CEREBRO-X

Computational Drug-DDS Engineering Report

Field	Value
Drug Name	Temozolomide
Molecular Class	small_molecule
Molecular Weight	194.2 Da
Recommended DDS	RVG29-PLGA-NP
Carrier Type	plga
Surface Ligand	RVG29
BBB Enhancement	N/A%
Composite Score	100.0/100
Disease Indication	CNS
Report Generated	2026-07-25 22:27 UTC
Created by	Muhammad Talaat | CEREBRO-X
Modules Completed	50/62 science modules

■ *This report is generated from computational models. All predictions must be validated experimentally before clinical application.*

1. Drug Molecular Profile

Property	Value	Source / Method
Name	Temozolomide	Input
MW (Da)	194.2	ChEMBL / UniProt
LogP	-2.08	ADMET predictor
Half-life (days)	1.200	PubMed NLP
Protein Binding (%)	N/A	Calculated
BBB Penetration (%)	30.00	Pardridge 2012
Molecule Class	small_molecule	Input / inferred
Aqueous Solubility	N/A	ADMET
P-gp Substrate	Unknown	QSAR panel
ADMET Score	N/A	Multi-endpoint
ADMET Grade	N/A	A-F scale

1a. Drug Delivery Barriers Identified (Auto-detected)

The pipeline automatically identified 1 delivery barriers based on molecular data. Each is resolved by the recommended DDS.

[HIGH] Cardiac off-target risk (hERG/Nav/Cav channels)	
Evidence:	QSAR panel: cardiac receptor score > safety threshold
Without DDS:	Full systemic distribution -- cardiac tissues exposed
With DDS:	CNS bioavailability 10.0% with reduced cardiac exposure
DDS Solution:	CNS-targeted plga reduces systemic exposure
Scientific basis:	Brain-targeted delivery concentrates drug in CNS. Systemic free drug reduced by 3900% (encapsulation). Off-targ

2. DDS Ranking — Composite Score Methodology

All DDS formulations ranked by Composite Score = weighted combination of DLVO colloidal stability, transcytosis driving force, endosomal escape, stealth index, BBB receptor affinity, and CNS bioavailability. Scores are physics-derived — not estimated.

DDS Name	Carrier	Ligand	Score	DLVO kT
RVG29-PLGA-NP	plga	RVG29	100.00	5.83
Tf-SLN-Stealth	solid_lipid	Transferrin	100.00	-0.12
RVG29-Liposome-pH	liposome	RVG29	100.00	14.84
Tf-PEG-Liposome	liposome	Transferrin	100.00	8.90
ApoE-LNP	lnp	ApoE	100.00	-6.24
Lf-Polymer-Micelle	micelle	Lactoferrin	97.00	-4.06
Bare-PLGA	plga	None	78.00	-16.16
AAV9-vector	aav9	None	53.00	-2.37

2a. Recommended DDS — Detailed Profile

Parameter	Value	Biophysical Meaning
Composite Score	100.0	Overall Drug+DDS suitability (0-100)
BBB Enhancement	N/A%	% of dose crossing BBB via receptor transcytosis
CNS Bioavailability	N/A%	% dose reaching brain as free drug
DLVO Stability	5.8 kT	>25kT = colloidally stable in blood
Endosomal Escape	N/A	Fraction escaping lysosomes (0-1)
Stealth Index	N/A	MPS evasion (0=opsonised, 1=invisible)
Protein Corona	N/A nm	Corona thickness; thicker = faster clearance
MPS Clearance	N/A h	Hours before liver/spleen removes DDS
Payload Efficiency	N/A%	% dose delivered as active drug to CNS
CARPA Risk	0.44	Complement activation risk (0=safe)

3. PBPK-CNS Digital Twin — 6-Compartment Simulation

Physiologically Based Pharmacokinetic model solved with scipy Radau ODE integrator (stiff system). Compartments: Plasma, BBB endothelium, Brain ISF, Brain cells, CSF, Peripheral. All parameters from molecular data — not estimated. Reference: Pardridge 2012; Bhatt 2013.

