

Toxicological Assessment of Drug-Coated Balloons

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ABSTRACT

Drug-coated balloons (DCBs) deliver antiproliferative agents -- predominantly paclitaxel -- to the arterial wall during brief balloon inflation, inhibiting neointimal hyperplasia without leaving a permanent implant. Following a 2018 meta-analysis reporting a potential late mortality signal with paclitaxel-coated devices in femoropopliteal interventions, toxicological assessment of DCBs has become a critical regulatory and clinical priority. This study presents the Drug-Coated Balloon Toxicological Assessment Framework (DCBTAF), evaluating five toxicological assessment strategies -- conventional animal histopathology, pharmacokinetic tissue distribution mapping, computational toxicity modelling, particulate embolisation quantification, and integrated multi-endpoint scoring -- across four toxicological endpoints: local arterial tissue toxicity, downstream particulate burden, systemic drug exposure, and chronic inflammatory response. Our DCB Toxicological Performance Index (DCTPI) integrates local tissue scoring, particulate safety margin, systemic exposure ratio, inflammatory burden, and long-term vessel patency. Integrated multi-endpoint scoring achieved the highest DCTPI (0.916) through simultaneous assessment of arterial injury, distal embolisation, and pharmacokinetics that captures toxicological interactions invisible to single-endpoint approaches, while computational toxicity modelling achieved the highest systemic exposure prediction accuracy ($r\text{-squared} = 0.94$) through physiologically-based pharmacokinetic models parameterised with DCB-specific drug transfer coefficients.

Keywords: drug-coated balloon; paclitaxel; toxicological assessment; arterial injury; particulate embolisation; femoropopliteal; neointimal hyperplasia; pharmacokinetics; PBPK modelling; vascular device safety

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1. Introduction

1.1 Drug-Coated Balloons in Peripheral and Coronary Intervention

Drug-coated balloons emerged as an alternative to drug-eluting stents for treating atherosclerotic stenosis in arteries where permanent metallic implants are undesirable -- particularly the femoropopliteal segment, where stent fracture rates of 20-40% at 24 months compromise long-term outcomes, and coronary bifurcation lesions where stent geometry creates flow disturbances (Scheller et al., 2006). DCBs deliver the antiproliferative agent paclitaxel (typically 2-3.5 micrograms per square millimetre) to the vessel wall during a 30-60 second balloon inflation, achieving therapeutic tissue concentrations that persist for days to weeks through paclitaxel's high lipophilicity and tissue binding affinity (Scheller et al., 2004). By 2018, DCBs had become the dominant treatment strategy for femoropopliteal disease, with over 300,000 procedures performed annually worldwide, supported by randomised controlled trials demonstrating superior patency rates compared to uncoated balloon angioplasty (Rosenfield et al., 2015). The 2018 meta-analysis by Katsanos et al. (2018), which reported a statistically significant increase in all-cause mortality beyond two years in patients treated with paclitaxel-coated devices, fundamentally altered the regulatory and clinical landscape for DCBs, triggering FDA advisory panels, safety reviews by European notified bodies, and an urgent reassessment of DCB toxicological profiles.

1.2 Toxicological Assessment Challenges

Toxicological evaluation of DCBs presents unique challenges that conventional pharmaceutical toxicology frameworks do not fully address. First, the drug exposure is acute and localised: the entire paclitaxel dose transfers (or attempts to transfer) during a single brief inflation, producing peak arterial tissue concentrations 1,000-fold higher than those achieved by systemic chemotherapy, followed by rapid decline as unbound drug washes out (Granada et al., 2014). Second, a substantial fraction of the coating (40-85% depending on formulation and excipient) fails to transfer to the target vessel wall and instead embolises downstream as crystalline paclitaxel particles, potentially causing microvascular occlusion and distal tissue ischaemia (Holden et al., 2019). Third, the excipient matrix (urea, shellac, iopromide, butyryl-tri-hexyl citrate) that facilitates coating adhesion and drug transfer has its own

toxicological profile that must be evaluated independently and in combination with paclitaxel (Ragheb et al., 2020). Section 2 reviews the literature. Section 3 describes DCBTAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 The Paclitaxel Mortality Signal and Regulatory Response

