



Therapeutic Products Directorate

Direction des produits thérapeutiques

Health Products and Food Branch

Direction générale des produits
de santé et des aliments



5 – Quality (CMC) considerations

**Presentation to APEC Preliminary Workshop
on Review of Drug Development
in Clinical Trials**

**Celia Lourenco, PhD,
Manager, Clinical Group I
Office of Clinical Trials
Therapeutic Products Directorate**

Slide 1

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop

Overview

- Objective in the assessment of quality
- CMC framework
- Summary of quality (CMC) requirements and some deficiencies frequently encountered
- Guidance documents and templates
- Exercise

Overarching Objective

Ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture

CMC Framework for Clinical Trials

- Schedule B provides a list of Pharmacopeias
- Division 5: CMC information in respect of the drug is required in a CT application
- Annex 2 to GMP available for reference but manufacturers not inspected
- ICH guidelines available for reference but considered of greater importance at the marketing stage
- Post-approval requirements (e.g., lot-release program for biologics)

Schedule B to the Food and Drugs Act

- European Pharmacopoeia (Ph.Eur.)
- Pharmacopée française (Ph.F.)
- Pharmacopoeia Internationalis (Ph.I.)
- The British Pharmacopoeia (B.P.)
- The Canadian Formulary (C.F.)
- The National Formulary (N.F.)
- The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
- The United States Pharmacopoeia (U.S.P.)

GMP for Drugs in Clinical Trials

- Interpretation of Division 2 of the regulations is in Annex 2 to the GMP
- Adapted from the Pharmaceutical Inspection Cooperation Scheme Annex 13: “Manufacture of Investigational Medicinal Products” to meet Canadian requirements

GMP Considerations

- Production of investigational drugs involves added complexity in comparison to marketed drugs due to:
 - lack of fixed routines
 - variety of clinical trial designs and consequent packaging designs
 - the need for randomization and blinding
 - increased risk of product cross-contamination and mix up
 - incomplete knowledge of the potency and toxicity of the product
 - lack of full process validation
 - marketed products may be used which have been re-packaged or modified in some way