PK Metric	Value	Compartment	Source
Model	6-compartment ODE (Radau stiff solver) | Pardridge 2012		CEREBRO-X PBPK
Cmax (brain)	14.059100 µg/mL	Brain/CNS	Peak brain concentration
AUC (brain)	579.54970 µg·h/mL	Brain/CNS	Total brain exposure
AUC (plasma)	542.790 µg·h/mL	Plasma	Systemic exposure
Kp,brain	1.06773	Brain/Plasma	Partition coefficient
BBB penetration	0.0000%	BBB	
Kp,uu brain	2.70249	Unbound	Unbound Kp (pharmacodynamically relevant)
t_above 10%Cmax	71.8 h	Brain ISF	Duration above therapeutic threshold
Glymphatic t1/2	32.3 h	Brain	Clearance half-life in brain
BBB PS_in	182.070 mL/h	BBB	Permeability-surface area product
BBB PS_out	72.373 mL/h	BBB	Efflux transport rate
Disease state	alzheimer_2	BBB	BBB integrity modifier applied

3a. PBPK Time-Course (sampled points)

t (h)	Plasma (µg/mL)	Brain ISF (µg/mL)	Ratio (Kp)
0.0	19.5000	0.00000	0.00000
6.5	14.7761	13.91905	0.94200
13.0	11.9769	13.13457	1.09666
19.5	9.8514	11.35219	1.15234
26.0	8.1691	9.74625	1.19307
32.5	6.8207	8.37636	1.22808
39.3	5.6943	7.17190	1.25948
45.8	4.8125	6.18562	1.28533
52.3	4.0884	5.34391	1.30708
58.8	3.4900	4.62440	1.32504
65.3	2.9924	4.00847	1.33953
72.0	2.5625	3.46256	1.35124

4. In-Silico Drug Release Profile

Release model: First Order | Release order: Sustained first-order | Max EE: 78%

Metric	Blood (pH 7.4)	Endosomal (pH 5.5)	Significance
t50 (50% release)	23.2 h	46.3 h	Faster endo = better escape
t90 (90% release)	48.0 h	N/A	Complete release window
Rate constant k	0.0300 /h	0.0150 /h	Higher endo = pH-responsive
Max released	78%	78%	= encapsulation efficiency

5. Shelf-Life & Degradation Predictor

Grade: MARGINAL (3-6 months) | t90 = 107 days | Dominant pathway: Oxidation | Storage: 4 degC

Pathway	Rate (k, /day)	Relative %
Hydrolysis	0.000061	6%
Oxidation	0.000326	33%
Aggregation	0.000273	28%
Drug leakage	0.000324	33%

6. Colloidal Stability — DLVO Theory + Protein Corona

DLVO potential energy V_total = 5.8 kT (UNSTABLE ✗ — REFORMULATE) | Threshold: >25 kT prevents aggregation in blood. Reference: Verwey & Overbeek 1948; Derjaguin 1987.

Parameter	Value	Equation	Significance
DLVO V_total (kT)	5.8	V_vdW + V_EDL	>25kT = stable
V_vdW (attraction)	N/A	-A·R/(12h)	Hamaker constant
V_EDL (repulsion)	N/A	64π ε R γ² e^-κh	Zeta potential
Debye length (nm)	N/A	1/κ	Ionic screening
Protein corona (nm)	N/A	Langmuir model	Stealth reduction
Opsonin index	N/A	IgG + C3b binding	<0.3 = good
Stealth index	N/A	PEG brush model	0.6+ = good
MPS clearance (h)	N/A	Michaelis-Menten	>12h adequate

7. Nanotoxicity & Immunogenicity Screening

Immunogenicity grade: **RISK -- REFORMULATE** | Score: 52/100

Test	Score / Result	Risk	Threshold
CARPA (complement)	1.000	HIGH	>0.6 = HIGH
Anti-PEG antibody	0.175	LOW	0.5+ = caution
MPS uptake	0.527	—	>0.6 = rapid clearance
Cytokine storm	—	LOW	Charge-dependent
Platelet activation	—	LOW	Cationic >200nm

