CEREBRO-X

Computational Drug-DDS Engineering Report

Field	Value
Drug Name	Nusinersen
Molecular Class	oligonucleotide
Molecular Weight	1593.8 Da
Recommended DDS	ApoE-LNP
Carrier Type	lnp
Surface Ligand	ApoE
BBB Enhancement	N/A%
Composite Score	100.0/100
Disease Indication	CNS
Report Generated	2026-07-25 22:20 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	Nusinersen	Input
MW (Da)	1593.8	ChEMBL / UniProt
LogP	0.18	ADMET predictor
Half-life (days)	N/A	PubMed NLP
Protein Binding (%)	N/A	Calculated
BBB Penetration (%)	96.86	Pardridge 2012
Molecule Class	oligonucleotide	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.

[CRITICAL] Large molecular weight -- passive BBB diffusion impossible	
Evidence:	MW = 1.6 kDa (Lipinski Rule 5 limit: 500 Da for passive)
Without DDS:	0% brain penetration -- purely physical barrier
With DDS:	Active transcytosis delivers 10.0% payload to CNS
DDS Solution:	lnp encapsulation (75% EE)
Scientific basis:	BBB tight junctions (pore ~1nm) physically block molecules >500Da. Encapsulation in lnp (80nm) enables recepto

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
ApoE-LNP	lnp	ApoE	100.00	-6.24
RVG29-Liposome-pH	liposome	RVG29	100.00	14.84
Tf-PEG-Liposome	liposome	Transferrin	100.00	8.90
RVG29-PLGA-NP	plga	RVG29	100.00	5.83
Tf-SLN-Stealth	solid_lipid	Transferrin	100.00	-0.12
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	-6.2 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	0.20	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)	177.258800 µg/mL	Brain/CNS	Peak brain concentration
AUC (brain)	2118.20410 µg·h/mL	Brain/CNS	Total brain exposure
AUC (plasma)	693.780 µg·h/mL	Plasma	Systemic exposure
Kp,brain	3.05312	Brain/Plasma	Partition coefficient
BBB penetration	0.0000%	BBB	
Kp,uu brain	6.11077	Unbound	Unbound Kp (pharmacodynamically relevant)
t_above 10%Cmax	27.7 h	Brain ISF	Duration above therapeutic threshold
Glymphatic t1/2	72.0 h	Brain	Clearance half-life in brain
BBB PS_in	691.600 mL/h	BBB	Permeability-surface area product
BBB PS_out	259.350 mL/h	BBB	Efflux transport rate
Disease state	healthy	BBB	BBB integrity modifier applied

3a. PBPK Time-Course (sampled points)

t (h)	Plasma (µg/mL)	Brain ISF (µg/mL)	Ratio (Kp)
0.0	0.2500	0.00000	0.00000
6.5	0.2562	0.75431	2.94377
13.0	0.4283	1.29894	3.03288
19.5	0.7302	2.22465	3.04660
26.0	1.2517	3.81998	3.05190
32.5	2.1503	6.56691	3.05402
39.3	3.7723	11.52394	3.05488
45.8	6.4889	19.82487	3.05520
52.3	11.1636	34.10823	3.05532
58.8	19.2071	58.68481	3.05536
65.3	33.0472	100.97188	3.05538
72.0	58.0152	177.25883	3.05539

4. In-Silico Drug Release Profile

Release model: First Order | Release order: Sustained first-order | Max EE: 75%

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	75%	75%	= encapsulation efficiency

5. Shelf-Life & Degradation Predictor

Grade: POOR (<3 months) | t90 = 77 days | Dominant pathway: Aggregation | Storage: 4 degC

Pathway	Rate (k, /day)	Relative %
Hydrolysis	0.000061	4%
Oxidation	0.000160	12%
Aggregation	0.000781	57%
Drug leakage	0.000368	27%

6. Colloidal Stability — DLVO Theory + Protein Corona

DLVO potential energy V_total = -6.2 kT (UNSTABLE ✗ — REFORMULATE) | Threshold: >25 kT prevents aggregation in blood. Reference: Verwey & Overbeek 1948; Derjaguin 1987.

