

Comprehensive Guide to Clinical Materials

A Handbook for Training Clinical Materials Professionals



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1 Introduction

Welcome to the Comprehensive Guide to Clinical Materials

Clinical Material (CM) supply chain management is an ever-expanding, complex, and fascinating field. Government agencies require that staff members are fully trained in the appropriate regulations and cGMPs. Keeping current with the rapidly changing global landscape is challenging. To assist members of the Clinical Materials Community of Practice (COP), ISPE provides educational opportunities in the form of conferences, training classes, magazine articles, and training guides.

The ISPE Clinical Materials Committee authored and published the Introductory US Clinical Trial Materials Training Guide in 1996 and revised it in 2002. That Guide serves as a tool for new staff members to introduce them to basic CM concepts. The CMC identified the need for a more advanced training guide that builds upon the topics in the Introductory Guide. As a result, CMC members, supported by members of the European Investigational Medicinal Products Group (IMPG), and members at large from the CM COP have authored this Comprehensive Guide to Clinical Materials.

Whereas the Introductory Guide is intended to be used as a handout and reference guide, this Comprehensive Training Guide is designed to be used in a classroom setting/leader led environment. Key learning points are summarized for each topic. It is intended that the trainer will cover each of the key learning points with session attendees using the more detailed notes provided behind each section. After the training event, the organization may choose to provide a full copy to each attendee for future reference.

It is critical for the reader to remember that there are often differences in interpretation surrounding regulations. Each company must translate regulations into practice according to its own interpretations. Most will codify their interpretation via Standard Operating Procedures (SOPs) or other tools. Of course, the information in this Guide cannot be construed as representing the viewpoint of any regulatory agency. The authors have attempted to gather what is considered a more common practice around each topic from their perspective.

Thank you for choosing this Guide as a training tool for the clinical materials professionals in your organization.

For more information about the CM COP or to contact us, please visit the ISPE Web site at www.ispe.org.

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3 Regulatory/GxP Information

Common Technical Document (CTD)

3.1 Critical Learning Points

- A. The CTD was developed by the International Conference on Harmonization (ICH).
- B. The CTD is the registration application that is to be submitted worldwide to obtain approval for human medicinal products.
- C. The CTD refers to an application **format** and prescribes the **organization** of information required to be submitted to regulatory authorities.
- D. The CTD does not address the content of the submission, i.e., the studies that have to be performed.
- E. The CTD is organized into five modules:
 - Module 1: Administrative and Prescribing Information
 - Module 2: Common Technical Document Summaries
 - Module 3: Quality
 - Module 4: Nonclinical Study Reports
 - Module 5: Clinical Study Reports
- F. Clinical studies related information will predominately be presented in the Quality and Clinical Study Reports Modules. In the Quality Module, this would include the information related to the formulations (including the formulation components, product formulas, manufacture, analytical methods and validations, specifications, and stability) as well as packaging of the clinical trial supplies (including the comparator drugs). In the Clinical Study Reports Module, the study protocols would be presented.
- G. The FDA has published guidance documents that assist the applicant in properly preparing the CTD Modules.

3.2 Background, Depth, and Breadth Information

- A. ICH is the acronym for the International Conference on Harmonization. Its goal is to harmonize the requirements for the registration of pharmaceuticals for human use. It was founded in 1990, and is a joint regulatory/industry project to improve the efficiency of developing and filing new human, medicinal products in Europe, Japan, and the United States. Since most new pharmaceutical products are developed in these three regions, harmonization of the technical requirements needed to obtain regulatory approval reduces duplication in the development effort, and makes new products available to patients without undue delay. Agreement has been reached on virtually all of the technical requirements needed in the Quality (CMC), Non-Clinical, and Clinical areas; therefore, unification of the total development effort has been achieved. However, prior to 2003, each region had its own set of requirements for the organization of the technical reports in the regulatory submission. In order to avoid the need to generate and compile different registration dossiers, the Common Technical Document (CTD) was developed.

- B. The CTD harmonizes the organization of the registration document such that it is suitable for submission in all three regions. Whereas previously the different regions relied on Expert Reports, tabulated and written summaries, and various guidance's for presenting the technical information, the CTD eliminates the need to compile different dossiers for worldwide filings. The CTD can be used as a replacement for the NDA or BLA in the U.S. It is currently not required to file a CTD in the U.S., but it is strongly recommended. In Europe and Japan, the CTD is to be used.
- C. The CTD addresses the format of the registration application. Document ICH M4 provides the information required to compile the CTD. The FDA, in their series on "Guidance for Industry," also presents their view on the CTD. Although applicants should not deviate from the prescribed overall organization of the CTD, latitude is given in modifying individual formats in the clinical and non-clinical summaries to achieve the best possible presentation of the technical information.
- D. The requirements for the technical content of the reports to be included in the CTD are defined in several ICH documents. Those for the Quality section are designated "Q," those for Efficacy "E," those for Safety "S," and those for joint Safety/Efficacy are "M." The FDA also has published guidance documents for each of the ICH documents that provide an interpretation of the ICH requirements consistent with the FDA's thinking.
- E. The CTD is to be organized into five modules. Module 1 is region specific, and the remaining four modules are common for all regions. Thus, the "exact" CTD document cannot be submitted worldwide, but those parts of the document that are concerned with the technical content of the application are generally, but not necessarily common. There are some specific requirements that the applicant may choose to include only in the applicable regions, and there may be preferences on the part of the applicant that influence the content of the dossier for a particular region. The CTD does not address the content of the application, it addresses the format and order in which the content is to be presented.
- Module 1 contains administrative and prescribing information. Examples are application forms and labeling. The documents in this module are specific to each region. The FDA provides industry guidance for this module in "General Considerations for Submitting Marketing Applications According to the ICH/CTD Format."
 - Module 2 contains the CTD summaries. There are seven sections in this module, and they are to be presented as follows:
 1. Table of Contents
 2. Introduction
 3. Quality Overall Summary
 4. Nonclinical Overview
 5. Clinical Overview
 6. Nonclinical Written and Tabulated Summaries
 7. Clinical Summary

The organization of the Module 2 summaries are described in the ICH documents M4Q (Quality), M4S (Safety), and M4E (Efficacy). The FDA has published these in their Guidance for Industry.