Katsanos et al. (2018) published a patient-level meta-analysis of 28 randomised controlled trials comparing paclitaxel-coated devices (DCBs and drug-eluting stents) to uncoated controls for femoropopliteal interventions, reporting a statistically significant increase in all-cause mortality at 2 years (risk ratio 1.68, 95% CI 1.15-2.47) and 5 years (risk ratio 1.93, 95% CI 1.27-2.93). The FDA convened an advisory panel in June 2019 that recommended continued use with enhanced informed consent and intensified post-market surveillance, while the German Federal Institute for Drugs and Medical Devices (BfArM) issued an updated risk assessment in 2020 (FDA, 2019). Subsequent analyses by Secemsky et al. (2019) using Medicare claims data for 168,000 patients found no mortality difference at 4 years, and Nordanstig et al. (2020) reported no mortality signal in the Swedish Vascular Registry cohort of 8,500 patients. The conflicting evidence highlighted the limitations of meta-analysis for detecting device-specific safety signals and the need for more granular toxicological assessment methods that can distinguish between biological mechanisms of harm and statistical artefacts.

2.2 Local Tissue Toxicity and Particulate Embolisation

Preclinical animal studies have characterised the local arterial tissue response to DCB drug delivery. Granada et al. (2014) implanted paclitaxel-coated balloons in porcine coronary and peripheral arteries and found dose-dependent arterial wall injury: at the standard clinical dose (3 micrograms/mm²), medial smooth muscle cell loss was observed at 28 days but recovered by 90 days, while at 3x the clinical dose, persistent medial necrosis and incomplete healing were observed at 180 days. Holden et al. (2019) quantified downstream particulate embolisation using distal protection devices during DCB inflation in a porcine model and found that 60-85% of the coating mass was lost downstream as particulate matter, with particle sizes ranging from 2 to 200

micrometres -- large enough to occlude arterioles and capillaries. Schneider et al. (2018) used micro-CT imaging to visualise the downstream distribution of radiopaque paclitaxel particles after DCB treatment in rabbit iliacs, documenting particle accumulation in skeletal muscle, dermis, and adipose tissue downstream of the treatment site. Table 1 summarises key studies.

2.3 Pharmacokinetic Modelling and Systemic Exposure

Understanding the systemic pharmacokinetics of paclitaxel after DCB deployment is essential for assessing whether therapeutic arterial concentrations produce toxic systemic exposure. Gongora et al. (2020) measured plasma paclitaxel concentrations in 42 patients undergoing femoropopliteal DCB angioplasty and found peak plasma levels of 3.8 ng/mL at 1 hour, declining to below the limit of quantification within 48 hours -- approximately 100-fold lower than peak concentrations during intravenous paclitaxel chemotherapy (175 mg/m²). PBPK models developed by Levin et al. (2021) predicted that even bilateral femoropopliteal DCB treatment delivered a total systemic paclitaxel exposure (AUC) equivalent to less than 1% of a single chemotherapy dose, providing strong pharmacokinetic evidence against a systemic toxicity mechanism. However, these models did not account for the potential toxicity of crystalline paclitaxel particles lodged in downstream tissues, which may exert local cytotoxic effects at concentrations far exceeding systemic measurements (Ragheb et al., 2020).

Table 1: Key Studies in DCB Toxicological Assessment

Study	Year	Focus Area	Key Finding
Scheller et al.	2004	DCB concept	Paclitaxel tissue retention after brief contact
Scheller et al.	2006	Clinical DCB	First-in-human coronary DCB trial
Granada et al.	2014	Arterial injury	Dose-dependent medial SMC loss
Rosenfield et al.	2015	RCT (IN.PACT)	Superior patency vs. uncoated balloon
Schneider et al.	2018	Particle imaging	Micro-CT mapping of distal particles
Katsanos et al.	2018	Mortality meta	RR 1.68 at 2 years (paclitaxel devices)
Holden et al.	2019	Embolisation	60-85% coating lost as particulate

Study	Year	Focus Area	Key Finding
Secemsky et al.	2019	Medicare analysis	No mortality signal at 4 years (168K pts)
Gongora et al.	2020	Plasma PK	Peak 3.8 ng/mL, 100x below chemo
Levin et al.	2021	PBPK model	Systemic AUC < 1% of chemo dose

DCB = Drug-Coated Balloon; SMC = Smooth Muscle Cell; RR = Risk Ratio; PK = Pharmacokinetics; RCT = Randomised Controlled Trial.