Parameter	Value	Equation	Significance
DLVO V_total (kT)	-6.2	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: **CAUTION** | Score: 36/100

Test	Score / Result	Risk	Threshold
CARPA (complement)	0.520	MODERATE	>0.6 = HIGH
Anti-PEG antibody	0.250	LOW	0.5+ = caution
MPS uptake	0.440	—	>0.6 = rapid clearance
Cytokine storm	—	LOW	Charge-dependent
Platelet activation	—	LOW	Cationic >200nm

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

Overall: SAFE | Cardiac risk: NO ✓ | Hepatic risk: NO ✓ | CNS off-target: NO ✓

Receptor	Free Drug Score	In-DDS Score	Risk
hERG_K+	0.000	0.000	LOW
Nav1.5	0.000	0.000	LOW
Cav1.2	0.000	0.000	LOW
CYP3A4_inhib	0.134	0.084	LOW
CYP2D6_inhib	0.196	0.122	LOW
CYP2C9_inhib	0.098	0.061	LOW
CYP1A2_inhib	0.257	0.161	LOW
CYP2C8_inhib	0.125	0.078	LOW
OATP1B1	0.217	0.136	LOW
MDR1_Pgp	0.000	0.000	LOW
BCRP	0.128	0.080	LOW
MRP2	0.155	0.097	LOW
DAT_dopamine	0.000	0.000	LOW
SERT_serotonin	0.000	0.000	LOW
5HT2A	0.000	0.000	LOW
D2_dopamine	0.000	0.000	LOW
GABA_A	0.000	0.000	LOW
NMDA	0.000	0.000	LOW
sigma1	0.225	0.141	LOW
ERalpha_estrogen	0.000	0.000	LOW

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: 33.4% | Best: Very elderly (>80) (37%) | Worst: Young adults (18-40) (29%) | Recommendation: Highest efficacy in Very elderly (>80) (predicted response 37%). Dose reduce by

Subgroup	Pop. Freq.	CNS Bioavail	Response%	Tox Risk	Dose Adj.
Young adults (18-40)	20% of patients	8.3%	29.3%	LOW	x1.29 standard dose
Middle-aged (40-65)	35% of patients	9.5%	33.5%	LOW	x1.14 standard dose
Elderly (65-80)	30% of patients	9.7%	34.3%	LOW	x0.72 standard dose
Very elderly (>80)	15% of patients	10.5%	36.9%	MODERATE	x0.46 standard dose

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: Gamma 25Kgy | Cost implication: Gamma or E-beam (~3x cost) | Feasible methods: gamma 25kGy, aseptic filtration 022um, VHP H2O2

Method	Survives?	Detail
autoclave 121C	NO ✗	Biologic MW=2kDa -- THERMAL DENATURATION
gamma 25kGy	YES ✓	Survives gamma sterilization
aseptic filtration 022um	YES ✓	Size 80 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	39.6 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: 75.0% → 74.2% (loss: 0.8%) | Decision: RELEASE BATCH | Confidence: 98%

11d. Adversarial Stress-Testing

Grade: 3/5 scenarios passed -- CONDITIONAL | 3/5 scenarios passed.

Scenario	Pass/Fail	Detail
Fever 40C	FAIL ✗	Tm=42.0degC -- RISK: may partially melt at fever temperature
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 70% 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
ApoE3 peptide	VERY HIGH	Custom synthesis	0.85	Qualify alternative supplier

12c. Digital Pharmacovigilance — Post-Elimination Fate

Unchanged excretion: 19.1% | Eco-persistence: 0.5 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: apoe | ΔG_single = -5.00 kcal/mol | ΔG_avidity = -2.59 kcal/mol | Kd = 14975652 nM (Weak (>100nM)) | n_ligands = 16085 | Residence time = 66.8 s

14b. Glymphatic Clearance Simulation

ECM binding index = 0.480 | t½ waking = 9.0 h | t90 clearance = 30.0 h | CAUTION: small particles cleared rapidly by glymphatics

14c. Microglial Activation & Neuroinflammation

Neuroinflammation score = 0.055 | Risk: LOW -- safe for CNS application | IL-6 fold-change = 1.6× | TNF-α = 1.4×

→ No mitigation needed

14d. FUS-Responsive Nanocarrier Design

Frequency = 0.5 MHz | MI target = 0.40 | BBB open window = 42 min | FUS uptake = 68.0% | Inject 80 nm DDS 5 min before FUS. FUS opens BBB for 42 min. Predicted 68% enhan

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

Top-1 DDS: ApoE-LNP **Composite**: 76.3/100 **Verdict**: GOOD

ApoE-LNP: composite CNS-principle score = 76.3/100 (GOOD). Carrier: lnp, size 0.0 nm, ζ +0.0 mV, ligand: ApoE. Strongest group: G4 Safety (94.7/100); 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	50.0
G2 Release Kinetics	58.8
G3 Stability	62.4
G4 Safety	94.7
G5 Glymphatic BBB	60.0
G6 Manufacturability	65.9
G7 DrugDDS Fit	64.2
G8 Translational	0.0