- Module 3 contains the CMC (Quality) information, and its presentation should be structured as per the format described in the M4Q Guideline.
- Module 4 contains the nonclinical study reports, and should be presented in the order described in Guideline M4S.

- Module 5 contains the human clinical study reports, and the order of presentation is described in Guideline M4E.
- F. Very specific guidance is provided both by ICH and the FDA containing both the technical content of the Quality Module as well as how it is to be presented in the CTD. For clinical trial materials, one should refer to these Guidances pertinent to the materials, formulations, manufacture, stability, and packaging information of the supplies used therein. For example: drug substance related information would be presented in the various subsections of **3.2.S.** of Module 3. Clinical trial product related information would be contained in the various subsections of **3.2.P.** of Module 3. For example, in **3.2.P.2.2**, one would describe the differences between the clinical formulation(s) and the final product formulation. In **3.2.P.2.3**, one would discuss the differences in the manufacturing process(es) used to make the pivotal clinical batches and the final product. Clinical protocols are presented in Clinical Study Reports Module. It is also to be noted that sometimes information related to clinical trial materials is pertinent to more than one module, and in those circumstances cross referencing among the modules is acceptable.
- G. Locations to the relevant ICH and FDA references can be found in Section 3.3.

3.3 References

1. <http://www.fda.gov>

cGMPs and their Relevance to Clinical Materials

3.4 Critical Learning Points

- A. Drug products used for investigational use should be produced in compliance with the cGMPs.¹ The cGMPs that apply to Investigational New Drugs are found in the Federal Register Part 21, Sections 210 and 211, and Sections 600 - 680. Additionally, the European Union has issued guidance under the European Guide to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.
- B. cGMP compliance applies to the finished drug product, the Active Pharmaceutical Ingredient (API), the placebo, and includes drugs produced by biotechnology. GMPs for APIs can be found in ICH Q7A.
- C. The manufacture of placebos for investigational use must adhere to cGMPs.
- D. Biological products are regulated in parts 600 through 680, which are supplemental to the requirements of part 211.
- E. Not all cGMP controls are appropriate for the manufacture of an investigational drug during its development.

3.5 Background, Depth, and Breadth Information

- A. Some cGMP regulations are designed for repetitive, commercial manufacture of an approved product. However, drug development in support of IND products is a staged process during which product specifications, formulations and manufacturing methods continually evolve, often at a rapid rate.² The FDA considers GMP compliance to be a “sliding scale.” This means that they must be more rigorously applied as products move forward in development.
- a. The goals of cGMP compliance during clinical development are:
 - i. to assure safe investigational products
 - ii. to assure the quality of investigational products
 - iii. to have the ability to reproduce investigational product of consistent quality as needed
 1. within a trial
 2. between trials
 3. throughout development to commercial manufacture³
 - b. During manufacture of Phase I material, less detailed application of the regulations will be expected. The FDA is considering a new guidance on approaches to complying with cGMP during Phase I.
 - c. When a product reaches Phase III clinical trials, the cGMPs are expected to be fully followed.⁴
 - i. At every clinical stage, implementation of the cGMPs should be consistent with good scientific methodology, product development, and quality principles.
 - ii. Determination of the suitability of a procedure and process should be evaluated by risk assessment and application of appropriate safeguards before, during, and after manufacture.
- B. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API. ICH Q7A covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recover from natural sources, or by combination of any of these processes.
- a. Quality
 - i. Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for approval of each batch.
 - ii. A quality unit(s) should be established, independent from production, for the approval or rejection of each batch of API for use in clinical trials.
 - iii. Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.
 - iv. Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.
 - v. Process and quality problems should be evaluated.
 - vi. Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.
 - b. Equipment and Facilities
 - i. Procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use, during all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs intended for use in clinical trials,
 - ii. Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.
 - c. Control of Raw Materials
 - i. Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or may be received with a supplier's analysis then subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice. In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

- d. Production
 - i. The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.
 - ii. Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.
 - e. Validation
 - i. Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced, or where process changes during API development make batch replication difficult or inexact.
 - ii. The combination of controls, calibration, and where appropriate, equipment qualification ensures API quality during this development phase.
 - iii. Process validation should be conducted when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.
 - f. Changes
 - i. Changes are expected during development as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.
 - g. Laboratory Controls
 - i. While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.
 - ii. A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.
 - iii. Expiry and retest dating as defined applies to existing APIs used in clinical trials.
 - iv. For new APIs, expiry dating requirements do not normally apply in early stages of clinical trials.
 - h. Documentation
 - i. A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.
 - ii. The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.
 - iii. A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.
- C. The intended use of placebos in medical treatment is to bring about a therapeutic effect, without a pharmacologically active agent, because of the psychic effect in some patients that may produce symptomatic relief. In addition, it is often used as a control in clinical trials for new drugs. Even though the chemicals from which the placebos are made are not intended to cause a direct pharmacologic response, the maintenance of their quality is important because of their use in patients, particularly in controlled drug studies. By its use, a placebo meets the definition of a “drug” contained in section 201(g) of the act. Therefore, to eliminate any doubt whether these regulations apply to placebos, the Commissioner has revised the definition to include them specifically.⁵
- D. Biological products are now manufactured according to cGMPs and regulated under parts 600 through 680 (21 CFR parts 600 through 680), in particular the establishment license and product license provisions. Sections 210.2 and 211.1 clearly provide that the more specific biologic regulations prescribed in 21 CFR Parts 600 through 680 will supplement or supersede, where appropriate, the more general drug cGMP regulations. The Commissioner believes it possible that provisions in the general cGMP regulations may be inappropriate for certain biological products and would make appropriate changes to assure that the cGMP requirements would not increase manufacturing costs without a commensurate increase in safety, purity, potency, or efficacy. However, no specific examples were submitted to the FDA in response to the proposal that can be considered as areas for exempting biological drug products.⁶

- E. The FDA has published a Guideline on the Preparation of Investigational New Drug Products (Human and Animal) (Ref: March 1991) that is a supplement to 21 CFR Parts 210 and 211 for Investigational New Drugs in the United States. The Guideline does not apply to investigational products manufactured using biotechnology.