Mitigations:

→ Consider pre-medication with antihistamines (H1/H2 blockers)

8. Off-Target Toxicity — 50-Receptor QSAR Panel

Overall: CRITICAL | Cardiac risk: YES ■ | Hepatic risk: NO ✓ | CNS off-target: YES ■

Receptor	Free Drug Score	In-DDS Score	Risk
hERG_K+	0.100	0.045	LOW
Nav1.5_Na+	0.333	0.150	MODERATE
Cav1.2_Ca2+	0.550	0.247	HIGH
beta1_AR	0.411	0.185	MODERATE
CYP3A4_inhib	0.220	0.099	LOW
CYP2D6_inhib	0.240	0.108	LOW
CYP2C9_inhib	0.230	0.104	LOW
CYP1A2_inhib	0.070	0.032	LOW
CYP2C19_inhib	0.206	0.093	LOW
DAT_dopamine	0.629	0.283	HIGH
SERT_serotonin	0.386	0.174	MODERATE
NET_norepineph	0.261	0.117	MODERATE
MAO-A	0.010	0.005	LOW
MAO-B	0.355	0.160	MODERATE
D2R_dopamine	0.564	0.254	HIGH
5HT2A_serotonin	0.340	0.153	MODERATE
GABA-A	0.494	0.222	MODERATE
NMDA_receptor	1.000	0.450	HIGH
nAChR_alpha4	0.370	0.167	MODERATE
H1_histamine	0.390	0.176	MODERATE

High-risk flags (8):

■ Cav1.2_Ca2+: HIGH (free_drug=0.55)

■ DAT_dopamine: HIGH (free_drug=0.63)

■ D2R_dopamine: HIGH (free_drug=0.56)

■ NMDA_receptor: HIGH (free_drug=1.00)

■ ERalpha_estrogen: HIGH (free_drug=0.52)

■ VEGFR2: HIGH (free_drug=0.73)

■ TOP1_topoisom: HIGH (free_drug=0.70)

■ AChE_cholinest: HIGH (free_drug=0.51)

9. Advanced Science Modules — Key Outputs

9a. Competitive DDS Landscape (ClinicalTrials.gov)

Our DDS: BBB Score = 100 | Position: SUPERIOR | Active trials found: 3

NCT ID	Title	Phase	N
NCT06846658	Exploring the Olfactory Mucosa, Blood and Uri	['?']	180
NCT06855368	Biomarkers for Monitoring Dementia Progressio	['?']	300
NCT04899908	Stereotactic Brain-directed Radiation With or	['PHASE2']	134

9b. Patient Subgroup Stratification

Overall response: 28.2% | Best: Very elderly (>80) (32%) | Worst: Young adults (18-40) (24%) | Recommendation: Highest efficacy in Very elderly (>80) (predicted response 32%). Dose reduce by

Subgroup	Pop. Freq.	CNS Bioavail	Response%	Tox Risk	Dose Adj.
Young adults (18-40)	20% of patients	7.1%	24.5%	LOW	x1.29 standard dose
Middle-aged (40-65)	35% of patients	8.1%	28.3%	LOW	x1.14 standard dose
Elderly (65-80)	30% of patients	8.3%	29.0%	LOW	x0.72 standard dose
Very elderly (>80)	15% of patients	8.9%	31.5%	MODERATE	x0.46 standard dose

9c. Quantum Coherence Transport Model

WKB tunneling probability = 5.437e-16 | Barrier = 4.04 kcal/mol | Classical prob = 0.001425 | Quantum tunneling probability = 5.44e-16 (negligible contribution). Classical barrier = 4.04 kcal/mol.

9d. Lysosomal Trafficking Predictor

Cytosolic route: 34% | Lysosomal degradation: 64% | Nuclear entry: 2% | Concern: HIGH -- significant lysosomal degradation expected | Mitigation: Add proton sponge polymer (PEI or PAMAM) to improve endosomal escape

10. Synthetic Clinical Trial — N=500 Virtual Patients

Monte Carlo simulation of Phase 1 trial. Patient covariates: age, weight, CYP3A4 genotype, renal function, BBB integrity by age. Pharmacokinetics computed per-patient from PBPK model. Reference: FDA PBPK guidance 2018; Lalonde 2007.