Top Strengths (Class A Surrogate)

Principle	Score	Method	Reference
P03	100.0	Novelty = 100 - frequency_of_combo_in_CNS_trials,	ClinicalTrials.gov landscape
P05	100.0	% subgroups responding (lower CYP risk = more univ	Whirl-Carrillo M et al (2012) Clin
P09	100.0	100 - sum(metabolite organ accumulation risks)	Djoumbou-Feunang Y et al (2019) J C

Weak Spots (Below 60)

Principle	Score	Method	Reference
P43	25.0	FUS-response by carrier acoustic properties	Hynynen K & Jolesz FA (1998) Ultras
P60	15.0	Swarm capability (most carriers: no)	Servant A et al (2015) Sci Robot 1:
P44	1.0	AUC over 24h therapeutic window proxy	Bies RR et al (2019) Annu Rev Pharm

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	53.4	MODERATE	Mean of 6 stress scenarios (pH4.5, pH2, pH8.5, 42°
P02	A	Cross-Species PK Scaling (Allometric)	75.0	MODERATE	BW^0.75 scaling + class-specific adjustment
P03	A	Competitive DDS Landscape Radar	100.0	LOW	Novelty = 100 - frequency_of_combo_in_CNS_trials,
P04	A	Quantum Coherence Transport Model	27.1	MODERATE	WKB tunneling: P ∝ exp(-2·barrier)
P05	A	In-Silico Patient Subgroup Stratifier	100.0	MODERATE	% subgroups responding (lower CYP risk = more univ
P06	A	Lysosomal Trafficking Predictor	58.4	MODERATE	Carrier endosomal_escape ⊕ drug-passive permeation
P07	A	Real-Time Literature Mining (PubMed)	80.0	LOW	log-count proxy of literature support
P08	A	Degradation Kinetics Under Oxidative S	43.0	MODERATE	Arrhenius k=A·exp(-Ea/RT) for carrier; minus penal
P09	A	Digital Pharmacovigilance Engine	100.0	MODERATE	100 - sum(metabolite organ accumulation risks)
P10	A	LNP Ionization State Predictor	60.0	LOW	Non-LNP carrier — falls back to drug-side ionizati
P11	A	Formulation Instability Fingerprint	100.0	MODERATE	100 - sum(weak-bond penalties from SMILES)
P12	A	CNS Disease-Stage-Aware Dosing	83.0	MODERATE	Score = 100·BBB_integrity_factor × (0.4 + 0.6·CNS-
P13	A	PBPK Digital Twin	0.7	MODERATE	AUC_brain/AUC_plasma proxy; 3-compartment surrogat
P14	A	In-silico Dissolution & Release Profil	100.0	MODERATE	t50 from carrier kinetics × drug-membrane partitio
P15	A	Shelf-life & Degradation Predictor	46.2	MODERATE	Arrhenius baseline × (0.7 + 0.3·EE) × drug_hydroly
P16	A	Scale-up & Manufacturability	48.0	MODERATE	Scale-readiness × shear-robustness, minus drug-pro
P17	A	Nanotoxicity & Immunogenicity Screenin	83.8	MODERATE	Mean of (hemolysis penalized by drug net+ charge,
P18	A	Active Targeting & Receptor Binding	85.4	HIGH	Ligand-affinity table × density × drug-compatibili
P19	A	QbD - Quality by Design Engine	100.0	MODERATE	Fraction of CQAs (size, zeta, EE, PDI, drug-loadin
P20	A	Cost-Efficiency Engine	62.8	LOW	Score = 100 - 3·($/mg estimate, drug+carrier+ligan
P21	C	Pre-IND Regulatory Reports	0.0	—	skipped_deep_validation_insufficient
P22	A	Protein Corona Predictor	79.3	MODERATE	100 × exp(-corona_thickness/10); thickness from ca
P23	A	Dynamic Crystal Polymorphism	80.0	MODERATE	100 - polymorph risk (rot_bonds + H-bond pattern)
P24	A	Shear-Stress & Scale-Up Collapse	59.6	MODERATE	log10(crit_shear/operating_shear) × 30; crit_shear
P25	A	Extractables & Leachables	100.0	MODERATE	100 - leachables risk by drug LogP × carrier
P26	A	Microbiome-Excipient Interactions	78.0	MODERATE	100 - mean_microbiome_degradability(carrier) - dru
P27	A	Lyophilization Cycle Optimizer	62.5	MODERATE	100 - (|Tg'| - 5) × 1.5
P28	A	3D-Printed Polypill Rheology	50.0	MODERATE	Carrier-specific printability index
P29	A	Biomimetic & Exosome Engineering	65.0	MODERATE	Stealth-from-macrophage score; PEG ≥5% boost
P30	A	QM/MM Stimuli-Responsive Cleavage	45.0	MODERATE	Score = 50 × |7.4 - pH_trigger|
P31	A	In-Silico Biodistribution	0.4	MODERATE	brain% = BBB · ligand · size_match · 100; 100 if ≥
P32	C	Automated FTO & IP Evader	0.0	—	skipped_deep_validation_insufficient
P33	A	BBB Quantum Breaker (Trojan-Horse Desi	54.6	MODERATE	(0.6·ligand + 0.4·size) × density_factor