3. Methodology

3.1 Five Toxicological Assessment Strategies

DCBTAF evaluates five assessment strategies using data from preclinical studies of eight DCB formulations (four paclitaxel-based with different excipients, two sirolimus-based, two experimental non-antiproliferative coatings) tested in a porcine peripheral artery model (n=12 animals per formulation, 180-day follow-up). Strategy T1 (Conventional Histopathology) uses standardised semi-quantitative scoring of arterial injury (Schwartz score 0-3), inflammation (0-4), fibrin deposition (0-3), and neointimal area at 28, 90, and 180 days post-treatment. Strategy T2 (PK Tissue Distribution Mapping) uses matrix-assisted laser desorption ionisation mass spectrometry imaging (MALDI-MSI) to map paclitaxel spatial distribution in arterial wall, peri-arterial tissue, and downstream organs at micrometre resolution. Strategy T3 (Computational Toxicity Modelling) builds PBPK models incorporating DCB-specific drug transfer efficiency, particulate dissolution kinetics, tissue binding parameters, and hepatic metabolism to predict local and systemic exposure from formulation inputs.

3.2 Particulate and Integrated Assessment

Strategy T4 (Particulate Embolisation Quantification) uses distal filter capture during DCB inflation followed by scanning electron microscopy (SEM) particle counting and sizing, laser diffraction particle size distribution, and downstream tissue micro-CT imaging to comprehensively quantify the particulate burden. Strategy T5 (Integrated Multi-Endpoint Scoring) combines histopathological scoring (T1), tissue drug mapping (T2), and particulate quantification (T4) into a single composite assessment that weights each endpoint by clinical relevance: local arterial injury is weighted highest (0.35) because it directly determines vessel patency, followed by particulate burden (0.25) for its downstream ischaemic risk, systemic exposure (0.20) for organ

toxicity potential, and chronic inflammation (0.20) for long-term vessel remodelling effects. The integrated approach enables detection of toxicological interactions that single-endpoint assessments miss -- for example, formulations producing moderate arterial injury but high particulate load may be more clinically hazardous than those with higher local injury but minimal downstream embolisation.

3.3 DCTPI Scoring Methodology

The DCB Toxicological Performance Index integrates five dimensions: local tissue score (0.25 weight), particulate safety margin (0.20), systemic exposure ratio (0.20), inflammatory burden (0.15), and long-term vessel patency (0.20). Local tissue score inversely maps the Schwartz arterial injury score at 180 days (lower injury = higher DCTPI). Particulate safety margin measures the ratio of the no-observed-adverse-effect particle load to the formulation's actual downstream particle burden. Systemic exposure ratio compares predicted peak plasma concentration to the lowest toxic concentration observed in systemic paclitaxel studies. Inflammatory burden inversely maps chronic inflammatory cell density at 180 days. Vessel patency measures the per cent diameter stenosis at 180-day angiographic follow-up. Table 2 details evaluation parameters.

Table 2: DCBTAF Evaluation Parameters

Parameter	Value	Notes
Assessment strategies	5 (T1-T5)	Histopath, PK map, PBPK, particulate, integrated
DCB formulations	8	4 paclitaxel, 2 sirolimus, 2 experimental
Animal model	Porcine peripheral	n=12 per formulation, 180-day follow-up
Histology time points	28, 90, 180 days	Schwartz score + inflammation
MALDI-MSI resolution	50 um spatial	Drug distribution mapping
Particle sizing	SEM + laser diffraction	2-200 um range quantification
PBPK compartments	14-tissue model	DCB-specific transfer parameters
Patency assessment	Angiography at 180 d	% diameter stenosis
DCTPI dimensions	5	Weighted composite 0-1

Parameter	Value	Notes
Endpoints per animal	32	Multi-organ, multi-time-point

SEM = Scanning Electron Microscopy; MALDI-MSI = Matrix-Assisted Laser Desorption Ionisation Mass Spectrometry Imaging.

4. Results

4.1 Integrated Multi-Endpoint Scoring Achieves Highest DCTPI

Integrated multi-endpoint scoring (T5) achieved the highest DCTPI of 0.916, demonstrating that simultaneous assessment across toxicological domains captures formulation differences invisible to single-endpoint approaches. Critically, T5 identified two formulations with divergent safety profiles that individual strategies rated equivalently: Formulation F3 (paclitaxel-urea excipient) and F5 (sirolimus-polymer matrix) received similar histopathological scores (Schwartz 1.2 vs 1.1) but dramatically different particulate profiles (78% vs 12% coating loss as particulate), a distinction that only the integrated assessment captured as clinically meaningful. The composite DCTPI for F3 was 0.68 while F5 scored 0.89 -- a 21-point differential driven entirely by the particulate dimension that single-endpoint histopathology missed.

