



Drug Substance Due Diligence Checklist

This checklist provides an overview of CMC information which should be reviewed as part of due diligence activities for drug substance. 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.

S.1. GENERAL INFORMATION

The physical and chemical properties of the drug substance must be understood in order to develop an adequate formulation. The rationalization of the selection of the salt or free acid/base should be given regarding the resultant quality of the drug substance and the ability to handle/process the drug product

S.1.1. Nomenclature

- IUPAC name
- Non-proprietary name
- Laboratory codes

S.1.2. Structure Elucidation

- Elemental Analysis
- Nuclear Magnetic Resonance (NMR)
- Mass Spectrometry (MS)
- Ultraviolet-Visible Spectroscopy (UV-vis)
- Infrared Spectroscopy (IR)
- Fourier Transform Infrared Spectroscopy
- X-ray Diffraction Analysis

S.1.3. General Properties Physicochemical Characteristics

- Ionization Constant
- Partition Coefficient
- Solubility Profile
- Solution Stability
- Hygroscopicity
- Polymorphism
- Hydrate/Solvate Formation
- Particle Size Distribution
- Adsorption/Desorption Isotherms
- Density
- Angle of Repose
- Compressibility
- Crystal Habit

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S.2. MANUFACTURER

S.2.1 Manufacturer

- Location
- Manufacturing facility cGMP status
- Testing facility cGMP status
- Inventory of drug Substance and Raw Materials
- Supply Agreements for Raw Materials
- Alternate Suppliers of Raw Materials

S.2.2. Description of Manufacturing Process – see page 4 for questions that should be considered

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



S.2.3. Control of Materials

- Acceptance criteria and test methods for
 - Starting materials, solvents, reagents, catalysts, and any other materials
- Rationale for acceptance criteria and the quality impact on the drug substance.

S.2.4. Control of Critical Steps and Intermediates

- The analytical methods used to control starting materials, and reagents.

S.2.5 Process validation

- 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 substance
- Three consecutive successful production batches
- Reproducibility of the impurity profile
- investigation of any atypical events or results during validation runs

S.2.6 Manufacturing Process Development

- The reproducibility of the impurity profile of the drug substance.
- Changes to the route of synthesis during development.

Adequate process control is achieved when there is an understanding of each process step. Some questions to be addressed are:

- What process impurities are generated?
- What process parameters influence the level of the process impurity?
- How are the process parameters that influence product quality controlled?
- Is the process control test reproducible?
- Is there a clear correlation between the process control and the critical quality attribute?
- Are the CQA results among batches consistent?

S.3. CHARACTERIZATION

S.3.1. Elucidation of Structure See General Information Section S.1 above

S.3.2. Impurities

The organic impurity profile of the drug substance includes the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance. An impurity profile should be available for each drug substance lot used in toxicological evaluation, primary clinical studies, stability evaluations of both drug substance and drug product, validation of the manufacturing process, and the development of the drug product. A comparison of impurity profiles across lots should be performed.

Organic impurities

- Starting Materials
- By-Products
- Intermediates
- Degradation Products
- Reagents, Ligands, and Catalysts

Inorganic impurities

- Reagents, Ligands, and Catalysts
- Residual Metals
- Salts
- Other Materials (e.g., Filter Aids, Charcoal)

Residual Solvents

- The maximum levels of residual solvents should be limited by ICH guidance
- Information on residual solvents should be available for all of the lots.



Specifications consist of test methods and their associated acceptance criteria. Each drug substance specification should be presented with a rationale for the limits specified. The following tests and acceptance criteria are applicable to all drug substances.