P#	Cls	Title	Score	Conf.	Method
P34	A	DNA Logic Gates & Bio-computing	25.0	MODERATE	DNA-based carriers score high
P35	A	Microgravity Formulation Engine	100.0	LOW	Sedimentation-Péclet proxy; smaller = better
P36	A	Geopolitical Supply-Chain Resilience	60.0	MODERATE	Supplier-diversity index by carrier + ligand
P37	A	Eco-Destructible Pharma	60.0	MODERATE	Biodegradability index by carrier class
P38	A	Glymphatic Clearance Trap	100.0	MODERATE	Stokes-Einstein: optimum 80-150 nm
P39	A	Microglial Activation & Neuroinflammat	100.0	MODERATE	100 - (cationic_charge + carrier_risk - PEG_protec
P40	A	Intranasal-to-Brain Delivery	55.0	MODERATE	Mucoadhesion + thermo-responsive boost
P41	A	Exosome Cargo Loading Thermodynamics	40.0	LOW	Not an exosome carrier — N/A
P42	A	Region-Specific Spatiotemporal Navigat	75.0	MODERATE	Ligand-region specificity table
P43	A	FUS-Responsive Nanocarriers	25.0	MODERATE	FUS-response by carrier acoustic properties
P44	A	CNS-Specific PBPK Time-Machine	1.0	MODERATE	AUC over 24h therapeutic window proxy
P45	C	FDA 21 CFR Part 11 Compliance	0.0	—	skipped_deep_validation_insufficient
P46	A	Polypharmacy & DDI Simulator	100.0	MODERATE	CYP-inhibition heuristic from SMILES
P47	B	Free Energy Perturbation (FEP+)	90.0	LOW	Vina-like ΔG proxy from MW + LogP (deep mode runs
P48	A	Off-Target Toxicity & QSAR (50-recepto	100.0	MODERATE	50-receptor QSAR surrogate (hERG, 5HT2B, AhR risks
P49	A	Organ-on-a-Chip Simulator	80.0	MODERATE	Microfluidic compatibility (size + PDI)
P50	A	Cryo-Chain Thermal Excursion Predictor	71.5	MODERATE	Distance from -20°C phase transition × 1.3
P51	A	Terminal Sterilization Survivability	60.0	MODERATE	Carrier gamma-radiation survival (25 kGy)
P52	A	Continuous Manufacturing Digital Twin	60.0	MODERATE	Continuous-process readiness by carrier
P53	A	Dark Data & Negative Results Vault	100.0	MODERATE	Similarity-to-documented-failure
P54	A	Pharmacogenomic-Guided Targeting	75.0	MODERATE	Class-based pharmacogenomic applicability
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	50.0	MODERATE	Microfluidic readiness for size 50-150 nm
P58	A	Impurity Cascade Predictor	80.0	MODERATE	Carrier residual-metals impurity profile
P59	A	4D Shape-Shifting Carriers	30.0	MODERATE	Stimuli-responsive bonus by release kinetics
P60	A	Swarm Nanorobotics Intelligence	15.0	LOW	Swarm capability (most carriers: no)
P61	A	Synthetic Clinical Trials & Virtual Hu	30.1	MODERATE	Virtual-cohort responder fraction
P62	A	Biobetter / Supergeneric Generator	65.0	LOW	Novelty distance from on-market CNS DDS

62 principles evaluated. Composite: 76.3/100 (GOOD)

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

Verdict: FAILED **Pass rate**: 39.3% (11/28 principles validated, threshold 70%)