The cGMP requirements for Investigational New Drugs are very similar to those for commercial drug products. Most of the provisions of the cGMPs apply without modification for clinical trial materials.

- a. These sections are shown in Table 3.1.

Table 3.1: cGMP Provisions that Apply to CTM Without Modification

Section of 21 CFR 21	Title
211.25	Personnel Qualifications and Responsibilities
211.34	Consultants
211.44	Lighting
211.46	Ventilation, Air Filtration, Air Heating, and Cooling
211.48	Plumbing
211.50	Sewage and Refuse
211.52	Washing and Toilet Facilities
211.56	Sanitation
211.58	Maintenance
211.63	Equipment Design, Size, and Location
211.65	Equipment Construction
211.68	Automatic, Mechanical, and Electronic Equipment
211.72	Filters
211.89	Rejected Components, Drug Product Containers, and Closures
211.94	Drug Product Containers and Closures
211.101	Charge-in of Components
211.105	Equipment Identification
211.113	Control of Microbiological Contamination
211.115	Reprocessing
211.122	Materials Examination and Usage Criteria
211.125	Labeling Issuance
211.134	Drug Product Inspection
211.137	Expiration Dating
211.142	Warehousing Procedures
211.167	Special Testing Requirements

Table 3.1: cGMP Provisions that Apply to CTM Without Modification (continued)

Section of 21 CFR 21	Title
211.173	Laboratory Animals
211.176	Penicillin Contamination
211.180	Records and Reports General Requirements
211.182	Equipment Cleaning and Use Log
211.184	Compound, Drug Product Container, and Labeling Records
211.186	Master Production and Control Records
211.188	Batch Production and Control Records
211.188	Production Record Review
211.194	Laboratory Records
211.198	Complaint Files
211.204	Returned Drug Products
211.208	Drug Product Salvaging

- b. Additional definitions not provided in 21 CFR Parts 210 and 211 are:
 - i. Verification: Documentation that a manufacturing process yielded the desired results.
 - ii. Validation: Documentation that a manufacturing process will yield the desired results.
 - iii. Review Date: Current shelf life of an active pharmaceutical ingredient, drug substance, and/or drug product which is supported by stability testing and may subject to further extension based on ongoing stability data.
 - iv. Expiration Date: Absolute shelf life of any material, which, when reached, renders the material non-useable.
- c. Some of the cGMP regulations need modification or interpretation when applied to clinical trial materials. Some examples are provided below.
 - i. 211.22 Responsibilities of the Quality Control Unit
 - 1. The developmental nature of clinical material manufacturing and packaging may require deviation from SOPs and cGMPs. The Quality Control Unit must approve the deviations and assure that they are adequately justified and documented.
 - ii. 211.42 Design and Construction Features of Buildings and Facilities
 - 1. In addition to penicillin and cephalosporin, other investigational compounds may require handling in a separate facility. The decision about the need for a separate facility or special handling techniques should be made on the basis of the best available scientific and medical knowledge about the new drug.
 - iii. 211.67 Equipment Cleaning and Maintenance
 - 1. Maintenance programs and schedules should be based on sound scientific data and reasoning. Cleaning programs and acceptance criteria should be supported by scientific data and should be established in a written program. If it is not possible to validate the cleaning program, equipment cleanliness should be verified prior to each use of the equipment. The maximum storage time period after cleaning that the equipment may be used without a recleaning or additional maintenance should be established.
 - iv. 211.80 General Requirements of Drug Product Containers and Closures
 - 1. Material status may be controlled by use of electronic systems provided the systems are validated and that they prevent the use of quarantined or rejected material.

- v. 211.82 Receipt and Storage of untested Components, Drug Product Containers, and Closures
 1. It is sometimes necessary to perform the release testing of packaging components in parallel with the use of these components in packaging and labeling operations. However, the completed package cannot be released until all of the components have been released. The procedures for the parallel testing and use of packaging components and the release of the completed product must be described in appropriate standard operating procedures and must be approved and monitored by the quality control unit.
- vi. 211.84 Testing and Approval of Components, Drug Product Containers, and Closures
 1. In the early stages of drug product development, it might not be possible to establish acceptance/rejection criteria with the same specificity as for late phase investigational materials or commercial products. The specifications should be based on scientifically sound, available data and should be updated as more information becomes available. In all stages of product development, the specifications used must be fully documented.
 2. Processing aids or highly toxic raw materials, other special materials, or materials transferred to another unit within a company's control do not need to be tested provided a manufacturer's certificate of analysis is obtained that shows the material conforms to established specifications. However, the lack of on-site testing should be justified and documented.
 3. Visual examination of the containers, labels, and documentation of batch numbers will assist in the identification of these materials.
- vii. 211.86 Use of Approved Components, Drug Product Containers, and Closures
 1. The development of investigational materials sometimes requires the need to deviate from the "first-in-first out" inventory control procedures that are common in the production of commercial drugs. It is the responsibility of the manufacturer of the drug product to make the determination whether such deviations are necessary and to justify and document the decision.
- viii. 211.100 Written Procedures; Deviations
 1. During the drug development process, written procedures and controls are often modified as new scientific data is acquired. However, at all development stages, the procedures used must be reviewed and approved prior to use, they must be followed and documented at the time of performance. Specific process parameters must be fully documented to allow review and approval by the quality control unit and to provide the basis for development of more specific procedures and records.
 2. All changes from the initial procedures must be based on sound scientific data and be reviewed and approved by the quality control unit.
- ix. 211.103 Calculation of Yield
 1. The production of investigational new drugs often requires the production of small batches that can require subdivision for several uses and applications. This can result in substantial yield discrepancies. These should be evaluated to ensure that they have not been caused by processing errors.
 2. Specifications regarding theoretical yield may be wider at initial development stages than at later stages in the drug's development. The initial yield specifications should be based on the scientific data that is available and the specifications should assure that the final product meets pre-established criteria for identity, strength, and purity. As the development process proceeds to later stages, the yield specifications will narrow and approach those that are appropriate for commercial production.
 3. If the yield discrepancies are significant or unexplained, the investigation product must not be released until an appropriate reconciliation materials used at each phase of production has been achieved and any investigations have been completed.
- x. 211.110 Sampling and Testing of In-Process Materials and Drug Products
 1. At early stages of the development process, in-process test specifications and final product specifications may be general because they are being refined as new data is obtained. The specifications used should be as complete as possible based on knowledge and experience with the product and dosage form.

