# *Compound Guidelines for NCE Candidacy*

## *I. Chemistry*

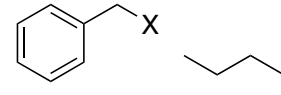
### *A. Proven structure [requirement], single stereoisomer [guideline]*

### *B. Ownership: Structure is outside others' generic scope [guideline] and is new [requirement]*

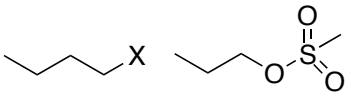
### *C. Drug–likeness [guideline]*

### *D. Absence of reactive functional groups [guideline]*

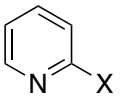
***Latent***




*Benzyl halide*

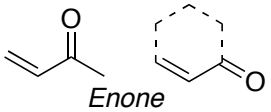



*Alkyl halide, sulfonate*




*2 or 4-Halopyridine*


*Epoxide (oxirane)*




*Enone*
*($\alpha,\beta$-unsatd ketone)*

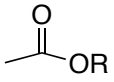
*Enoate*
*Enal*
*Vinyl nitrile*
*Vinyl sulfone*


*Aldehyde*


*Thiol*

*Metal Chelators*

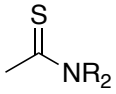
***Metabolic***



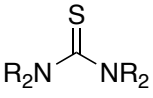

*Ester*



*Alkyne*



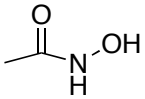

*Thioamide*



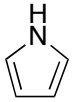

*Thiourea*




*Nitro*



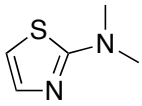

*Hydroxamate*




*Pyrrole*

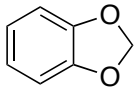

*Furan*


*Thiophene*

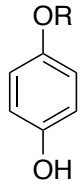



*2-Aminothiazole*

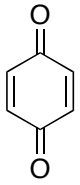

*Hydrazine*



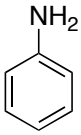

*Benzodioxolane*



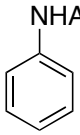

*4-Alkoxyphenol*



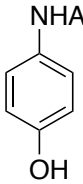

*Quinone*



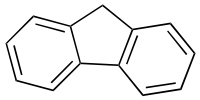

*Aniline*




*Acetanilide*




*p-Hydroxy-*
*acetanilide*



*Fluorene*
*(& other PAH)*

### *E. Practical process–scale synthesis [requirement]*

1. ***Synthesis is concise (<10 linear steps)***
2. ***Intermediate chemistry is scaleable (reagents, safety)***
3. ***Starting materials are reliable***
4. ***COG (cost of goods) affordable***
5. ***Final product (API, active pharmaceutical ingredient) has reproducible purity***
6. ***Impurities are known & characterized (safety)***

### *F. Pharmaceutics*

1. ***Acceptable crystalline polymorph for formulation (purity & physical properties)***
    1. ***Solubility (good 0.5 mg mL$^{-1}$ water pH 6.5, better 2 mg mL$^{-1}$)***
    2. ***mp > 125 °C***
    3. ***Thermal stability at rt (2 y solid form shelf life = <0.5% change 40 °C, 40 d)***
    4. ***Non-hygroscopic***
    5. ***Nota bene pharmaceutical formulation preference:***
        ***carboxylic acid, strong amine salt > weak acid, amine salt > neutral***

# *Compound Guidelines for NCE Candidacy*

*[continued]*

## *II. Pharmacokinetics*

### *A. Absorption*

1. *Good (>25%) cell culture permeability, minimal transporter efflux (in vitro assay)*
2. *Reasonable rodent dosing to >10x predicted efficacious exposure*
3. *Validate w canine & primate (%F & blood level) to 1x predicted efficacious exposure*

### *B. Clearance*

1. *Predict satisfactory human clearance from rodent, canine, primate (≤ 10 mL $min^{-1}$ $kg^{-1}$)*
2. *%F > 30%* after *first-pass metabolism*
3. *First pass oxidative metabolism <30% by liver P450 polymorphs Cyp2D6 & Cyp2C19*
4. *$IC_{50}$ of > 3 µM for major P450 isozymes (or >1000x target $IC_{50}$)*
5. *Clearance kinetics consistent with projected dosing & pharmacological exposure*

### *C. Plasma Binding (by albumin and $\alpha$-1 glycoprotein) is <99% (all safety animals).*

1. *<95% acceptable, 96–99% workable (can be beneficial), >99% unacceptable)*

### *D. Metabolites*

1. *Major animal metabolites are known (safety, efficacy, IP issues assessed)*

### *E. Mechanism of action & Biomarker identification*

1. *Discrete target (human target isolated & profiled, compare to other safety animals)*
2. *Target polymorph issues assessed*
3. *Biomarker identified*
   a. *Using the target or target sequelae*
   b. *Using the physiological response*
   c. *Using precedent (new drug exposure compared to known efficacious drug)*

## *III. Safety*

### *A. Safety (in vitro assays)*

1. *>100x $IC_{50}$ selectivity compared to receptor/enzyme subtypes*
2. *Genetic toxicology negative (GeneTox)*
   a. *Non–mutagenic Ames bacterial [non-GLP]*
   b. *Negative in mammal chromosomal DNA damage assay [non-GLP]*
3. *hERG negative (<20% cardiovascular ion channel at 100x efficacious plasma level)*
4. *Clean in non-target human receptor profiling*

### *B. Safety (pharmacological assays)*

1. *No distress in vivo, no adverse drug effect ex vivo in animals (e.g. canine whole animal cardiovascular evaluation, large animal target pharmacology: identify best animal parallel to human PK/PD projection)*