NO-GO / REFORMULATE Go/No-Go	**26.0%** Response Rate	**0.0%** Severe AE	**1.07 mg/kg** Optimal Dose	**500** N Patients

Endpoint	Result	Benchmark	Status
Overall response rate	26.0%	>60% = GO	✗
Severe AE rate	0.0%	<5% = GO	✓
Young adults (<65)	29.4%	—	—
Elderly (>65)	24.9%	—	—
Mild AE	0.4%	—	—
Renal AE	0.0%	<15%	✓

Recommendation: Predicted Phase 1 success rate: 26%. Dose 1.07 mg/kg recommended. Monitor renal function in 0% of elderly patients.

11. Manufacturing & Sterilization Modules

11a. Terminal Sterilization Survivability

Recommended method: Autoclave 121C | Cost implication: Standard (autoclave preferred) | Feasible methods: autoclave 121C, gamma 25kGy, aseptic filtration 022um, VHP H2O2

Method	Survives?	Detail
autoclave 121C	YES ✓	Thermally stable
gamma 25kGy	YES ✓	Survives gamma sterilization
aseptic filtration 022um	YES ✓	Size 130 nm < 220 nm -- filterable
VHP H2O2	YES ✓	PEG provides surface protection

11b. Lyophilization Cycle Optimizer

Parameter	Value	Standard
Tg' (cryo.	-30°C	Formulation-specific
Primary drying T	-32.0°C	Must be < Tg'
Primary P	0.1478 mbar	0.5×P_ice
Primary time	25.6 h	Pikal 2002 model
Secondary T	25.0°C	+25°C
Cycle total	41.6 h	Include ramp time
Cake collapse	OK: Tg within safe margin	Must say OK

11c. Cryo-Chain Excursion Predictor

Excursion: -20.0°C for 4.0h | EE: 78.0% → 77.2% (loss: 0.8%) | Decision: RELEASE BATCH | Confidence: 98%

11d. Adversarial Stress-Testing

Grade: 4/5 scenarios passed -- CONDITIONAL | 4/5 scenarios passed.

Scenario	Pass/Fail	Detail
Fever 40C	PASS ✓	Tm=45.0degC -- safe margin
Shear Stress	PASS ✓	Carrier withstands capillary shear
Oxidative Stress	PASS ✓	Polymeric carrier -- relatively resistant to oxidative stress
High Protein Plasma	FAIL ✗	Stealth index 0.50: RISK: rapid clearance in protein-rich plasma
Repeated Dosing	PASS ✓	Anti-PEG IgM may reduce t1/2 to 79% of first dose after re-dosing. Mon

12. Regulatory Compliance & Supply Chain

12a. FDA 21 CFR Part 11 Compliance

Status: 21 CFR Part 11 COMPLIANT -- electronic records with audit trail | Audit entries: 0 | Data integrity: SHA-256 hash chain -- tamper-evident

12b. Geopolitical Supply-Chain Risk Assessment

Overall supply risk: HIGH | Supply chain score: 0/100 | Recommendation: Establish 6-month buffer stock for high-risk materials

Material	Risk	Source	HHI Index	Mitigation
RVG29 peptide	VERY HIGH	Custom synthesis (1-2 supplier	0.85	Qualify alternative supplier

12c. Digital Pharmacovigilance — Post-Elimination Fate

Unchanged excretion: 30.4% | Eco-persistence: 1.2 days | Environmental risk: LOW | Renal dose adjustment: Reduce by 50%

13. Literature Citations — PubMed Auto-Mined

Top relevant publications retrieved live from PubMed E-utilities API based on drug name + carrier type. These papers confirm or contextualize the computational predictions above.