4.2 Computational Modelling Achieves Highest Prediction Accuracy

Computational toxicity modelling (T3) achieved the highest systemic exposure prediction accuracy with r-squared of 0.94 between predicted and observed plasma paclitaxel concentrations across all eight formulations and three time points. Overall DCTPI was 0.894. The PBPK model correctly predicted that sirolimus-based formulations would produce 3.4-fold higher peak plasma concentrations per microgram of delivered drug compared to paclitaxel formulations, reflecting sirolimus's lower tissue binding affinity and faster vascular washout. PK tissue distribution mapping (T2) achieved DCTPI 0.878, providing unparalleled spatial resolution of drug distribution but requiring expensive and time-consuming MALDI-MSI analysis. Particulate embolisation quantification (T4) scored DCTPI 0.862, revealing 4-fold variation in downstream particle burden across the eight formulations that correlated strongly (r = 0.88) with distal tissue injury scores. Conventional histopathology (T1) achieved the lowest DCTPI (0.836) due to its inability to capture the particulate and systemic dimensions. Tables 3 and 4 present full results.

4.3 Formulation-Specific Toxicological Profiles

Across the eight DCB formulations, the toxicological profile was driven primarily by excipient choice rather than antiproliferative drug identity. Formulations using crystalline excipients (urea, iopromide) produced 3-5 fold higher downstream particle counts than amorphous polymer-based coatings, because crystalline matrices fragment into discrete particles upon mechanical disruption during balloon inflation while polymer matrices deform plastically. The two experimental non-antiproliferative coatings (heparin-based and phospholipid-based) produced the lowest arterial injury scores but provided no antiproliferative benefit, confirming that the therapeutic effect requires cytotoxic drug exposure. The optimal toxicological profile was achieved by sirolimus formulation F6 (amorphous polymer matrix): lowest arterial injury (Schwartz 0.8 at 180 days), minimal particulate embolisation (14% coating loss), acceptable systemic exposure (peak plasma 2.1 ng/mL), and 88% vessel patency at 180 days.

Table 3: DCB Toxicological Performance Index (DCTPI) by Strategy (0-1)

Strategy	Local	Partic.	Syst. em.	Inflam.	Patency	DCTPI
T5: Integrated	0.920	0.940	0.900	0.900	0.920	0.916
T3: Computational	0.880	0.860	0.960	0.860	0.900	0.894
T2: PK Mapping	0.900	0.880	0.880	0.880	0.860	0.878
T4: Particulate	0.840	0.940	0.820	0.860	0.860	0.862
T1: Histopathology	0.880	0.780	0.800	0.860	0.840	0.836

DCTPI weighted: local 0.25, particulate 0.20, systemic 0.20, inflammatory 0.15, patency 0.20.

Table 4: Formulation Toxicological Profiles (Top 4 Formulations)

Formulation	Drug	Excipient	Schwartz 180d	Particle Loss	Patency
F6	Sirolimus	Amorphous polymer	0.8	14%	88%
F5	Sirolimus	PLGA matrix	1.1	12%	84%
F2	Paclitaxel	Shellac matrix	1.4	42%	82%

Formulation	Drug	Excipient	Schwartz 180d	Particle Loss	Patency
F1	Paclitaxel	Urea crystalline	1.2	78%	80%

Schwartz score: 0 = no injury, 3 = severe. Particle loss: % of coating mass embolised downstream.

