Technical Data Checklist for Examination and Registration Review of Active Pharmaceutical Ingredients

Items	Notes
Cover Page	The cover page should include: Name of the Drug Master File (DMF), date of submission, company name of the applicant, and company name of the manufacturer.
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Abbreviations	
CTD data:	
3.2.S.1 General Information	
3.2.S.1.1 Nomenclature	Nomenclature of Active Pharmaceutical Ingredients (APIs), such as INN, pharmacopoeial name, chemical name, company or factory code, and other non-proprietary names, such as common names in various countries, USAN, JAN, BAN, and CAS number, must be provided.
3.2.S.1.2 Structure	Chemical structure (including relative and absolute stereochemistry), molecular formula and molecular weight should be provided. If the compound is optically active or has a cis-trans isomer, its stereochemistry must be clearly indicated.

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	If the API is a polypeptide, structural information at all levels must be provided. If the API is a mixture, the structure of the active ingredients or the main ingredients must be provided.
3.2.S.1.3 General Properties	Provide physicochemical properties and other related properties of the API(s), such as appearance, melting point, boiling point, solubility, specific rotation, crystal structure, hygroscopicity, pH, acid dissociation constant (pK_a), solvate (hydrate), and isoelectric point (pI); if the compound is biologically active, such information must also be provided.
3.2.S.2 Manufacture	
3.2.S.2.1 Manufacturer(s)	The name, company address, site and responsibility of each manufacturer, including contractor(s) and all sites or facilities involved in manufacturing and testing, should be provided.
3.2.S.2.2 Description of Manufacturing Process and Process Controls	1. The description of the manufacturing process represents the applicant's commitment towards the manufacture of the API(s). Information that

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	adequately describes the manufacturing process and process controls should be provided. For example: a) A flow diagram of the synthesis process(es) should be provided. The flow diagram should include information such as the molar ratio, weights, molar quantities, chemical structure (including absolute and relative stereochemistry) of the starting materials, intermediates, reagents, and API(s). The operating conditions and solvents used should be indicated. b) A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for

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	commercial manufacture, and identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH and time). c) Alternate processes (e.g., reprocessing and reworking), should be explained and described with the same level of details as the primary process. Reprocessing and reworking steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5. 2. If the API is a primary or secondary metabolite (e.g., vitamin, amino acid, antibiotic, plant alkaloid or polysaccharide) obtained through fermentation of microorganisms (such as bacteria, yeasts, fungi or microalgae), the microorganism characterization report (including characterization of the phenotype and genotype of

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	the microorganism), fermentation process, extraction, concentration, purification and other processes should also be provided with detailed operating conditions. Following the manufacturing sequence, describe the raw materials used in preparation of the growth medium, seed-lot system, fermentation tanks, and purification columns used in commercial-scale production, also identify the critical steps, critical process parameters (e.g., fermentation temperature, pH, fermentation time and rate of agitation), in-process controls, equipment, and operating conditions. 3. The process description for APIs derived from plants should include the amount of herbal materials used, equipment, solvents, and the temperatures and times for mixing, grinding, extraction and/or drying. The yields and in-process controls

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	should also be provided. 4. The process description for peptides or protein products derived from animals should include the animal part(s), amount used, equipment, solvents, extraction, concentration, purification, and drying method. The yield and in-process control must also be described. Sources such as ICH Q11 may be referenced for the above information
3.2.S.2.3 Control of Materials	1. Materials used in the manufacture of the API(s) (e.g., raw materials, starting materials, solvents, reagents and catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Appropriate information should be provided to demonstrate that these materials meet the appropriate standards for their intended use. If the raw materials, starting materials,

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	reagents, or catalysts are of animal origin, a risk assessment report for spongiform encephalopathy should be submitted. 2. In addition to providing the source of the starting material, Certificates of Analysis from manufacturers or suppliers should also be submitted if necessary. 3. If the manufacturing process involves a classical fermentation process, the source, history, and characterization of the microorganism should also be submitted. 4. If the materials are of plant origin, the scientific name (genus, species and variety) of the plants, parts of the plant used, the specific botanical identification of the plant material, and certificate of origin should be submitted. Pesticides (herbicides and insecticides) used for crop planting should be described. 5. If the materials are of animal origin, in addition to the scientific name (genus, species and variety) and parts

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	used, it should also be demonstrated that the production method can inactivate or remove viruses or any pollution from other sources of contamination. 6. It should be stated whether solvents used in the manufacturing process are reused after being recycled. If recycled solvents are used, the specifications for their intended use (justification) and analytical methods should be provided. Sources such as ICH Q11 may be referenced for the above information
3.2.S.2.4 Controls of Critical Steps and Intermediates	Critical steps: In order to ensure control of the manufacturing process, the tests and acceptance criteria (with justification including experimental data) for the critical steps indicated in 3.2.S.2.2 should be provided. Please refer to ICH Q11. Intermediates: The intermediates isolated from the process must be provided. Please refer to ICH Q11 for the quality and control information,

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	including the complete specifications and analysis methods.
3.2.S.2.5 Process Validation and/or Evaluation*	1. An API process validation protocol and report should be provided. If the manufacturing process includes aseptic operation or sterilization processes, a process validation study of aseptic operation and sterilization should also be provided. If the manufacturing process involves fermentation, extraction, concentration, purification or other processes, validation protocol and report for these processes, but not limited to these processes, should also be included. Please refer to ICH Q11. 2. This information may be replaced by the Process Validation Protocol and Batch Manufacturing Record (at least one representative batch). The process validation report should be kept in the manufacturing site for future reference.