2. Process validation should be conducted as additional uniform batches that are made under replicated conditions that approximate commercial scale and intent.
3. In-process specifications must be reviewed and approved before they are implemented and they must be documented to allow review and approval by the quality control unit.
- xi. 211.111 Time Limitations on Production
 1. Time limits will be estimates based on experience during early drug development stages and may be defined in SOPs.
 2. Each step of the manufacturing process must be well documented with regard to time to permit development of more specific time limits as product development proceeds.
- xii. 211.130 Packaging and Labeling Operations
 1. Additional controls must be used to assure correctness, accountability, and reconciliation of clinical trial labels which often look the same.
 2. For blinded labels, the lot number does not need to be visible on the clinical material container provided some combination of identifiers are present on the label, e.g., patient number, protocol number, kit number, etc. which enables the easy identification of the lot or control number from the code-breaking information that is supplied separately.
- xiii. 211.32 Tamper-Resistant Packaging Requirements for Over-the-Counter Human Drug Products
 1. This requirement is not applicable during the IND stages of drug development.
- xiv. 211.150 Distribution Procedures
 1. It is the responsibility of the sponsor to determine whether it is necessary to distribute the clinical materials out of the normal sequence of oldest materials first.
 2. Sufficient procedures must be in place to ensure that quarantined or expired drug products are not distributed.
- xv. 211.160 Laboratory Controls
 1. In early stages of development in-process and final product specifications may be more general because they are still being refined based on new scientific data. The specifications should be as complete and detailed as knowledge of the product permits.
- xvi. 211.165 Testing and Release for Distribution
- xvii. Test methods should be validated; however, the degree of validation will vary with the development phase of the product. At early stages, the methods should provide accurate information.
 1. For Phases I and II, the formulations evaluated are typically not the same as the final formulation that will be marketed. Test method validation at these stages should prove accuracy, sensitivity, specificity, and reproducibility of the method.
 2. Analytical methods used in stability testing should be stability indicating.
 3. Drug product that fails to meet established specifications or standards and other relevant quality control criteria must be rejected. In limited circumstances, it can be appropriate to change a specification rather than reject a lot. Such situations should be considered on a case-by-case basis using the input of all appropriate disciplines and the decision must be reviewed and approved by the quality control unit.
 4. Reprocessed material must meet appropriate standards, specifications, and any other relevant criteria before use.
- xviii. 211.166 Stability Testing
 1. Adequate stability studies that demonstrate the acceptable stability of the drug product in the containers used in the clinical trials must be in place and supported by suitable, approved written procedures.
 2. The formulation may change from one phase to the next and stability studies on the actual formulation may be performed concurrently with the clinical study. The stability study must support the duration and storage conditions of the clinical study.
 3. At least one batch of each formula used in clinical studies should be placed on stability unless bracketing of similar formulations in the same container/closure system can be scientifically justified.

- xix. 211.180 Records and Reports
 1. Production and control records related to batches of clinical trial materials should be retained for at least two (2) years after the date of termination or discontinuance of the relevant IND, or for at least two (2) years after the date of approval of the relevant new drug application.
- xx. 211.196 Distribution Records
 1. Where applicable, the product name, strength, description, and lot or batch number should be identified on the distribution records.
 2. In blinded studies, this information may be eliminated from documentation received by the clinical site. In these situations, there must be an appropriate means of identification of each product container that will allow this information to be readily obtained.
- xxi. 211.204 Returned Drug Products
 1. At the end of a clinical study, the remaining supplies are inventoried to support the verification of dosing compliance and overall study drug accountability.
 2. Procedures must be established for the return, destruction, accountability, and further use of clinical supplies.
- d. Additional Considerations
 - i. Product Imprinting
 1. 21CFR Part 206.7 specifies the requirements for imprinting solid oral dosage forms of drug products for human use. Placebo products intended for clinical investigations are not subject to the requirements of this rule if they are designed to copy the active drug products used in that investigation.
 2. If an investigational drug product is imprinted, a placebo copy may be imprinted. However, a placebo made to match a “branded” active drug product is limited by trade dress protection to the innovator of that product.
 3. If a “branded” placebo is to be made, an agreement granting permission to do so should be reached with the product innovator prior to such manufacture.
 - ii. Use of Contract Vendors
 1. A contract vendor is responsible for complying with the cGMPs during the preparation of investigational drug products.
 2. The contract vendor is an extension of the sponsor and the sponsor retains the ultimate responsibility for the final product quality and integrity.
 - iii. Testing Placebo Products for Absence of Active Substances
 1. Evidence showing the lack of active substance in placebo formulations should be provided prior to releasing placebo formulations for use in clinical studies. (Draft Guidance for Industry – INDs for Phase 2 and 3 studies of drugs, including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing and Controls Content, and Format – page 13, section V.)