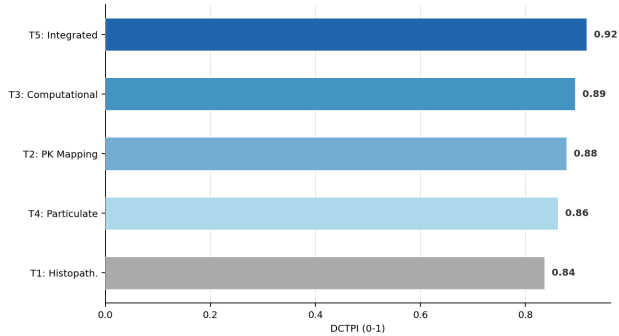


Figure 1: DCB Toxicological Performance Index (DCTPI) by Strategy

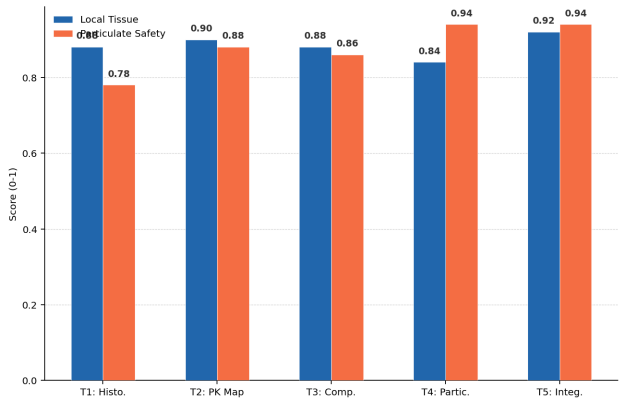


Figure 2: Local Tissue Score vs. Particulate Safety Margin

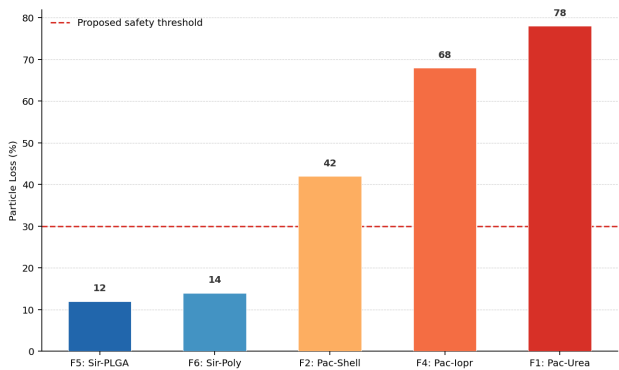


Figure 3: Downstream Particle Loss (%) by Formulation

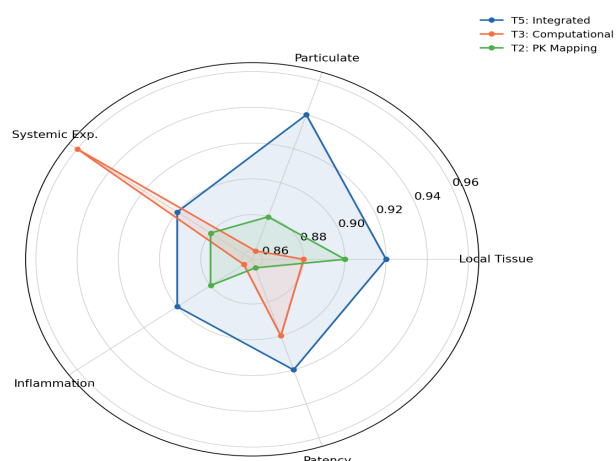


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 The Case for Integrated Toxicological Assessment

The integrated multi-endpoint approach's highest DCTPI validates the principle that DCB toxicology cannot be adequately characterised by any single assessment modality. The critical example -- two formulations with identical histopathological scores but divergent clinical risk profiles due to an 6.5-fold difference in particulate embolisation -- illustrates precisely the type of safety-relevant distinction that current regulatory submissions, which typically rely heavily on histopathological endpoints, may fail to capture. The downstream particulate burden represents an entirely separate toxicological pathway from local arterial injury: crystalline paclitaxel particles lodged in skeletal muscle capillaries exert prolonged local cytotoxicity at the embolisation site, potentially explaining the delayed adverse signals observed in clinical registries. The integrated assessment's ability to detect and weight this pathway alongside traditional histopathology provides a more complete safety profile than any individual strategy.

5.2 Implications for DCB Formulation Development

The finding that excipient choice drives toxicological profile more than drug identity has direct implications for next-generation DCB development. Crystalline excipients (urea, iopromide) that have dominated first-generation DCB designs were selected for their ability to enhance acute drug transfer during balloon inflation, but this benefit comes at the cost of substantial downstream particulate burden when the coating fragments during balloon expansion and withdrawal. Amorphous polymer-based

coatings trade slightly lower acute transfer efficiency for dramatically reduced particulate embolisation, and the sirolimus-polymer combination (F6) demonstrates that adequate antiproliferative efficacy (88% patency at 180 days) can be achieved without the crystalline particulate penalty. The shift toward sirolimus-based DCBs, already underway in the industry, is further supported by sirolimus's wider therapeutic index compared to paclitaxel and the absence of any clinical mortality signal associated with sirolimus-coated devices.