GMP Annex 2 Content

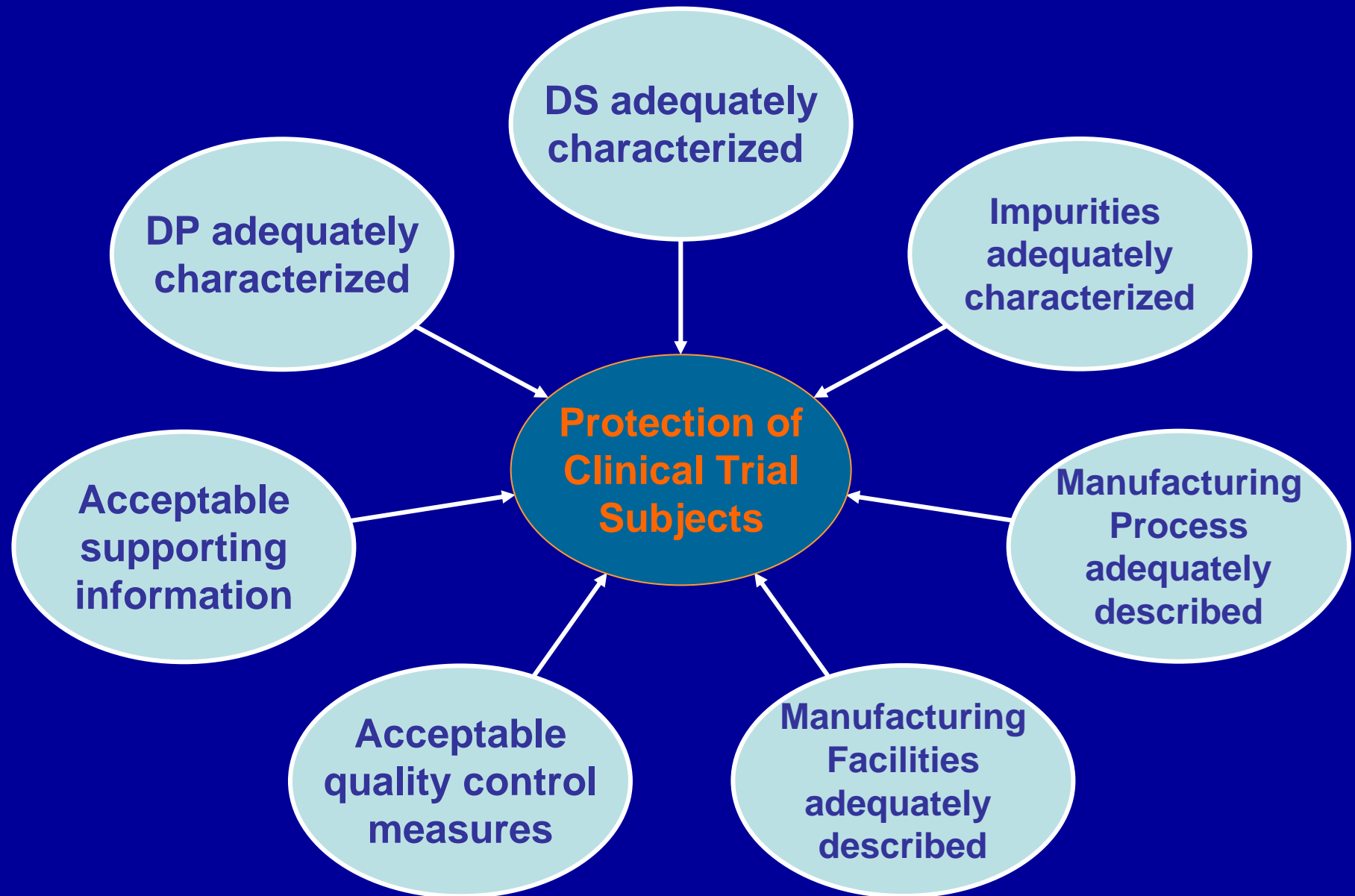
- Quality management
- Personnel
- Premises and Equipment
- Documentation
- Production
- Quality control
- Release of batches
- Shipping
- Complaints
- Recalls and returns
- Destruction

Preliminary Considerations

Use a benefit/risk approach in the evaluation of quality:

- What is the phase of trial and stage of development?
- Link between quality and clinical: what is the intended use of the product?
- Is product type / class known to have quality concerns?
- What is the level of experience of the manufacturer?

CMC Assessment in Clinical Trials



CMC Data Requirements: Pharmaceuticals

Introduction

- Summary of product information
- Excerpt from protocol synopsis
- Information on the comparator product
- Information for cross-referencing sections to previous submissions

Drug Substance

General Information:

- Nomenclature (INN, compendial name, chemical name, company code, other non-proprietary name(s), CAS number)
- Structure (structural formula, molecular formula, molecular mass)
- General Properties: physical description, physical form (polymorphic form, solvate, hydrate), solubilities, pH & pKa

Manufacture

- Manufacturers: name and addresses of sites involved in the manufacture of clinical batches of drug substance, DMF numbers
- Description of the Manufacturing Process and Controls: flow diagram and narrative description of the synthesis
- Control of Materials: information for drug substances from sources at risk of transmitting BSE/TSE

Characterization

Elucidation of Structure and other Characteristics:

- Evidence of structure (e.g., IR, UV, NMR, MS, elemental analysis)
- Discussion on the potential for isomerism and identification of stereochemistry
- Summary of studies on polymorphic forms
- Summary of particle size distribution studies

Impurities

- Drug-related impurities (including chemical name, structure and origin)
- Process-related impurities (solvents, reagents)
- Actual levels of impurities found in clinical batches

Control of Drug Substance

- Specifications, including tests, type of analytical procedures, and acceptance criteria (phase II/III)
- Batch analysis: description of batches to be used in the trial (batch no., batch size, date and site of production), and summary of results