3.6 References

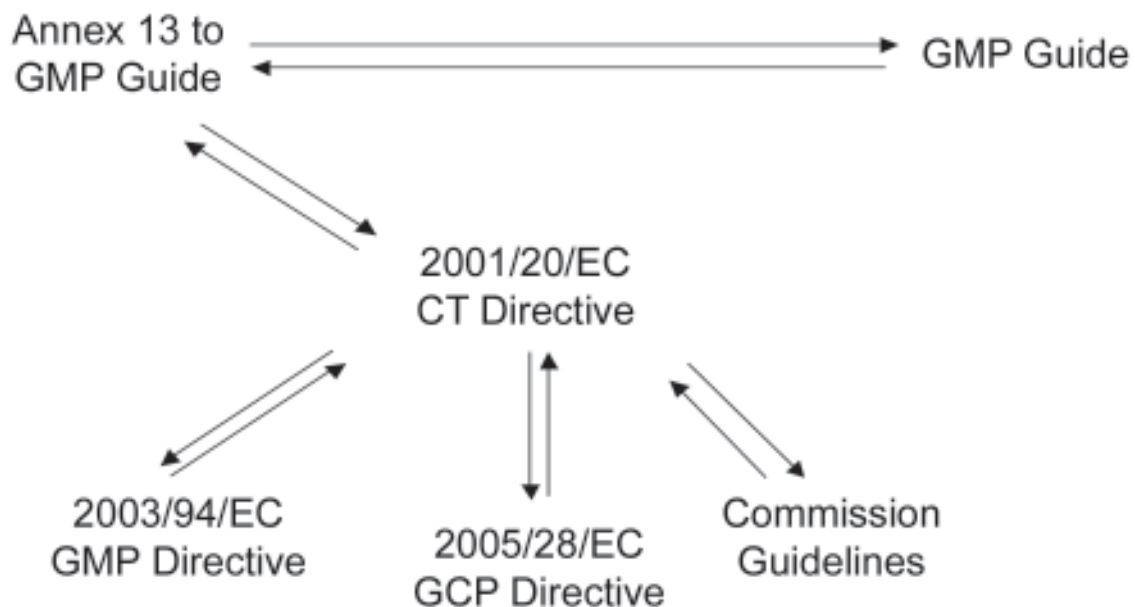
1. Guideline on the Preparation of Investigational New Drug Products (Human and Animal), FDA, March 1991) (501(a)(2)(B) Food Drug and Cosmetic Act).
2. Maiorino, Nancy, ISPE Annual Meeting, November 2003.
3. Joneckis, Chris, CBER, FDA, Rome Italy, 1 March 2005.
4. Malarky, Mary, CBER, FDA, May 2000.
5. 1978 Preamble (29 September 1978 (43 Federal Register 45014) response to comment #9).
6. Ibid., Preamble.

New EU Regulatory Environment - Implications for Clinical Supplies Management

3.7 Critical Learning Points

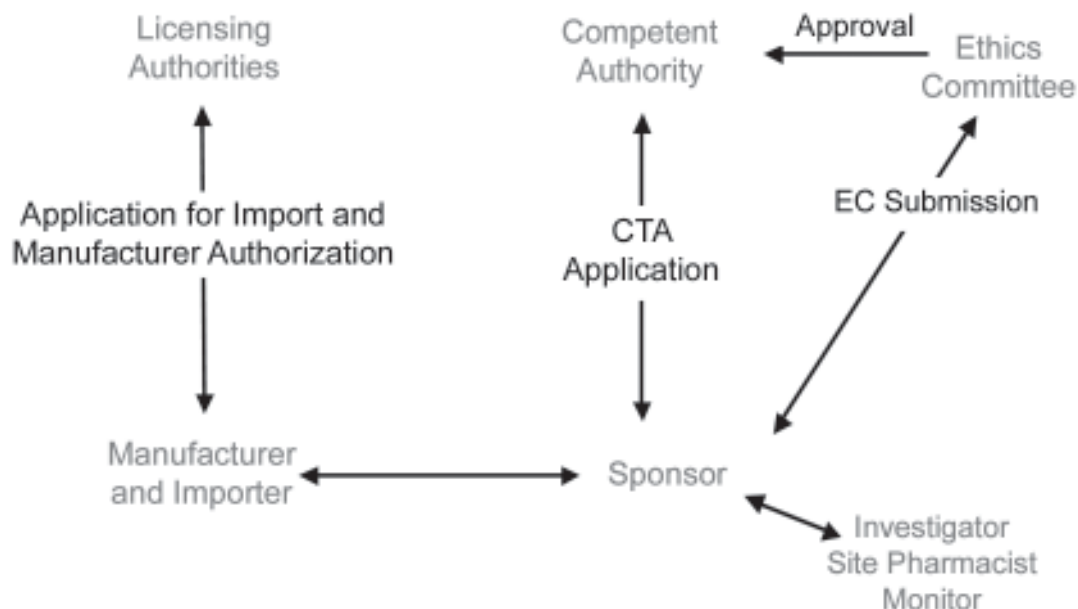
A. Understand the new EU regulatory environment on clinical supplies (IMPs):

Figure 3.1: Overview of the European GMP Legal Framework for IMPs



B. Understand the associated roles and responsibilities in clinical trials:

Figure 3.2: The CT European “Scene and Actors”



3.8 Background, Depth, and Breadth Information

A. Overview of the EU regulatory framework for clinical supplies:

1. The EU Clinical Trials Directive (2001/20/EC)
 - CT Directive deals with the implementation of GCP primarily.
 - The CT Directive was due to be implemented nationally by Member States by 1 May 2004.
 - Content overview:

Figure 3.3



- Articles that impact on IMP Supply
 - Scope – All phases (including Phase 1) of clinical trials require the authorizations of the national Competent Authority and the favorable opinion of an Ethics Committee.
 - Article 13 – Manufacture and import of investigational medicinal products, GMP requirements apply for all IMP supplied to all phases
 - Article 14 – Labeling
 - Article 15 – Verification of compliance with GCP and GMP
- Article 13 – Manufacture and Import of Investigational Medicinal Products requires:
 - Holding an authorization for manufacture or importation of IMPs is required.
 - Need for a Qualified Person (QP) certification that batches have been manufactured in compliance with EU GMP, a product specification file and the Clinical Trial Authorization (CTA).
 - For non-EU manufacturers, it is also the responsibility of the QP to assure that GMP equivalent to EU GMP are applied.
 - A globally acting company needs to define its strategy for assuring non-EU country manufacturer's EU GMP equivalence.

