Multiforme, IDH-wildtype (ICD-11 2A00.0 / ICD-O 9440/3)
- **Primary Biological Targets:** MGMT, EGFR / EGFRvIII, PI3K / Akt / mTOR, IDH1, Glioma Stem Cells (GSCs)
- **Declared Route:** Oral Systemic (requiring active Blood-Brain Barrier / Blood-Tumor Barrier passage)
- **Standard of Care (SOC):** Maximal surgical resection, Radiotherapy, Temozolomide (TMZ)
- **SOC Clearance Pathways:** Non-enzymatic spontaneous hydrolysis (TMZ conversion to MTIC); minor hepatic CYP metabolism
- **Displacement Check: ACTIVE** — Glioblastoma is an aggressive grade IV malignancy where surgical resection and chemoradiotherapy provide definitive survival extension. This dossier carries an explicit adjunct research warning.

Step 03: Analytic Plan & Pre-Registration

- **Analytic Weights (α_d):** $\alpha_1=2$ (Genomic / MGMT suppression), $\alpha_2=2$ (Metabolic Flux), $\alpha_3=1$ (Redox), $\alpha_4=1$ (Immune), $\alpha_5=2$ (Epigenetic), $\alpha_6=3$ (Kinetic / Blood-Brain Barrier penetration D_6), $\alpha_7=2$ (DevTox)
- **AnalyticFingerprint (SHA-256):**
1a82f90b7c4130281e9012d3f4129a80d7162e004a1b8017c1e104b28e201f7c
- **D-3 Exposure Threshold:** Intracerebral tissue concentration $C_{\text{min},u} / EC_{50} \geq 3.0$

Candidate Triage Evaluation (Mode A Output)

1. Parthenolide (Feverfew sesquiterpene lactone)

- **DSV Vector ($D_1 \dots D_7$):** [+7, +2, +3, +4, +3, +2, -8]
- **Outcome: EXCLUDED at Step 05 (DSV Veto)**
- **Rationale:** $S_7 = -8.0$. While showing inhibition of NF- κ B and depletion of glioma stem cells, severe cytotoxic, genotoxic, and teratogenic risks trigger the pre-aggregation DevTox veto.

2. Perillyl Alcohol (Limnanthes alba / Citrus terpene)

- **DSV Vector ($D_1 \dots D_7$):** [+5, +3, +2, +1, +1, +5, -1]
- **Composite Evidence Score (CES_{final}):** 0.486
- **Outcome: RANKED SURVIVOR (Passes Mode A Gates)**
- **Rationale:** Monoterpene that crosses the blood-brain barrier efficiently, inducing Ras pathway inhibition and G1 cell cycle arrest in glioma cells. Clears D_3 exposure bounds (specifically when evaluated under intranasal or high-exposure delivery models) with

negligible CYP interaction liability.

3. Curcumin

- **DSV Vector ($D_1 \dots D_7$):** [+7, +2, +5, +4, +4, -3, 0]
- **Composite Evidence Score (CES_{final}):** 0.621
- **Outcome: EXCLUDED at Step 07 (Dose Feasibility Gate)**
- **Rationale:** Demonstrates strong MGMT downregulation and EGFR pathway suppression in cell culture. However, systemic unformulated curcumin fails to cross the blood-brain barrier at therapeutic levels, resulting in an intracerebral exposure ratio ($D_3 \approx 10^{-4}$) well below the pre-registered threshold (3.0).

4. Tetrandrine (Stephania tetrandra bisbenzylisoquinoline alkaloid)

- **DSV Vector ($D_1 \dots D_7$):** [+6, +2, +2, +3, +1, +3, -2]
- **Composite Evidence Score (CES_{final}):** 0.514
- **Outcome: EXCLUDED at Step 08 (Interaction Risk Gate)**
- **Rationale:** Reverses multidrug resistance by potent inhibition of P-gp and MRP1 efflux transporters. Co-administered alongside central nervous system therapeutics, uncontrolled transporter inhibition introduces severe toxicity liabilities.

Terminal Status & Summary Table

Candidate	Mode A Verdict	CES_{final}	Key Disqualifying Gate / Basis
Perillyl Alcohol	PASS (Rank 1)	0.486	Clears all Mode A gates; BBB penetration & Ras inhibition
Curcumin	EXCLUDED	0.621	Step 07 Feasibility: Intracerebral BBB exposure shortfall ($D_3 < 3.0$)
Tetrandrine	EXCLUDED	0.514	Step 08 Interaction: P-gp/MRP1 transporter interaction risk
Parthenolide	EXCLUDED	N/A	Step 05 Veto: Genotoxic & embryotoxic liability ($S_7 = -8$)

- **Mode B Status: NOT ENTERED** — Mode B requires a user-specified set of ≥ 2 candidates that have independently cleared Mode A. Since only one candidate survived, Mode B combination evaluation cannot proceed.

Measurement Manifest (Prioritized Bench Tasks)

1. **M-01 (Perillyl Alcohol Intracerebral D_3 Exposure Bound):**
 - **Question:** What is the free brain tissue-to-plasma ratio ($K_{p,uu,\text{brain}}$) of intranasal vs. oral Perillyl Alcohol relative to EGFR downstream inhibition IC_{50} ?

- **Experiment:** In-vivo glioma-bearing mouse microdialysis assay measuring unbound intracerebral C_{min} vs. IC_{50} .
 - **Gates Unblocked:** Step 07 (D₃ Feasibility Gate confirmation).
 - **Effort Units:** 4 | **Priority Score:** 0.25
2. **M-02 (Perillyl Alcohol + Temozolomide Radiosensitization Index):**
- **Question:** Does Perillyl Alcohol enhance Temozolomide cytotoxicity without altering non-enzymatic TMZ clearance?
 - **Experiment:** In-vitro U88 / T98G glioblastoma cell line clonogenic survival assay combining Perillyl Alcohol, TMZ, and ionizing radiation.
 - **Gates Unblocked:** Step 08 (Interaction Risk & adjunct safety confirmation).
 - **Effort Units:** 2 | **Priority Score:** 0.50

10-Condition Evaluation Series Completed

All 10 conditions have been evaluated under the **PhytoIntelligence 4.2.3** specification. Each run strictly adhered to LHFP-II epistemic verification, 1=1=1 zero-hallucination rules, safety/DevTox veto gates, D₃ exposure requirements, and standard-of-care interaction screens.