Container Closure System & Stability

- **Container Closure System:**
 - Description of the container closure system(s) for the storage and shipment of the drug substance
- **Stability:**
 - Stability Summary and Conclusions (summary of studies to support the clinical trial)
 - Post-approval Stability Protocol and Stability Commitment: if full long term data is not available at the time of filing, provide the stability protocol and a commitment for the continued monitoring of the drug substance stability according to the protocol
 - Summary of raw data (reference to volume)

Drug Product Description & Composition

- Description of the dosage form
- Composition of the dosage form (list of components and amounts, composition of mixtures)
- Description of reconstitution diluent(s), if applicable
- Qualitative composition of placebo (phase II/III)

Pharmaceutical Development

- Discussion on development of the dosage form, the formulation and manufacturing process (Phase II/III)
- For sterile, reconstituted products, summary of compatibility studies with diluents / containers

Drug Product - Manufacture

- Manufacturers: name and addresses of sites involved in the manufacture of clinical batches of drug product, DMF numbers
- Batch Formula
- Description of manufacturing process and process controls: flow diagram, narrative description, sterilization / lyophilization conditions for sterile products

Control of Excipients (1)

Specifications:

- Specifications for non-compendial excipients and for compendial excipients with supplementary tests not listed in the monograph(s)
- Confirmation that none of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drug Regulations* (e.g., chloroform, arsenic)

Control of Excipients (2)

Excipients of human or animal origin:

- List of excipients that are of human or animal origin
- Summary of the information regarding adventitious agents for excipients of human or animal origin
- For excipients obtained from sources that are at risk of transmitting BSE/TSE agents, a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area

Control of Excipients (3)

Novel Excipients:

- Summary of the details on the manufacture, characterization, and controls, with cross references to supporting safety data (non-clinical and/or clinical) on novel excipients (i.e., those used for the first time in a drug product or by a new route of administration)

Control of Drug Product

Specifications:

- Specifications for the drug product: tests, type of analytical procedure, acceptance criteria (Phase II/III)
- Batch analysis: batch no., batch size, data and site of production for clinical batches, and summary of results

Characterisation of impurities:

- Information on the characterisation of impurities, not previously provided in the drug substance impurities section (e.g., summary of actual and potential degradation products)

Container Closure System

- Description of the container closure system, including unit count or fill size, container size or volume
- Materials of construction of each primary packaging component
- For sterile products, details of washing, sterilization and depyrogenation procedures for container closures

Stability

- Stability summary and conclusions:
 - Summary of studies to support the clinical trial (batch numbers, conditions, packaging, etc.)
 - Summary and discussion of results
 - Proposed storage conditions and shelf life
- Post-approval stability protocol and stability commitment: if full long term data is not available at the time of filing, the stability protocol should be provided with a commitment to monitor the clinical trial samples throughout the duration of the trial or the proposed shelf life
- Raw stability data (reference to submission volume)

CMC Considerations for Biologics

Issues

- Complexity of manufacturing process, drug substance, and drug product
- Added difficulty in control of drug substance and drug product, including impurities
- Additional potential risks associated with:
 - host cell contaminants derived from bacteria, yeast, insect, plants, and mammalian cells
 - host contaminants can result in allergic reactions and other immunopathological effects
 - nucleic acid contaminants have the potential for integration into the host genome
 - additional risk of viral infections for products derived from insect, plant and mammalian cells, or transgenic plants and animals

Key Requirements (1)

- Information on raw materials, especially materials of biological origin (e.g., cell banks, albumin, enzymes, fetal calf serum, human plasma)
- Control and removal of adventitious agents (e.g., viruses, prions, bacteria)
- Endotoxin control
- Sterility of finished product, especially for aseptically-filled products

Key Requirements (2)

- Demonstration of knowledge of the active pharmaceutical ingredient (API):
 - Characterization of the API
 - Understanding of impurities
 - Process-related: objectional impurities such as solvents, heavy metals, aggregates, etc.
 - Product-related: intrinsic to the product but can be problematic since they can be significantly more or less active or may be more immunogenic (e.g., oxidized, clipped, deamidated impurities)
- Demonstration of understanding of the manufacturing process

