LEAD CHEMICAL SERIES SELECTED

GLOBAL DRUG DEVELOPMENT

Goals/Definition

Selection of lead series that meet criteria for progression to Lead Optimization.
Drug target validated and lead identified for optimization.**

CRITERIA	SAMPLE CONTENT REQUIREMENT	GUIDELINES FOR LEVEL OF DETAIL NEEDED AT EACH GATE
▪ Screening Strategy Established and Target validated (if possible)	a) Mechanism of action & target validation (e.g., biomarkers, assays, *in vitro* / *in vivo* assessments, etc.)** b) Lead identification strategy defined • Lead identification screening process (e.g., compound library, HTS, computer-based design, combinatorial chemistry, assays, phenotypic *in vitro* / *in vivo* assessments, etc.) • Selection criteria for 'actives' • Screening cascade strategy	▪ Summary of key data to substantiate conclusions ▪ Illustrative data tables or figures may be reported in an appendix
▪ Lead identification *** CMC experts should be engaged to assess physicochemical properties**	a) Screening assays (developed and validated) b) Profile hits (e.g., binding affinity, dose-response, specificity, assays, *in vitro* assessments, etc.) c) Structure-activity relationships d) Assessment of physicochemical properties* e) For phenotypic hits, mechanism of action defined if feasible f) Off-target profiling (e.g., secondary pharmacology, hERG, cytotoxicity, etc.) g) Assessment of reactive metabolite liability h) Drug-drug interaction considerations i) Lead optimization strategy defined	▪ Summary of key data to substantiate conclusions ▪ Illustrative data tables or figures may be reported in an appendix

**** It is understood that not all programs will be able to validate the target at this stage in the process**