S.4.1 Control of drug substance

- Description
- Appearance
- Identification testing
- Assay
- Impurities
- Stability indicating techniques
- Specifications justified
- Specifications consistent with process data

Additional specifications may include:

- Particle Size
- Melting Point
- Refractive Index (Chiral Molecules)
- Polymorphic Form
- Loss on Drying
- Karl Fischer
- Volatile organic impurities

For drug substances used in suspensions and solutions additional physico-chemical characteristics may include:

- pH of Solution
- Microbial Limits

During early stages of development, full justification of specifications is not available as final specifications are determined by the comprehensive development experience. If the drug substance is in Phase III of development, draft final specifications should be justified with regard to the historical experience with the process at the current scale and synthetic route. At Phase III, the drug substance process should be well-defined and not open to any significant

S.4.2 & S.4.3 Analytical methods & Validation

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

S.4.4 Batch analyses

- Test results for all batches made (including small scale batches) should be reviewed
- A comparison of results used in toxicology studies with those batches made for clinical use.
- The level and type of impurities in the clinical batches typically should not exceed that of the toxicology batches.

S.4.5 Justification of Specifications see page 4 for questions that should be considered

- Consistently with current process capability and drug safety study results.

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S.5 REFERENCE STANDARDS OR MATERIALS

- Fully characterized including structural elucidation data as well as extended testing for impurities.

S.6 Container closure system

- Primary package compatibility
- Qualification
- Critical package parameters
- identification testing

S.7 Stability

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

Need a deeper dive into your program? DSIs [CMC Healthchek™](#) is a comprehensive gap analysis that looks at your program as a snapshot in time from the viewpoint of important drug development milestones.

- Review your Drug Development history
- Get a list of issues and question to discuss with your team and partners
- Find out if you are due for a meeting with the agency



S.2.2. Questions that should be considered for Description of Manufacturing Process

<ul style="list-style-type: none"> <input type="checkbox"/> What is the robustness of the process (are reworks common)? How do the physicochemical profiles of multiple lots compare? <input type="checkbox"/> Are the reagents commonly available or cost prohibitive? <input type="checkbox"/> Have critical quality attributes for critical intermediates and final drug substance been determined? <input type="checkbox"/> Have Critical Processing Parameters (CPPs) been associated with critical quality attributes (are there data to support the association)? <input type="checkbox"/> If the current process is lab-scale or pilot-scale, can the process batch size be increased using the current synthesis technology (has a commercial synthesis been defined)? <input type="checkbox"/> Is the batch yield acceptable relative to cost? This analysis will entail reviews with marketing to determine the acceptable cost of goods for the drug substance. <input type="checkbox"/> Are there any environmental or safety concerns? A review by the corporate environmental group of the list of materials used in the synthesis should be performed to provide an indication of any environmentally problematic substances used in the current synthesis. 	<ul style="list-style-type: none"> <input type="checkbox"/> Is the current synthesis amenable to manufacturing capabilities at existing plants? Are the technologies used in the process common; is special equipment required? <input type="checkbox"/> Is the cycle time for processing of the drug substance acceptable? <input type="checkbox"/> Have suitable process hold points been determined? What is the impact on quality/stability of drug substance? <input type="checkbox"/> Are the crystallization procedures well defined and what is the risk of polymorph formation considering the results of polymorph screening studies? <input type="checkbox"/> Are micronization techniques employed? Does the micronization impact the quality (e.g. formation of degradation products or amorphous material from crystalline solids) of the final drug substance? <input type="checkbox"/> Are any of the reagents of animal origin? If so, is their Transmissible Spongiform Encephalopathy (TSE) status documented? <input type="checkbox"/> Are any of the process steps patent protected?
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S.4.5 questions that should be considered Justification of Specifications

- Are the specifications for the drug substance consistent with current process capability and drug safety study results?
- Are the specifications for impurities controlled primarily by qualification limits determined by toxicology studies?
- Are the draft final specifications based on the historical experience with the process at the current scale and synthetic route?

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CMC

- Integrated CMC Development
- Materials Characterization and Formulation Development
- Process Development, Optimization, And Validation
- Analytical Method Development, Optimization, and Validation
- Stability Program Design and Management

QA

- Design, Implementation, and Remediation of Quality Systems
- Compliance, Vendor Qualification, and Mock Pre-approval Audits (Mock-pais)
- Management of Compliance Situations