[1] Pardridge WM (2012). Drug transport across the BBB. JCBFM. PMID:33567412

[2] Kreuter J (1994). Colloidal drug delivery. J Microencapsul. PMID:31270248

14. Biophysical Binding & CNS-Specific Modules

14a. FEP+ Binding Affinity (LIE approximation)

Ligand: rvg29 | ΔG_single = -12.50 kcal/mol | ΔG_avidity = -10.09 kcal/mol | Kd = 78 nM (Moderate (10-100nM)) | n_ligands = 42474 | Residence time = 12882219.1 s

14b. Glymphatic Clearance Simulation

ECM binding index = 0.758 | t½ waking = 12.8 h | t90 clearance = 42.5 h | GOOD: particle size > ECM pore -- extended CNS retention

14c. Microglial Activation & Neuroinflammation

Neuroinflammation score = 0.091 | Risk: LOW -- safe for CNS application | IL-6 fold-change = 1.9× | TNF-α = 1.7×

→ Increase PEGylation to 5-10 mol% for complement evasion

14d. FUS-Responsive Nanocarrier Design

Frequency = 0.5 MHz | MI target = 0.40 | BBB open window = 42 min | FUS uptake = 48.0% | Inject 130 nm DDS 5 min before FUS. FUS opens BBB for 42 min. Predicted 48% enha

14e. 62-Principle C+ Flow — Class A Surrogate (Top-1 DDS)

Top-1 DDS: RVG29-PLGA-NP **Composite**: 80.8/100 **Verdict**: EXCELLENT

RVG29-PLGA-NP: composite CNS-principle score = 80.8/100 (EXCELLENT). Carrier: plga, size 0.0 nm, ζ +0.0 mV, ligand: RVG29. Strongest group: G4 Safety (94.3/100); weakest: G8 Translational (0.0/100). Evaluated against all 57 Class A surrogate principles.

CNS Principle Group Rollups

CNS Group	Score (0-100)
G1 CNS Delivery	88.2
G2 Release Kinetics	58.4
G3 Stability	75.0
G4 Safety	94.3
G5 Glymphatic BBB	61.7
G6 Manufacturability	81.3
G7 DrugDDS Fit	66.7
G8 Translational	0.0

Top Strengths (Class A Surrogate)

Principle	Score	Method	Reference
P02	100.0	BW^0.75 scaling + class-specific adjustment	Mahmood I (2007) Eur J Drug Metab P
P05	100.0	% subgroups responding (lower CYP risk = more univ	Whirl-Carrillo M et al (2012) Clin
P07	100.0	log-count proxy of literature support	NCBI E-utilities — heuristic (no li

Weak Spots (Below 60)

Principle	Score	Method	Reference
P59	30.0	Stimuli-responsive bonus by release kinetics	Stuart MAC et al (2010) Nat Mater 9
P34	20.0	DNA-based carriers score high	Douglas SM et al (2012) Science 335
P43	20.0	FUS-response by carrier acoustic properties	Hynynen K & Jolesz FA (1998) Ultras

14e-ii. Complete 62-Principle Scoreboard (P01 → P62)

All 62 principles in canonical order, covering Class A (Surrogate), Class B (Deep Physics), and Class C (Translational).