- Article 13 – Comparators
 - For a comparator product from a non-EU country with a Marketing Authorization, but no GMP certifying documentation, the QP must ensure that relevant analyses, tests, or checks have been performed according to the information provided in the clinical trial submission.
 - Some EU countries divergence is currently leading to the lack of predictability in the regulatory acceptance of non-EU comparators with an impact on the flexibility and efficiency of sourcing comparators for global studies.
- Article 14 – Labeling
 - Requires particulars on label to appear in at least the official language(s) of the Members States
 - Annex 13 defines the list of particulars that should be included, on the immediate container and outer packaging, unless its absence can be justified, e.g., use of a centralized electronic randomization system.
 - Commercial products having a marketing authorization in the Member State where the trial will be run, when used in its original packaging configuration (no repack or blinding), and to treat patients with the same indications as those covered by the marketing authorization, do not need to be completely relabeled. In this specific instance, a sticker with a limited amount of information can simply be added on the original container without obscuring the original labeling.
 - Several Member States require samples of the label in the national language to be provided with the submission.
- Article 15 – GMP Inspections
 - GMP inspections are mandatory for EU manufacturers and importers in order to obtain a manufacturing or import authorization.
 - The directive has provisions for EU competent authorities to inspect non-EU manufacturers if deemed necessary, “they should be reserved for higher risk situations rather than being routinely employed” (Community Compilation of procedures).
 - Applicants should consider making early contact when planning a submission.

2. Revised Annex 13 – Selection

- Note – Not all products used in a clinical trial are considered as IMPs; therefore, they are out of scope (e.g., labeling, information for the submission). Such products may be used as support or escape medication for preventive, diagnostic, or therapeutic reasons. They also may be used to induce a physiological response.
- Product Specification File – Should include, or refer to, the following documents:
 - specifications and analytical methods for starting materials, packaging materials, intermediate, bulk, and finished product
 - manufacturing methods
 - in-process testing and methods
 - approved label copy
 - relevant clinical trial protocols and randomization codes, as appropriate
 - relevant technical agreements with contract givers, as appropriate
 - stability data
 - storage and shipment conditions
- Release of Batches - Release of investigational medicinal products should not occur until after the Qualified Person has certified batch compliance with EU GMP or equivalent, the product specification file and the approved submission.

- EU GMP Equivalence – For non-EU manufacturers, 'The QP should determine that equivalent standards of GMP apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through participation in audit of the manufacturer's quality systems.'
- Two-Step Release Procedure – Before any shipment to trial site, it is needed to have:
 - batch certification by QP (technical green light)
 - regulatory release = Positive Ethics Committee opinion and approved submission (regulatory green light)
- Chain of Responsibilities – When IMPs are manufactured and packaged at different sites under the supervision of different QPs, written agreements must be in place to clearly define their respective roles and responsibilities in the release process and on quality matters.

3. GMP Directive 2003/94/EC – Key Elements

- Compliance with the Approved CTA – Clarification provided that the QP batch certification should be done against the submission "as accepted by the Competent Authorities."
- Importation of IMPs – When investigational medicinal products are imported from non-EU countries, analytical control is not mandatory. The potential need for testing will depend on the GMP assessment for importation by the QP.
- Training of Personnel – "The personnel shall receive initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of Quality Assurance and GMP..."
- Batch Documentation Retention Time – "Five years after end or formal discontinuation of the trial"
- Validation Requirements – "The manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of the product development. At least the critical process steps, such as sterilization, shall be validated."
- Retained samples – "Two years after completion or discontinuation of the trial"

4. GCP Directive 2005/28/EC – Content Impacting Clinical Supplies

- Provides the requirements for the application and maintenance of the manufacturing or importation authorizations for IMPs.
- A manufacturing authorization is not required "for reconstitution use or packaging, where those processes are carried hospitals, health centers or clinics, by pharmacists or persons legally authorized in the Member States to carry such processes and if the investigational medicinal products intended to be used exclusively in those institutions."

5. Member States Specificities

- The referenced Commission directives are setting the minimum requirements in the EU and have to be transposed into the national laws to become effective in the Member States. It means that some of them:
 - are or have been late for implementing the new requirements
 - have added, through this transposition process, national requirements going beyond the requirements laid down in the EU directives (e.g., labeling requirements)
 As a result and although the new regulations have brought harmonization across Europe, specific national requirements for clinical supplies are still to be taken into consideration.

		With Secondary Packaging					Primary Packaged Only	Commercial Pack (Article 14 of Directive 2001/20/EC)	Period of Use Update
		Any Carton	Primary Container (I)	Primary Container (NI)	Blister or Small Packaging Units (NI)				
(a) (i)	Name of the sponsor, contract research organization, or investigator	✓	✓	✓	✓	✓	✓	✓	
(a) (ii)	Address and Telephone Number of the sponsor, contract research organization, or investigator (the main contact for information on the product, clinical trial, and emergency unblinding). Unless patient is provided with a leaflet or card that provides these details and has been instructed to keep it in their possession at all times.	✓	✓				✓		
(b)	Pharmaceutical Dosage Form	✓	✓	✓			✓		
	Route of Administration	✓	✓	✓ (unless OSDF)	✓ (unless OSDF)		✓		
	Quantity of Dosage Units and in the case of Open Trials, The Name/Identifier	✓	✓	✓	✓		✓		
(c)	Strength/Potency	✓	✓	✓	✓		✓		✓ (original must not be obscured)
	The batch and/or code number to identify the contents and packaging operation								
	A trial reference code allowing identification of the trial, site, investigator, and sponsor if not given elsewhere	✓	✓	✓	✓		✓		
(d)	A trial reference code allowing identification of the trial, site, investigator, and trial subject							✓	
	The trial subject identification number/treatment number and where relevant, the visit number	✓	✓	✓	✓		✓		
	The name of the investigator (if not included in (a) or (d))	✓	✓				✓		
(e)	Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	✓	✓				✓		
(f)	For clinical trial use only or similar wording	✓	✓				✓		
(g)	The storage conditions	✓	✓				✓		
(h)	Period of use (use-by date, expiry date, or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity	✓	✓				✓		✓
(i)	Keep out of reach of children except when the product is for use in trials where the product is not taken home by subjects	✓	✓				✓		

