Chemistry, manufacturing and controls requirements

The chemistry, manufacturing and controls (CMC) section is a very important part of any clinical trial or marketing application. Drugs can be denied marketing approval if the quality of the product and the manufacturing process cannot be shown to be of a sufficiently high standard to satisfy regulators.

The following outlines the key parts of the CMC portion of a file, as per the International Conference on Harmonisation (ICH) requirements.

Exhibit 1: CMC requirements for a new pharmaceutical

	Section	Inclusions
Drug substance	General information	Recommended international non-proprietary name (INN), compendial name (if relevant), chemical name, company or lab code, other non-proprietary names, chemical abstracts service (CAS) registry number, structure, general physicochemical and other relevant properties.
	Manufacture	Name, address and responsibility of each manufacturer involved in process, description of manufacturing process and controls, control of materials, controls of critical steps and intermediates, process validation and/or evaluation, manufacturing process development.
	Characterisation	Elucidation of structure and other characteristics, impurities.
	Control of drug substance	Specification, analytical procedures, validation of analytical procedures, batch analyses, justification of specification.
	Reference standards or materials	
	Container closure system	Description, identity and specifications.
	Stability	Stability summary and conclusions, post-approval stability protocol and stability commitment, stability data.
Drug product	Description and composition	Description, composition, type of container closure system.
	Pharmaceutical development	Components of the drug product (drug substance, excipients), formulation development, overage, physicochemical and biological properties, manufacturing process development, container closure system, microbiological attributes, compatability.
	Manufacture	Manufacturer's name, batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation and/or evaluation.

Control of excipients	Specifications, analytical procedures, validation of analytical procedures, justification of specifications, excipients of animal or human origin, novel excipients.
Control of drug product	Specifications, analytical procedures, validation of analytical procedures, batch analyses, characterization of impurities, justification of specifications.
Reference standards or materials	
Container closure system	
Stability	Stability summary and conclusion, post-approval stability protocol and stability commitment, stability data.

Source: International Conference on Harmonisation, *Common Technical Document for the Registration of Pharmaceuticals for Human Use* [Guideline M4Q(R1)], http://www.ich.org/LOB/media/MEDIA556.pdf

The ICH guideline Q1A(R2) (*Stability Testing of New Drug Substances and Products*) defines the stability data package required for new drug substances and products submitted for approval in each of the major regions that accept the ICH guidelines (i.e., US, Japan and EU).

Stability testing

The purpose of stability testing is to determine how the drug substance or product performs under different environmental conditions such as temperature, humidity and light. It also establishes a re-test period for the drug substance or a shelf-life for the drug product, as well as recommended storage conditions.

Drug substance stability testing

At least three batches of a drug substance should be tested. The ICH guideline Q1A(R2) states that, "Batches must be manufactured at least to pilot scale by the same synthetic route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches." The stability testing should be conducted on products that have been stored in the same type of container that is intended for market use (e.g., bottles, blister packages).

For drug substances with a proposed twelve-month re-test period, ideally batches should be tested every three months over the first year and every six months over the second year, and annually thereafter.

Under accelerated storage conditions, in a six-month study, batches should be tested at the zero-, three- and six-month mark.

Drug product stability testing

Stability testing should be conducted from three primary batches of the same formulation and packaged in the same container closure system as intended for market use. The manufacturing process should simulate the one used for production batches and should provide a product of the same quality and that meets the same release specifications as the batches intended for the market. Two of the three batches should be pilot scale batches; the third one can be smaller, if justified. Where possible, the three batches should be made using different batches of drug substances.

Note that additional stability and compatibility studies may be required if a product is to be combined with either another product or diluted in a vehicle for administration.

Exhibits 2, 3 and 4 below detail the general stability data required for drug substances and drug products, as well as the stability requirements when they are refrigerated or frozen.

Exhibit 2: General stability data required for drug substance or drug product

Study	Storage condition	Minimum time period covered by data at time of submission
Long-term**	25°C±2°C/60% RH ±5% RH or 30°C±2°C/65% RH ±5% RH	12 months
Intermediate*	30°C±2°C/65% RH ±5% RH	6 months
Accelerated	40°C±2°C/75% RH ±5% RH	6 months

** It is up to the applicant to decide whether long-term stability studies are performed at which of the two conditions.

* If 30°C±2°C/65% RH±5% RH is the long-term condition, there is no intermediate condition.

Source: International Conference on Harmonisation, *Stability Testing of New Drug Substances and Products* [Guideline Q1A(R2)], http://www.ich.org/LOB/media/MEDIA419.pdf

Exhibit 3: Stability requirements for refrigerated drug substance or drug product

Study	Storage condition	Minimum time period covered by data at time of submission
Long-term	5°C±3°C	12 months
Intermediate	25°C±2°C/60% RH ±5% RH	6 months

Source: International Conference on Harmonisation, *Stability Testing of New Drug Substances and Products* [Guideline Q1A(R2)], http://www.ich.org/LOB/media/MEDIA419.pdf

Exhibit 4: Stability requirements for frozen drug substance or drug product

Study	Storage condition	Minimum time period covered by data at time of submission
Long-term	-20°C±5°C	12 months

Source: International Conference on Harmonisation, *Stability Testing of New Drug Substances and Products* [Guideline Q1A(R2)], http://www.ich.org/LOB/media/MEDIA419.pdf