Combined score (surrogate pass-through + real physics): 11/28 principles scored PASSED (39.3%). Of these, only 7/28 principles ran independent deep computation (passed 3/7 = 42.9%); 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	✗	53.4	53.38	LOW	Full MD stress simulation — surrogate value confirmed (
P02	✓	75.0	29.1	MODERATE	Multi-parameter allometric scaling (Mahmood 2007): half
P04	✗	27.1	0.1353	LOW	Full QM tunneling (QCElemental + ASE) — surrogate value
P08	✗	43.0	43.0	LOW	Full radical-chain reaction MD — surrogate value confir
P10	✓	60.0	60.0	MODERATE	Constant-pH MD simulation — surrogate value confirmed (
P11	✓	100.0	100	MODERATE	DFT bond dissociation energies — surrogate value confir
P12	✓	83.0	83.0	MODERATE	Stage-specific PBPK with full BBB physiology — surrogat
P13	✗	4.2	0.0021	MODERATE	3-compartment PBPK ODE (scipy.integrate.odeint): blood
P16	✗	48.0	48.0	LOW	CFD of 1000L bioreactor — surrogate value confirmed (fu
P18	✓	92.0	-9.2	HIGH	MM/GBSA-style ΔG estimate from validated ligand-recepto
P23	✓	80.0	80.0	MODERATE	CSP via DFT — surrogate value confirmed (full-physics H
P24	✗	59.6	59.64	LOW	Full CFD + MD coupling — surrogate value confirmed (ful
P29	✓	65.0	65	MODERATE	Full membrane-fusion MD — surrogate value confirmed (fu
P30	✗	45.0	45.0	LOW	Full QM/MM (PySCF or ORCA) — surrogate value confirmed
P31	✗	40.0	0.02	MODERATE	7-organ whole-body distribution with size + charge + li
P33	✗	54.6	54.6	LOW	Atomistic docking + SMD pulling — surrogate value confi
P38	✓	96.1	9.6	HIGH	Stokes-Einstein D = k_B·T/(6πηr) at 37°C, η_CSF = 7×10■
P40	✗	55.0	55	LOW	Full nasal cavity CFD — surrogate value confirmed (full
P41	✗	40.0	40	LOW	Full membrane mechanics MD — surrogate value confirmed
P43	✗	25.0	25	LOW	Full acoustic radiation force MD — surrogate value conf
P44	✗	0.0	0.0	MODERATE	4-compartment CNS-PBPK ODE with glymphatic clearance: B
P47	✗	73.8	-6.71	LOW — LI	LIE approximation (fallback — Vina unavailable)
P50	✓	71.5	71.5	MODERATE	Full coarse-grained MD lipid phase transition — surroga
P51	✓	60.0	60	MODERATE	Full radical-chain damage MD — surrogate value confirme
P57	✗	50.0	50	LOW	Full CFD of mixer geometry — surrogate value confirmed
P58	✓	80.0	80	MODERATE	Full QM/MM cascade simulation — surrogate value confirm
P59	✗	30.0	30	LOW	Full coarse-grained MD morphological transition — surro
P61	✗	30.1	30.0	LOW	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 11/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P32: Deep validation passed only 11/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P45: Deep validation passed only 11/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P55: Deep validation passed only 11/28 principles. Translational deliverables withheld until a higher-ranked DDS passes deep validation.

P56: Deep validation passed only 11/28 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	ApoE-LNP	FAILED	39.3%	—
#2	AAV9-vector	FAILED	32.1%	—
#3	RVG29-Liposome-pH	FAILED	39.3%	—

#1 ApoE-LNP — FAILED

Failure reason: Deep validation FAILED: only 11/28 principles validated (39.3%, threshold 70%). Critical failures: P01, P04, P08, P13, P16.

Transition reason: Falling back to rank #2 because deep physics showed insufficient evidence for this DDS.

Failed principles: P01, P04, P08, P13, P16, P24, P30, P31

#2 AAV9-vector — FAILED

Failure reason: Deep validation FAILED: only 9/28 principles validated (32.1%, threshold 70%). Critical failures: P01, P04, P08, P13, P16.

Transition reason: Falling back to rank #3 because deep physics showed insufficient evidence for this DDS.

Failed principles: P01, P04, P08, P13, P16, P18, P24, P30

#3 RVG29-Liposome-pH — FAILED

Failure reason: Deep validation FAILED: only 11/28 principles validated (39.3%, threshold 70%). Critical failures: P01, P04, P08, P13, P16.

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

Failed principles: P01, P04, P08, P13, P16, P24, P30, P31

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	PASS ✓	hERG/Nav/Cav QSAR
Clinical trial GO	NO-GO / REFORMULATE	Response 26% | AE 0.0%
Sterilization feasible	3 method(s)	Gamma 25Kgy
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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