Regulatory Briefing Note – Case Study 2

Study Title: 90-Day Inhalation Toxicity of PG/VG with and without Nicotine in Sprague Dawley Rats

Study Type: Non-clinical (OECD TG 413) with Systems Toxicology Integration

Date: [Insert Date]

# 1. Study Overview

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| --- | --- |
| Attribute | Details |
| Species | Sprague Dawley rats |
| Duration | 90 days (OECD TG 413 compliant) |
| Arms | Standard Toxicology (10 rats/sex/group); Systems Toxicology (6 females/group) |
| Groups | 8: Air, Saline, PG/VG (Low, Med, High), PG/VG + Nicotine (Low, Med, High) |
| Endpoints | Clinical observations, hematology, organ weights, histopathology, lung/nasal transcriptomics |

# 2. Key Findings

- Dose-dependent changes observed in respiratory tissues for PG/VG groups

- Transcriptomic alterations involved oxidative stress and xenobiotic metabolism pathways

- Nicotine (0.023 mg/L) modified gene expression but had minimal systemic toxicity impact

# 3. Limitations

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| --- | --- |
| Area | Detail |
| Omics Design | Transcriptomics performed only in females – no male molecular data |
| Group Design | No nicotine-only group to isolate nicotine-specific effects |
| Controls | Saline vehicle may not fully isolate PG/VG vehicle effects |

# 4. Statistical Enhancements (Low–Moderate Resource Impact)

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| --- | --- | --- |
| Enhancement | Purpose | Regulatory Value |
| ANCOVA | Adjust for baseline weight/clinical values | Controls confounding; improves precision |
| Mixed Effects Models | Handle repeated measures (e.g., weight over time) | Accounts for within-animal variability |
| Effect Size Reporting | Emphasize biological relevance (e.g., Cohen’s d) | Improves interpretation beyond p-values |
| Principal Component Analysis (PCA) | Visualize group separation and detect outliers | Aids exploratory review and QC |
| Sensitivity Analysis | Assess model robustness | Supports reproducibility and transparency |
| Power Analysis | Estimate the ability to detect meaningful effects and justify sample size | Strengthens interpretation of null results; supports study design rationale |

# 5. Regulatory Submission Readiness

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| --- | --- |
| Element | Status |
| OECD Compliance | ✅ TG 413 format met |
| GLP Standards | ✅ [Confirm if GLP-compliant] |
| SEND Formatting | ⚠️ Required for toxicology data |
| Raw Omics Submission | ⚠️ Required: .CEL/.FASTQ files + processing pipeline |
| Sex Representation | ⚠️ Omics restricted to females; justification needed |
| Mode of Action Analysis | ✅ Pathway enrichment provided; consider BMD modeling |

# 6. Recommendations

- Integrate mixed models and ANCOVA in final analysis to improve interpretability

- Justify female-only systems toxicology or expand to include males in future studies

- Include SEND datasets, effect sizes, and sensitivity analyses in formal regulatory dossier