B. The roles and responsibilities in EU clinical trials: **Table 3.3**

Activity	Sponsor	Manufacturer/ Importer	Qualified Person	Monitor	Site Pharmacist
2001/20/EC					
Submission of the Clinical Trial Authorization application to the Competent Authority	Responsible	-	-	-	-
Submission of the application to the Ethics Committee	Responsible	-	-	-	-
Hold the Manufacturing Authorization	-	Responsible	-	-	-
Have a Qualified Person at disposal	-	Responsible	Fulfil legal requirements for QPs	-	-
2003/94/EC					
IMPs are manufactured according to GMPs at least equivalent to EU GMPs	-	Responsible	Responsible (Batch certification)	-	-
IMP is manufactured according to the submission (CTA)	-	Responsible	Responsible (Batch certification)	-	-
Complaints and Recalls (see also Annex 13)	-	Responsible	Involvement	-	-
Retention Samples	-	Responsible	-	-	-

Table 3.3 (continued)

Activity	Sponsor	Manufacturer/ Importer	Qualified Person	Monitor	Site Pharmacist
Annex 13					
Quality System for manufacturing IMPs under GMP	Awareness	Responsible		-	-
Product Specification File	-	Responsible	Have access	-	-
Batch Certification (technical green light)	-	-	Responsible	-	-
Batch Release (regulatory green light)	Responsible	-	-	-	-
Order	Responsible	Operate under	Ensure compliance with	-	-
Shipping Instructions	Responsible	-	-	-	-
Site Transfer of IMPs	-	Re-label as necessary	Evaluate for re-certification as necessary	Provide product storage history at site	Provide product storage history at site
Change of "Use-By" Date	Responsible	May perform	Authorize new date	May perform	May perform
Complaints (see also 2003/94/EC)	Responsible		Involvement	Assess potential impact on subjects	Assess potential impact on subjects
Recalls	Responsible		Involvement	Understand the obligations	Understand the obligations
Return and Destruction	Define conditions	Store and keep inventory records	-	Verify documents at site	Assure drug accountability at the site

3.9 References

1. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
3. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
4. Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regard investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products. Published in the official journal, 9 April 2005.
5. EU GMP Guide and annexes on the EudraLex Web site: <http://pharmacos.eudra.org/F2/home.html>

4 Project Planning and Management and Clinical Trial Design

Study Protocols

4.1 Critical Learning Points

- A. Clinical Trial protocols are an essential part of the drug development/approval process and a regulatory requirement.
- B. Each protocol contains standard sections.
- C. Development of a protocol is a collaborative effort.
- D. Protocol approval occurs at many levels and approval must be given by several groups involved in the Clinical Trial process.
- E. Involvement of the Clinical Trial Material Project Manager (CTM PM) begins at the inception of a Clinical Trial.
- F. Generation of the packaging/labeling section is the responsibility of the CTM PM.
- G. Many other protocol sections impact the final package design and quantity of CTM required for a Clinical Trial.

4.2 Background, Depth, and Breadth Information

- A. By US statute, each Clinical Trial must have a written protocol. ("Protocol for and Conduct of a Clinical Investigation," US 21 Code of Federal Regulations 54.120).¹ The FDA also published a "Good Clinical Practice: Consolidated Guidance" in the *Federal Register* on 9 May 1997 (62 FR 25692). The Guidance is applicable to drug and biological products.² The Guidance was developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH GCP Guidance provides a unified standard for the European Union, Japan, and the US to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. For more information about the ICH refer to "Overview of ICH: A description of the structure and harmonization process."³

The ICH GCP Guidance defines Good Clinical Practice as "A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected." (E6 1.24)

The ICH GCP Guidance defines a protocol as "A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents." (E6 1.44)

For information about the evolution of Clinical Trials see Reference 4.

- B. Minimum requirements for protocol content are suggested in the ICH GCP Guidance. Content from protocol to protocol may vary based upon many factors such as size of the projected trial, Phase, characteristics of the investigational drug, and number of sites and/or countries.

See references for protocol requirements² and for an in depth description of clinical protocols.⁵

- C. After selection of the clinical trial design,⁶ creation of the protocol can be initiated. Cross-functional teams are responsible for the preparation and review of this key trial document. Core members of the team might include Clinical Research, Clinical Data Management, Trial Team Leader, Trial Monitors, Medical, Medical Communications, Regulatory, and Statistics. Although not core members, other disciplines are essential to the development of a protocol and should contribute during the preparation and review process. These groups might include Clinical Trial Material Project Management, Pharmaceutical Sciences and Toxicology.^{5,7} Refer to your company's SOP or guideline for generation and approval of protocols for specific detail. Many companies utilize protocol templates which standardize text for some sections.
- D. The protocol approval process by the sponsor company occurs at many levels. The pathway might include review by the cross-functional team; next the head of the related Therapeutic Area, and final approval by the company's Protocol Review Committee or equivalent. The next step normally required is filing to the appropriate regulatory authority(ies) for review. Prior to initiating the study at the investigational site, an Institutional Review Board/Independent Ethics Committee (IRB/IEC) also reviews and approves the protocol. Another responsibility of the IRB/IEC is to review and approve the Informed Consent form. Informed Consent is a process by which a trial subject voluntarily confirms his or her willingness to participate in a trial after having been informed of all relevant aspects of the trial.^{2,8,9}
- E. Whether a core member of the clinical trial team or by indirect influence, the CTM PM should be intimately involved in all stages of protocol development. Information contributed by the CTM PM can greatly impact a clinical trial. For example, if a blinded comparator(s) is required, the timeline for acquiring or developing the comparator could take nine to 12 months. This information could influence the selection of the trial initiation date. Early exposure to proposed protocols also may allow for advanced manufacturing planning as well as ensuring appropriate stability data is available for the type of packaging required.¹⁰
- F. The CTM PM is responsible for information relating to the investigational drug in each protocol. This information is described in the following sections of the ICH GCP Guidance, "Manufacturing, Packaging, Labeling and Coding Investigational Product(s)" (E6 5.13), "Supplying and Handling Investigational Products(s)" (E6 5.14), and "Treatment of Subjects" (E6 6.6). In general, the CTM PM should provide any information relating to the formulation, blinding, packaging, labeling, identification, kit design, handling, and storage of the investigational drug.^{2,10}
- G. It is a good practice to review and, if appropriate, assist in the development of all sections impacting the investigational drug during the protocol generation and review process. Look for information regarding method of treatment assignment, randomization, and stratification; dose selection and timing; blinding of study treatments, subject replacement procedures, visit schedules, and product needed in addition to the investigational drug(s) such as rescue medication. Another helpful section is the trial summary or synopsis which lists the number of trial centers, sites/country(ies), trial duration, type of blinding, and trial Phase.^{2,10}

