Appendix 3: Due Diligence Check list

Supplier Qualification			
Due Dilligence Check list			
Subject	**information requested**	**compliance Y/N**	**Remarks / Follow up**
General Project Information	Molecular structure of the material		
	Toxicity and/or genotoxicity,		
	Intended therapeutic area,		
	Current phase of availability (clinical / commercial / generic,…)		
	Timelines & milestones till filing		
	Forecast:		
	Short term (before launch)		
	Long term (after launch)		
	Sufficient capacity to assure supply chain		
	Intended dosage of the drug		
	Intended route of administration of the drug		
	Sterile or non-sterile material		
	Description of intermediates steps		
	Anti Counterfeiting measurements		
	Audit sustainability (qualification of the total supply chain)		
	Compliance: Previous inspections by Health Authorities		
	Inspectional history		
	Observations		
	Corrective actions implementation		
	Quality System		
	Organization chart of the Quality Unit		
	High level quality & compliance policies (e.g. validation policy)		
	Responsibilities of the Quality Unit		
	Personnel qualification/training program (cGMP)		
	Quality System (policies & procedures management system)		
	Internal audit program		
	Periodic quality review systems		
	Complaint handling system		
	Deviations / failure investigation system		
	Batch record review system		
	Validation policy / master validation plans or protocols		
	Management of Change (Change Control) system		
	Management of Contract manufacturers (if applicable)		

Quality Systems			
	Use of Quality By Design		
	Continuous Quality Improvement		
	Quality system certification (copy of certificate, date of last inspection)		
	Use of Risk Management		
	Facilities & Equipment		
	Visit to manufacturing unit(s)		
	Contamination prevention measures		
	Equipment qualification system		
	Facility qualification / environmental controls (HVAC, area classification)		
	Utilities qualification (water system, gases)		
	Equipment cleaning & cleaning validation program		
	Preventive maintenance & calibration programs		
	Computer systems validation plans & part 11 compliance		
	Equipment cleaning & use records		
	Documentation & Records		
	Master production instructions and batch production records Definition of criticality (processes/parameters)		
	Laboratory (quality control) records		
	Specification management system		
	Materials Management		
	Sampling and testing of incoming materials		
	Quarantine system / handling of rejects		
	Materials storage		
	Laboratory controls		
	Visit QC laboratory		
	Lab equipment qualification procedure		
	Equipment maintenance / calibration program		
	Reference standards management procedure		
	Purity and Assay method validation		
	Stability program overview		
	Microbiological testing		
	Production		
	Process validation master plans or protocols		
	Validation report		
	In process sampling & testing		
	Periodic review of validated systems		
	Packaging & Labelling procedures		
	closure integrity assurance		

	label reconciliation		
Plant Tour	Complete manufacturing flow (including warehouses) and supply chain flow		
	Equipment spaces (easy to handle cleaning and technical interventions)		
	Contamination prevention		
	multipurpose or dedicated area's		
	Utilities: Water system, HVAC, Nitrogen, Steam, Cool media		
	Equipment calibration and maintenance (production and QC)		
	Available production capacity		
Documentation	Organization of the Quality Unit		
	Validation approach and execution		
	Process		
	Methods		
	Cleaning		
	Equipment Qualification		
	Facilities (HVAC, water, air, nitrogen, etc.)		
	Documents and records		
	master records		
	batch production records		
	laboratory records		
	Record Retention and Archiving		
	Rework/reprocessing		
	Training and personnel qualification		
	Quality systems (change control, deviation handling, failure investigations, stability program, etc.)		
	Regulatory inspection documents (FDA 483s, EMEA inspection observations, FDA EIRs, etc.)		
	critical parameters		
	specification setting		
	Technology Transfer approach and Technology transfer reports		
Process			
Syntheses	synthesis description		
	synthesis scheme		
	Critical / Key reagents, solvents & building blocks		
	Yield per step		
	Overall yield		
	Number of steps		
	Regulatory status (starting material, critical intermediates and critical raw materials)		
	Extreme conditions (temperature, pressure, reagents, ...		
	Special equipment required		
	Critical parameters (edge of failure testing)		

Chemical S	Critical process parameters and their associated critical quality attributes		
	Quality of used reagents and solvents		
	Robustness		
	building blocks		
	Supplier (main supplier, back-up suppliers)		
	Manufacturing site of the supplier (Source)		
	Availability		
	Synthesis of the building blocks		
	Supplier qualification or plan		
	Alternative synthetic routes		
	Chemical development history/report		
Bio Chemical	Manufacturing process: Cell culture or Fermentation,		
	Recombinant DNA used		
	Irradiation or Chemical mutagenesis		
	Cultivation Process		
	Purification Process		
	Raw materials (media, buffers,…)		
	Bioburden controls		
	Viral contamination prevention controls		
	Endotoxin controls		
	Working cell bank maintenance		
	Proper inoculation and culture expansion		
	Process monitoring		
	Aseptic conditions		
ufacturing Process Chemical & Bio	Processing ability		
	Process capability		
	Process robustness		
	Process flow diagram availability		
	Process trendings (Yield, Quality, …)		
	Rework / Reprocess		
	Process Cycle times per step and total cycle time from starting building blocks		
	Co-operation or outsourcing activities		
	Disaster plan availabl		
	Alternate suppliers of critical raw materials identified		
	Production capacity/year		
	Cleaning procedures and limit setting		
	Validation protocols and reports		
	Multi-purpose or a dedicated facility		

Manu	If multi-use: what other product types are produced at this site,		
	chemicals, hormones, steroids, cytotoxics, other high potency drugs, …		
	Type of equipment is used per step (glass-lined, SS, Hastelloy)		
	Process hold points		
Physical Properties	Melting point		
	Solubility profile		
	Polymorphism, documentation on most stable polymorph		
	Salts & hydrates		
	Hygroscopicity		
	Crystallinity		
	Density		
	Bulk volume Particle size		
Analytics & Stability	Stability indicating methods		
	Optical methods available if necessary		
	Micro biological testing if required (Micro load, endotoxine, viral, …)		
	Analytical methods validated		
	In-process controls validated		
	Stability test results at required conditions		
	Identification, characterization and specification of impurities and/or degradation products		
	specifications and justification		
	Residual solvents		
	Residual catalyst		
	Particle size specifications		
	Sample evaluation		
	Use testing		
Regulatory & Economics	**Regulatory**		
	IND, CTA, CTX or other regulatory filing availability		
	Regulatory history and corrective actions		
	Regulatory CM&C meetings performed		
	Intended countries to be filed in,		
	Evaluation of the patent situation		
	Economics		
	actual cost price (DS, building blocks, …)		
	Identification and evaluation of the cost drivers		
	Maximum cost price		
	SHE system certification (e.g. ISO 14001)		
	Industrial Hygiene aspects		

Safety, Health & Environment	Thermal stability		
	Synthesis steps with extreme conditions (temperature, pressure, reagents)		
	Product & process safety issues		
	Minimum Ignition Energy		
	Dust explosion constant		
	Calorimetric information		
	DSC (exotherm processes)		
	Self-ignition temperature		
	Treatability and destination of all waste streams		
	Recycling of side streams		
	Toxic emissions (solid, liquid or gaseous)		
	Environmental aspects of all used reagents		
	ozone depleting substances, persistent organic pollutants, endocrine disruptors, genetically modified organisms, plant or animal origin (BSE), heavy metals, …		
	Compliance to REACH		
	Ecotox data		