CMC Development Memo: SEI-DNL343v2 Oscillatory Formulations

1. Introduction

This document outlines the preliminary Chemistry, Manufacturing, and Controls (CMC) considerations for the SEI-DNL343v2 sustained-release and oscillatory delivery formulations. These designs aim to resolve pharmacodynamic challenges identified in the failed DNL343 program by engineering time-controlled ISR inhibition in the CNS while minimizing glial toxicity and peripheral stress responses.

2. Formulation Concepts

- Formulation A: PLGA matrix microencapsulation with programmed degradation profile (sustained release).
- Formulation B: Layered osmotic pump tablet for biphasic (pulsed) ISR inhibition.
- Formulation C: PEGylated nanoparticle delivery with stimulus-responsive pulsation (heat/light).

Each candidate aims to create a plasma concentration-time curve that oscillates within a defined ISR-correction window.

3. CMC Development Plan

Phase 1:

- Define target pharmacokinetic profile (Cmax, Tmin, Tmax, AUC)
- Select initial release platform via in silico simulation overlay
- Synthesize small batches of each prototype

Phase 2:

- Conduct in vitro release studies (PBS, serum conditions)
- Analyze degradation profile (HPLC, NMR, DLS, SEM)

- Conduct initial in vivo PK study (rodent model)

Phase 3:

- Scale-up optimization (GMP pilot batch)

- Stability testing under ICH conditions

- Complete specification sheet: assay, content uniformity, release kinetics, residual solvents, endotoxin

4. Regulatory Strategy

A Type C FDA meeting will be requested to present the proposed oscillatory PK rationale and delivery approach. Discussion points will include justification of novel release profiles, planned CMC documentation, and early agreement on specification windows and testing strategies. Comparability studies will be required if transitioning from sustained to pulsatile form during IND amendment.