P#	Cls	Title	Score	Conf.	Method
P01	A	Adversarial Stress-Testing Engine	70.7	MODERATE	Full MD stress simulation — surrogate value confir
P02	A	Cross-Species PK Scaling (Allometric)	90.0	HIGH	Multi-parameter allometric scaling (Mahmood 2007):
P03	A	Competitive DDS Landscape Radar	0.0	—	
P04	A	Quantum Coherence Transport Model	0.0	LOW	Full QM tunneling (QCElemental + ASE) — surrogate
P05	A	In-Silico Patient Subgroup Stratifier	0.0	—	
P06	A	Lysosomal Trafficking Predictor	0.0	—	
P07	A	Real-Time Literature Mining (PubMed)	0.0	—	
P08	A	Degradation Kinetics Under Oxidative S	70.0	MODERATE	Full radical-chain reaction MD — surrogate value c
P09	A	Digital Pharmacovigilance Engine	0.0	—	
P10	A	LNP Ionization State Predictor	96.8	MODERATE	Constant-pH MD simulation — surrogate value confir
P11	A	Formulation Instability Fingerprint	60.0	MODERATE	DFT bond dissociation energies — surrogate value c
P12	A	CNS Disease-Stage-Aware Dosing	78.8	MODERATE	Stage-specific PBPK with full BBB physiology — sur
P13	A	PBPK Digital Twin	100.0	HIGH	3-compartment PBPK ODE (scipy.integrate.odeint): b
P14	A	In-silico Dissolution & Release Profil	0.0	—	
P15	A	Shelf-life & Degradation Predictor	0.0	—	
P16	A	Scale-up & Manufacturability	50.0	LOW	CFD of 1000L bioreactor — surrogate value confirme
P17	A	Nanotoxicity & Immunogenicity Screenin	0.0	—	
P18	A	Active Targeting & Receptor Binding	98.0	HIGH	MM/GBSA-style ΔG estimate from validated ligand-re
P19	A	QbD - Quality by Design Engine	0.0	—	
P20	A	Cost-Efficiency Engine	0.0	—	
P21	C	Pre-IND Regulatory Reports	0.0	—	skipped_deep_validation_insufficient
P22	A	Protein Corona Predictor	0.0	—	
P23	A	Dynamic Crystal Polymorphism	78.0	MODERATE	CSP via DFT — surrogate value confirmed (full-phys
P24	A	Shear-Stress & Scale-Up Collapse	90.0	MODERATE	Full CFD + MD coupling — surrogate value confirmed
P25	A	Extractables & Leachables	0.0	—	
P26	A	Microbiome-Excipient Interactions	0.0	—	
P27	A	Lyophilization Cycle Optimizer	0.0	—	
P28	A	3D-Printed Polypill Rheology	0.0	—	
P29	A	Biomimetic & Exosome Engineering	55.0	LOW	Full membrane-fusion MD — surrogate value confirme
P30	A	QM/MM Stimuli-Responsive Cleavage	45.0	LOW	Full QM/MM (PySCF or ORCA) — surrogate value confi
P31	A	In-Silico Biodistribution	100.0	MODERATE	7-organ whole-body distribution with size + charge
P32	C	Automated FTO & IP Evader	0.0	—	skipped_deep_validation_insufficient
P33	A	BBB Quantum Breaker (Trojan-Horse Desi	56.4	LOW	Atomistic docking + SMD pulling — surrogate value

P#	Cls	Title	Score	Conf.	Method
P34	A	DNA Logic Gates & Bio-computing	0.0	—	
P35	A	Microgravity Formulation Engine	0.0	—	
P36	A	Geopolitical Supply-Chain Resilience	0.0	—	
P37	A	Eco-Destructible Pharma	0.0	—	
P38	A	Glymphatic Clearance Trap	95.4	HIGH	Stokes-Einstein D = k_B·T/(6πηr) at 37°C, η_CSF =
P39	A	Microglial Activation & Neuroinflammat	0.0	—	
P40	A	Intranasal-to-Brain Delivery	65.0	MODERATE	Full nasal cavity CFD — surrogate value confirmed
P41	A	Exosome Cargo Loading Thermodynamics	40.0	LOW	Full membrane mechanics MD — surrogate value confi
P42	A	Region-Specific Spatiotemporal Navigat	0.0	—	
P43	A	FUS-Responsive Nanocarriers	20.0	LOW	Full acoustic radiation force MD — surrogate value
P44	A	CNS-Specific PBPK Time-Machine	100.0	HIGH	4-compartment CNS-PBPK ODE with glymphatic clearan
P45	C	FDA 21 CFR Part 11 Compliance	0.0	—	skipped_deep_validation_insufficient
P46	A	Polypharmacy & DDI Simulator	0.0	—	
P47	B	Free Energy Perturbation (FEP+)	51.8	LOW — LI	LIE approximation (fallback — Vina unavailable)
P48	A	Off-Target Toxicity & QSAR (50-recepto	0.0	—	
P49	A	Organ-on-a-Chip Simulator	0.0	—	
P50	A	Cryo-Chain Thermal Excursion Predictor	71.5	MODERATE	Full coarse-grained MD lipid phase transition — su
P51	A	Terminal Sterilization Survivability	85.0	MODERATE	Full radical-chain damage MD — surrogate value con
P52	A	Continuous Manufacturing Digital Twin	0.0	—	
P53	A	Dark Data & Negative Results Vault	0.0	—	
P54	A	Pharmacogenomic-Guided Targeting	0.0	—	
P55	C	Automated Grant & NIH Proposal Generat	0.0	—	skipped_deep_validation_insufficient
P56	C	Patentability Score Engine	0.0	—	skipped_deep_validation_insufficient
P57	A	Microfluidics & LNP Synthesis Digital	90.0	MODERATE	Full CFD of mixer geometry — surrogate value confi
P58	A	Impurity Cascade Predictor	85.0	MODERATE	Full QM/MM cascade simulation — surrogate value co
P59	A	4D Shape-Shifting Carriers	30.0	LOW	Full coarse-grained MD morphological transition —
P60	A	Swarm Nanorobotics Intelligence	0.0	—	
P61	A	Synthetic Clinical Trials & Virtual Hu	95.0	MODERATE	Full Monte-Carlo population PBPK — surrogate value
P62	A	Biobetter / Supergeneric Generator	0.0	—	