Key Requirements (3)

- Specifications:
 - Should be appropriate to control the clinical trial product to the stage of development to ensure safety and quality
- Stability:
 - Long-term
 - Accelerated
 - In-use (for multi-use products)
- Case-specific issues:
 - Novel excipients

Additional Considerations (1)

- As the drug product progresses through development, changes normally occur in the manufacturing process in order to improve product quality and yields
- The potential impact of such changes for extrapolation of pre-clinical data or earlier clinical trials to later development clinical trials, should be considered
- The comparability of the test material during a development program should be demonstrated when a new or modified manufacturing process or other significant changes in the product or formulation are made in an ongoing development program

Additional Considerations (2)

- Comparability can be evaluated on the basis of biochemical and biological characterisation (i.e., identity, purity, stability, and potency)
- In some cases additional studies may be needed (i.e., pharmacokinetics, pharmacodynamics and/or safety)
- The scientific rationale for the approach taken should be provided
- Overall, the goal is to demonstrate that improvements in processes lead to improvements in product quality while preserving or improving safety

Unique requirements for Radiopharmaceuticals

- Radioactive nature of the drug substance and/or drug product impacts on CMC requirements
- Radioactive dose range
- For kits, expiry time/date, storage conditions, and stability data before and after reconstitution
- Information on radionuclide and decay characteristics
- Radionuclidic and radiochemical purity and impurity

Key Messages in Quality Review

- Use a systematic approach where every component of the quality information contributes to the overall assessment
- Compare all drug substance and drug product batch results and look for variability, inconsistencies
- Ensure stability testing is adequate for the type of product and intended use
- Use a benefit / risk approach where other factors such as the phase of development, subject population, and manufacturer's experience contribute to the assessment
- CMC is expected to progress through product development phases
- Often involves a case-by-case judgement call on extent of quality data requirements at time of application or as a post-approval commitment


Guidance Documents

- Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications
- Preparation of the Quality Information for Drug Submissions in the CTD Format:
 - Conventional Biotherapeutic Products
 - Vaccines
 - Blood Products
 - Biotechnological Products

Templates - Pharmaceuticals

- Quality Overall Summary - Chemical Entities (Clinical Trial Applications Phase I) (QOS-CE (CTA - Phase I))
- Quality Overall Summary - Chemical Entities (Clinical Trial Applications - Phase II/III) (QOS-CE (CTA - Phase II/III))
- Quality information for Phase II trials cannot be cross-referenced to the Quality information submitted with Phase I trials
- Quality information for Phase III trials cannot be cross-referenced to the Quality information submitted with Phase II trials

Templates - Biologics

- QOS template is not available for biologics
- Manufacturers are advised to use the exact headings as indicated in the guidance documents
- Headings that have a  are applicable to clinical trial applications
- With subsequent CTA filings for the same drug (e.g. Phase II or III studies), where much of the quality information may be similar, the sponsor is encouraged to build upon the previously completed QOS (e.g. Phase I or II study), by making any necessary revisions or adding relevant information to update the submission and clearly identifying the changes using either coloured text or a different font

References

Quality Guidance Documents	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/ctd_convbio_e.pdf http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/ctd_biotech_e.pdf http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/ctd_blood-sang_prods_e.pdf http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/ctd_vacc_e.pdf http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qual_cta_dec_e.pdf
Quality templates	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qoscecta_sgqecdec_ph_i_e.pdf http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qoscecta_sgqecdec_ph_ii_iii_e.pdf
Annex 2: Manufacture of Drugs Used in Clinical Trials	www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/cln_trials-essais_cln_e.pdf

Thank You!

Questions?

Exercise

- Drawing upon your experience, and if necessary, by reviewing the guidance documents provided to you for chemical entities and conventional biotherapeutics, discuss the following question in your groups.
 - Prepare a summary of your discussion and record your findings on the flip chart.
 - Chose a speaker who will present your findings to the entire group.
1. When is drug quality considered more important in the drug development process? When is it considered less important?

Time: 60 min

Plenary discussion