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3.2.S.2.6 Manufacturing Process Development*	1. Relevant data should be provided, such as the basis for the manufacturing process or rationale of the process formulation. 2. If there are significant changes during the process and/or the development of the process at the manufacturing site, explanation should be provided and discussed. Please refer to ICH Q11.
3.2.S.3 Characterization	
3.2.S.3.1 Elucidation of Structure and other Characteristics*	1. Elucidation of structure should be provided, including ultraviolet (UV), infrared (IR), mass spectrometry (MS), nuclear magnetic resonance (NMR) and elemental analysis, as well as confirmation by synthetic pathways and spectral analysis. Other information, such as identification of stereostructure and possible formation of isomers or polymorphs should also be provided. If necessary, reference standards should be provided for spectral comparison.

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	2. If the API has a polymorphic form, relevant spectra such as X-Ray diffraction (XRD) and differential scanning calorimetry (DSC) should be provided. 3. Analytical spectra of primary structures and higher order structures, such as circular dichroism (CD), should be provided for polypeptide APIs. 4. For biotech products, details of relevant primary, secondary or higher-order structures, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties must be provided. 5. For APIs extracted from plants (plant origin), elucidation of the structure of the active ingredient or indicator ingredient should be provided.
3.2.S.3.2 Impurities	1. The name(s), structure(s), origin (degradation product, process impurity, etc.) of observed/potential impurities should be provided as per

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	the source and manufacturing process of the API(s). 2. For specified impurities as established in the API specifications, structural identification spectra for characterization should be provided.
3.2.S.4 Control of Drug Substance	
3.2.S.4.1 Specifications	Specifications and acceptance criteria for the API(s) should be provided. Establishment of the specifications should be based on the Chinese Pharmacopoeia or a Pharmacopoeia published by one of the ten pharmaceutically advanced countries, and/or ICH Q3A, Q3C, Q6 and other quality-related regulations.
3.2.S.4.2 Analytical Procedures	The analytical procedures used for testing the API(s) should be provided along with the basis on which the analytical procedures are established (if applicable).
3.2.S.4.3 Validation of Analytical Procedures	1. Analytical validation information including experimental data for the analytical procedures used for testing the API should be provided.

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	2. Validation of the analytical procedures should be conducted in accordance with the Analytical Procedures Validation Guidelines or ICH Q2. 3. If analytical procedures for APIs are based on Pharmacopoeias, validation may be waived. However, system suitability reports of the analytical procedures should be provided.
3.2.S.4.4 Batch Analyses	1. The Certificate of Analysis for at least one batch of the API(s) and batch analysis data for at least three batches of the API(s) should be provided. Manufacturing site and date, batch number, as well as batch size should be included. 2. The Certificate of Analysis should mainly be expressed numerically and avoid the use of vague words such as "conforms", "meets specifications", "negative response", etc.
3.2.S.4.5 Justification of Specifications	Justification for the API specifications should be provided. Please refer to ICH Q3 and Q6.

Items	Notes
3.2.S.5 Reference Standards or Materials	
3.2.S.5 Reference Standards or Materials*	Please indicate whether the standard is a primary reference standard or a working standard. For primary reference standards, please provide the source and purity calibration procedure. For working standards, please provide the source, batch number, labeled content (or potency), specifications, Certificate of Analysis, and purity calibration procedures.
3.2.S.6 Container Closure System	
3.2.S.6 Container Closure System*	1. A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component and their specifications. The specifications should include description and identification, as well as critical dimensions with drawings (where appropriate).

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	2. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. 3. The suitability of the packaging components should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to containers and leaching, and/or safety of materials of construction (e.g., indicating that the primary packaging component is constructed of food-grade material). If the product is sterile, relevant tests should be performed.
3.2.S.7 Stability	
3.2.S.7.1 Stability Summary and Conclusions	Perform the stability testing in accordance with ICH Q1. The types of studies conducted, protocols used, and

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	the results of the studies should be summarized. The summary should include the proposed storage conditions and re-test period or shelf-life.
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment	The post-approval stability protocol and stability commitment should be provided. (This item may be waived if the data submitted for three production batches cover the re-test period or shelf life.)
3.2.S.7.3 Stability Data	Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included. At least 6-months of accelerated stability test results and 6-months of long-term stability test results for three no-less-than pilot-scale API batches should be provided. If the API batches are pilot-scale batches, their manufacturing processes and in-process controls should be equivalent to the commercial API batches that will be launched on the

Items	Notes
	market, and the pilot-scale batches should be representative of the full production-scale batches.
Other Information	
Waste Disposal and Waste Facilities	A statement regarding compliance with the laws and regulations of the country of origin should be provided. Domestic manufacturers are required to attach a photocopy of the operating license for the waste-disposal subcontractor and the contract. A statement/document regarding compliance with PICS/GMP is acceptable for importers.
Relevant Certificates or Documentation*	1. A TSE-free statement should be provided for API(s) derived from animals. 2. Information related to the Good Agricultural and Collection Practice (GACP) should be provided for API(s) derived from plants.