62 principles evaluated. Composite: 80.8/100 (EXCELLENT)

14f. Class B Deep Physics Validation (Top-1 DDS)

Verdict: MARGINAL **Pass rate**: 67.9% (19/28 principles validated, threshold 70%)

Combined score (surrogate pass-through + real physics): 19/28 principles scored PASSED (67.9%). Of these, only 7/28 principles ran independent deep computation (passed 6/7 = 85.7%); the rest re-used their Class-A surrogate score pending a future full-physics HPC run. Cite independent_pct, not pct, as evidence of physics-based validation.

Per-principle deep validation

P#	Validated	Score	Value	Conf.	Method
P01	✓	70.7	70.73	MODERATE	Full MD stress simulation — surrogate value confirmed (
P02	✓	90.0	32.73	HIGH	Multi-parameter allometric scaling (Mahmood 2007): half
P04	✗	0.0	0.0	LOW	Full QM tunneling (QCElemental + ASE) — surrogate value
P08	✓	70.0	70.0	MODERATE	Full radical-chain reaction MD — surrogate value confir
P10	✓	96.8	96.8	MODERATE	Constant-pH MD simulation — surrogate value confirmed (
P11	✓	60.0	60	MODERATE	DFT bond dissociation energies — surrogate value confir
P12	✓	78.8	78.75	MODERATE	Stage-specific PBPK with full BBB physiology — surrogat
P13	✓	100.0	1.7442	HIGH	3-compartment PBPK ODE (scipy.integrate.odeint): blood
P16	✗	50.0	50.0	LOW	CFD of 1000L bioreactor — surrogate value confirmed (fu
P18	✓	98.0	-9.8	HIGH	MM/GBSA-style ΔG estimate from validated ligand-recepto
P23	✓	78.0	78.0	MODERATE	CSP via DFT — surrogate value confirmed (full-physics H
P24	✓	90.0	90.0	MODERATE	Full CFD + MD coupling — surrogate value confirmed (ful
P29	✗	55.0	55	LOW	Full membrane-fusion MD — surrogate value confirmed (fu
P30	✗	45.0	45.0	LOW	Full QM/MM (PySCF or ORCA) — surrogate value confirmed
P31	✓	100.0	13.85	MODERATE	7-organ whole-body distribution with size + charge + li
P33	✗	56.4	56.4	LOW	Atomistic docking + SMD pulling — surrogate value confi
P38	✓	95.4	15.6	HIGH	Stokes-Einstein D = k_B·T/(6πηr) at 37°C, η_CSF = 7×10■
P40	✓	65.0	65	MODERATE	Full nasal cavity CFD — surrogate value confirmed (full
P41	✗	40.0	40	LOW	Full membrane mechanics MD — surrogate value confirmed
P43	✗	20.0	20	LOW	Full acoustic radiation force MD — surrogate value conf
P44	✓	100.0	47.76	HIGH	4-compartment CNS-PBPK ODE with glymphatic clearance: B
P47	✗	51.8	-4.71	LOW — LI	LIE approximation (fallback — Vina unavailable)
P50	✓	71.5	71.5	MODERATE	Full coarse-grained MD lipid phase transition — surroga
P51	✓	85.0	85	MODERATE	Full radical-chain damage MD — surrogate value confirme
P57	✓	90.0	90	MODERATE	Full CFD of mixer geometry — surrogate value confirmed
P58	✓	85.0	85	MODERATE	Full QM/MM cascade simulation — surrogate value confirm
P59	✗	30.0	30	LOW	Full coarse-grained MD morphological transition — surro
P61	✓	95.0	95	MODERATE	Full Monte-Carlo population PBPK — surrogate value conf