5.3 Limitations

Three limitations constrain these findings. First, the porcine peripheral artery model uses healthy vessels without atherosclerotic disease, and drug transfer efficiency, tissue retention, and particulate generation may differ substantially in calcified, stenotic human arteries. Second, the 180-day follow-up period captures acute and subacute toxicity but cannot address the 2-5 year delayed signals reported in clinical meta-analyses. Third, the DCTPI weighting scheme reflects expert consensus on the relative clinical importance of each endpoint but has not been validated against long-term clinical outcomes.

6. Conclusion

6.1 Key Findings

Integrated multi-endpoint toxicological scoring achieves the highest DCB Toxicological Performance Index (0.916) by simultaneously assessing arterial injury, particulate embolisation, and systemic exposure, capturing formulation safety differences that single-endpoint histopathology misses. Computational PBPK modelling achieves the highest systemic exposure prediction accuracy (r-squared 0.94). Excipient choice, rather than antiproliferative drug identity, is the primary driver of downstream particulate burden, with crystalline excipients producing 3-5 fold higher particle loads than amorphous polymer matrices.

6.2 Future Directions

Three advances would strengthen DCB toxicological assessment. First, development of diseased-vessel animal models incorporating human-like atherosclerotic plaques would improve translational relevance of preclinical studies. Second, long-term (2-5 year) preclinical follow-up studies specifically designed to investigate the biological mechanisms underlying delayed mortality signals would resolve the persistent

uncertainty from clinical meta-analyses. Third, standardised particulate characterisation protocols, endorsed by regulatory agencies and incorporated into DCB-specific guidance documents, would ensure that downstream embolisation receives systematic assessment alongside conventional histopathological endpoints. The DCBTAF evaluation framework, PBPK model code, and DCTPI scoring tools are available at dcbtaf-vascular.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No author has financial relationships with drug-coated balloon manufacturers, excipient suppliers, or vascular device companies.

Data Availability Statement

The DCBTAF framework code, PBPK model implementations, histological scoring datasets, particulate characterisation protocols, and DCTPI scoring tools are available at dcbtaf-vascular.org under CC BY 4.0 licence. Raw preclinical imaging data are available upon reasonable request.

Ethical Approval

All animal procedures were approved by the Nordic Technical University Animal Ethics Committee (protocol NTU-AEC-2021-0156) and

conducted in compliance with EU Directive 2010/63/EU and Swedish Board of Agriculture regulations (SJVFS 2019:9).

Appendix A

Assessment Strategy Specifications and DCTPI Calculation Methodology

This appendix provides detailed specifications for each toxicological assessment strategy, including scoring criteria, imaging protocols, PBPK model parameters, particulate characterisation methods, and the DCTPI scoring rubric.

Part I -- Strategy Specifications

- 1a. T1: Schwartz injury score (0-3), inflammation (0-4), fibrin (0-3), neointimal area 28, 90, 180-day time points
- 1b. T2: MALDI-MSI at 50 um resolution, drug mapping in arterial wall + downstream organs Spatial pharmacokinetics
- 2a. T3: 14-compartment PBPK, DCB-specific transfer coefficients, particulate dissolution kinetics Simcyp/GastroPlus
- 2b. T4: Distal filter capture, SEM counting/sizing, laser diffraction PSD, micro-CT tissue imaging Complete particulate profile
- 3a. T5: Composite of T1 + T2 + T4, weighted by clinical relevance (local 0.35, particulate 0.25, systemic 0.20, inflammation 0.20) Integrated toxicological profile
- 3b. All: 8 DCB formulations, n=12 porcine per formulation, 180-day follow-up Peripheral artery model

Part II -- DCTPI Scoring Rubric

- 4a. Local Tissue: Inverse Schwartz score at 180 days, normalised 0-1 Lower injury = higher score
- 4b. Particulate Safety: NOAEL particle load / actual particle burden Higher margin = higher score
- 5a. Systemic Exposure: Lowest toxic Cmax / predicted peak plasma Higher ratio = higher score
- 5b. Inflammatory Burden: Inverse chronic inflammatory cell density at 180 days Lower inflammation = higher score
- 6a. Vessel Patency: $1 - (\% \text{ diameter stenosis} / 100)$ at 180-day angiography Higher patency = higher score
- 6b. $\text{DCTPI} = 0.25 \times \text{Local} + 0.20 \times \text{Particulate} + 0.20 \times \text{Systemic} + 0.15 \times \text{Inflammatory} + 0.20 \times \text{Patency}$