Drug Product Due Diligence Checklist

This checklist provides an overview of CMC information which should be reviewed as part of due diligence activities for drug product. This review follows the format of the Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use: Module 3, Quality, of the ICH Harmonized Tripartite Guideline. CMC due diligence provides assurance that a given compound meets requisite technical and quality elements to allow for successful commercialization of the drug.

P1 Description and composition of the drug product

- ☐ Qualitative/quantitative description
- ☐ Excipient function defined
- ☐ Excipient stability effect
- ☐ Excipient physical role
- ☐ Excipient in vivo absorption effect
- ☐ Excipient manufacturability effect

P2 Pharmaceutical Development

- ☐ Drug substance characterized

P2.1.1 Excipients

- ☐ GRAS status (21 CFR Part 170.3)
- ☐ Compendial status of excipient
- ☐ Food grade status of excipient (Council Directive89/107/EEC)
- ☐ Supplier cGMP status
- ☐ Supplier internal audit results
- ☐ Excipient used in any approved products in EU/US
- ☐ Use of excipient in pharmaceutical product documented in literature
- ☐ Safety profile of excipient
- ☐ Synthetic route of excipient identified
- ☐ If compendial, are all excipient impurities controlled by monograph?
- ☐ Excipient impurities characterized (potential for interaction)
- ☐ Manufacturer control of excipient impurities

Excipients play practical physical roles in dosage forms, serving as diluents, to allow formulation of appropriately sized tablets, disintegrants to enhance formulation disintegration, and coatings to protect or mask undesirable attributes of the drug substance.

P2.1.2 Drug substance/excipient compatibility

(solid dosage forms)

- ☐ Drug/excipient mixing studies (thermal analysis)
- ☐ Short-term accelerated stability
- ☐ Multiple analysis techniques used for accelerated studies
- ☐ Effect of water on compatibility

(liquid dosage forms)

- ☐ pH stability
- ☐ Cosolvents
- ☐ Particulates
- ☐ Buffering agents
- ☐ Effect of aggregation
- ☐ Effect of oxygen
- ☐ Thermal stability
- ☐ Sterile dosage forms
- ☐ Suspension characteristics
- ☐ Sedimentation
- ☐ Resuspendibility
- ☐ Homogeneity
- ☐ Particle size effects
- ☐ Anitmicrobial additives
- ☐ Lyophilization products
- ☐ Freeze drying parameters
- ☐ Buffer components
- ☐ Diluent compatibility
- ☐ Sterilization technique
- ☐ Heat sterilization data
- ☐ Preservation studies

Excipients typically are the major fraction of the solid dosage form. As such, the characterization of the individual drug/excipient interaction is an important part of understanding the overall behavior of the dosage form. It is well known from studies of drug substances that water associated with the drug substance solid can influence chemical degradation rates, dissolution, powder flow, and other physical properties.

P2.3 Manufacturing process development

- ☐ Defined quality attributes
- ☐ Process development changes
- ☐ Process/clinical studies correlation
- ☐ Critical process parameters
- ☐ Critical quality attributes
- ☐ Multivariate analysis
- ☐ Historical batch data
- ☐ Rework
- ☐ Filter compatibility for liquids
- ☐ Cleaning validation

P2.4 Container closure system

- ☐ Functional requirements
- ☐ Critical component parameters
- ☐ Compatibility testing

P2.5 Drug product microbiological attributes

- ☐ Nonsterile products
- ☐ Sterile products
- ☐ cGMP controls
- ☐ Process design implications
- ☐ Compendial requirements
- ☐ Endotoxin control

A detailed analysis of the process should include a review of the quantities of excipients and reagents, the identification of critical steps and process controls, the type and size of processing equipment used, and the operating conditions. A review of the materials used in the manufacturing process should include availability and any safety concerns

P3.1 Manufacturer

- ☐ Location
- ☐ Manufacturing facility cGMP status
- ☐ Testing facility cGMP status
- ☐ Inventory of drug product and key ingredients
- ☐ Contractual obligations
- ☐ Alternate suppliers of critical materials

Process validation is documented evidence that the process, operated at the established parameters, can perform effectively and reproducibly. The approaches to validation of a drug product are outlined in several regulatory guidance documents.

P3.3 Description of manufacturing process and process controls

- ☐ Process flow diagram
- ☐ Batch records
- ☐ Critical quality attributes
- ☐ Scale-up
- ☐ Process controls
- ☐ Safety
- ☐ Key starting materials
- ☐ Operating conditions
- ☐ Batch size
- ☐ Batch records
- ☐ Scale-up (commercial process defined)
- ☐ Process capable of being run in existing plants
- ☐ Cycle time
- ☐ Process hold points identified
- ☐ Reagents of animal origin and TSE status
- ☐ Safety
- ☐ Environmental issues
- ☐ Robustness of process and rework frequency
- ☐ Ingredient availability and cost
- ☐ Patent protected process steps
- ☐ Special equipment required

P3.5 Process validation

- ☐ Process validation data available
- ☐ Validation master plan or protocol
- ☐ CPPs and their associated CQAs identified
- ☐ Documentation of key process data during validation
- ☐ Acceptance criteria for key process intermediates and final drug product
- ☐ Three consecutive successful production batches
- ☐ Reproducibility of the impurity profile

CMC CHECKLIST

P5.1 Control of drug product

(all)

- ☐ Description
- ☐ Identification testing
- ☐ Assay
- ☐ Impurities
- ☐ Specifications justified
- ☐ Specifications consistent with process data

(solid dosage forms)

- ☐ Disintegration
- ☐ Dissolution
- ☐ Stereoisomeric purity
- ☐ Residual solvents/moisture
- ☐ Microbial limits

(liquid dosage forms)

- ☐ pH of solution
- ☐ Particle size of suspended drug
- ☐ Clarity of solution (turbidity)
- ☐ Color of solution
- ☐ Viscosity
- ☐ Volume of fill
- ☐ Preservative testing

Specifications consist of test methods and their associated acceptance criteria. The tests and acceptance criteria above are dependent to exact dosage form. For the control of excipients, reagents, and drug products, sufficient detail should be provided in order that the methods could be adequately run in the laboratory.

P5.2 Analytical methods

- ☐ Review of analytical methods—details adequate
- ☐ Validated methods
- ☐ Methods provide sufficient specificity
- ☐ Accuracy
- ☐ Linearity
- ☐ Precision
- ☐ Robustness
- ☐ Control of potential impurities

P5.4 Batch analyses

- ☐ Test results for all batches made (including small scale batches) should be reviewed

P7 Container closure system

- ☐ Primary package compatibility
- ☐ Qualification
- ☐ Critical package parameters

P8 Stability

- ☐ A review of all stability batches
- ☐ Impurity profile
- ☐ Forced degradation studies
- ☐ Degradation pathway elucidate

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- Design, Implementation, and Remediation of Quality Systems
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