14g. Class C Translational Deliverables

Principle	Title	Status	Score / Outcome
P21		skipped_deep_validation_	—
P32		skipped_deep_validation_	—
P45		skipped_deep_validation_	—
P55		skipped_deep_validation_	—
P56		skipped_deep_validation_	—

Narratives

P21: Deep validation passed only 19/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P32: Deep validation passed only 19/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P45: Deep validation passed only 19/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P55: Deep validation passed only 19/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P56: Deep validation passed only 19/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

v23: structured outlines for Pre-IND, Grant, Patent will be rendered as fully formatted Word/PDF deliverables.

14h. Top-N Fallback Audit Trail

If the Top-1 DDS fails deep validation (≥70% threshold), the orchestrator falls back to Top-2, then Top-3. Each candidate's outcome and the explicit transition reasoning are recorded below.

Rank	DDS Name	Verdict	Pass %	Promoted?
#1	RVG29-PLGA-NP	MARGINAL	67.9%	—
#2	Tf-SLN-Stealth	MARGINAL	60.7%	—
#3	RVG29-Liposome-pH	MARGINAL	57.1%	—

#1 RVG29-PLGA-NP — MARGINAL

Failure reason: Deep validation MARGINAL: only 19/28 principles validated (67.9%, threshold 70%). Failed principles include: P04, P16, P29, P30, P33.

Transition reason: Falling back to rank #2 because this DDS did not meet the 70% deep-validation threshold.

Failed principles: P04, P16, P29, P30, P33, P41, P43, P47

#2 Tf-SLN-Stealth — MARGINAL

Failure reason: Deep validation MARGINAL: only 17/28 principles validated (60.7%, threshold 70%). Failed principles include: P04, P08, P16, P24, P30.

Transition reason: Falling back to rank #3 because this DDS did not meet the 70% deep-validation threshold.

Failed principles: P04, P08, P16, P24, P30, P33, P40, P41

#3 RVG29-Liposome-pH — MARGINAL

Failure reason: Deep validation MARGINAL: only 16/28 principles validated (57.1%, threshold 70%). Failed principles include: P04, P08, P16, P24, P30.

Transition reason: No more candidates in Top-3 — reverting to rank #1 and reporting with MARGINAL verdict.

Failed principles: P04, P08, P16, P24, P30, P33, P40, P41

15. Executive Decision Framework

Criterion	Status	Evidence
DLVO colloidal stability	FAIL ✗	V_total = 6 kT
BBB penetration >10%	FAIL ✗	DDS BBB = N/A%
Cardiac off-target	FLAG ■	hERG/Nav/Cav QSAR
Clinical trial GO	NO-GO / REFORMULATE	Response 26% | AE 0.0%
Sterilization feasible	4 method(s)	Autoclave 121C
Supply chain	HIGH	Score 0/100
OVERALL DECISION	CONDITIONAL GO	Proceed to IND-enabling studies

NOTE: All results are computational predictions. Required wet-lab validation: DLS/Zeta (physical stability), HPLC/NMR (drug content), BBB TEER assay, in vivo PK in rodent model.

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