4.3 References

1. US 21 Code of Federal Regulations 54.120.
2. E6 Good Clinical Practice: Consolidation Guidance, <http://www.fda.gov/cder/guidance/959fnl.pdf>.
3. Underdonk, Christy, Food and Drug Administration, Office of International Programs, "Overview of the ICH: A Description of the Structure and Harmonization Process," <http://www.fda.gov/cder/audiences/iact/Brussels%20publicmeetin/sld001.htm> and <http://www.fda.gov/cder/audiences/iact/iachome.htm>
4. Mohan, Kshitij, and Harold E. Sargent, "Clinical Trials, An Introduction," *Medical Device and Diagnostic Industry*, January 1996, pp. 114-119.
5. Spilker, Bert, *Guide to Clinical Trials*, Lippincott, Williams, and Wilkins, 2000, Part II, pp. 145-273.
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7. Erich, Jan A., David F. Bernstein, and Kevin Sills, "Defining the Clinical Supply Process: The Manufacturing, Packaging, and Labeling Protocol," *Pharmaceutical Technology*, March 1996.
8. Spilker, Bert, *Guide to Clinical Trials*, Lippincott, Williams, and Wilkins, 2000, Chapter 27, "Informed Consent and Ethics Committee/Institutional Review Board Processes," pp. 202-218.
9. Spilker, Bert, *Guide to Clinical Trials*, Lippincott, Williams, and Wilkins, 2000, Chapter 126, "Interactions of Regulatory Departments, Regulatory Authorities, and Medical Departments," pp. 1006-1027.
10. Eli, Massimo, Jim Freeman, Jorgen Midander, Rob Pizzie, and Bob Shaffer, "Proactive Strategies for Matching Clinical Supply with Clinical Demand," *Pharmaceutical Engineering*, September/October 2003, Vol. 23, No. 5, pp. 8-16.

Randomizations

4.4 Critical Learning Points

- A. Randomization can be defined as "the process of assigning trial subjects to treatment and control groups using the element of chance; random treatment assignments are performed to reduce bias."¹
- B. A randomization scheme determines the order of treatment assignments to patients.
- C. Various terminologies (e.g., kit list, double randomization, random codes) have been used to describe a file with a randomized sequence of treatment linked to a unique number. This list is used for packaging purposes.
- D. A randomization scheme and kit list is linked when a Centralized Randomization System is utilized.
- E. Randomization files must be handled in a controlled manner.

4.5 Background, Depth, and Breadth Information

- A. The term 'Randomization' is often associated with the process by which patients in a clinical trial are assigned to treatment groups (e.g., active or placebo). As the name infers, patients are *randomly* allocated to receive one of two or more treatments. The purpose of randomization is to reduce bias in the process of treatment assignments. This means that patients are assigned to treatment groups without regard to patient characteristics or study personnel desires or biases. This is accomplished through the simple principle that bias can not occur if study personnel do not have knowledge, nor can they predict, the next treatment assignment.

The practice of randomizing patients to treatment groups was first highlighted in the 1930s and 1940s in Britain and was led by Dr. Austin Bradford Hill. Prior to the practice of randomization, patients were often allocated to treatment groups using the practice of 'alternation', i.e., alternately allocating patients from one treatment to another.²

- B. In a Randomized Clinical Trial (RCT), patients are typically allocated to a treatment assignment based upon a fixed randomization list or by a dynamic randomization process.

For trials where a fixed list is utilized, a randomization scheme is created prior to the start of the trial, usually by a statistician. A randomization scheme is a list of randomized treatment assignments and the order of the list dictates which treatment a patient will be assigned. For example (Table 4.1), if the treatment order in the scheme is 'active,' 'placebo,' 'active,' then the first and third patient entered in the trial will be assigned to the active treatment and the second patient to the placebo treatment.

Table 4.1: Example of a Randomization Scheme

Patient	Treatment
1	Active
2	Placebo
3	Active

The creation of a randomization scheme is based upon a number of factors, including the number of patients, the block size, the number of treatment groups, the treatment ratio, and stratification factors. The predominant type of randomization scheme is called a permuted block design. The permuted block design strongly enforces a balanced allocation of treatment assignments over the duration of the recruitment period. This is accomplished by ensuring that for every n patients, the desired treatment ratio (e.g., 1:1 or 2:1) is maintained. The value of n is termed the 'block size.' For example (Table 4.2), if the block size was four and the treatment ratio was 1:1, the treatment assignments within the block would include two active assignments and two placebo assignments listed in a random order.³

Table 4.2: Example of a Permuted Block Randomization Scheme

Patient	Block	Treatment
1	1	Active
2	1	Placebo
3	1	Placebo
4	1	Active
5	2	Placebo
6	2	Active
7	2	Placebo
8	2	Active

As opposed to a randomization scheme which is a fixed list, an adaptive randomization is dynamic and the treatment assignments change based upon the type of patients randomized. An adaptive (or dynamic) randomization method is most often used when the number of patients to be recruited is limited, yet it is important that each treatment group be balanced with respect to certain patient characteristics. As each patient is randomized, the probability of the next patient being assigned to a given treatment group changes based upon the patient characteristics of the patients already assigned to that treatment group.

- C. Various terminologies (e.g., kit list, double randomization, random codes) have been used to describe a file with a randomized sequence of treatments linked to a unique number. This list is used for the purpose of packaging; however, the structure of this list and how it relates to the randomization scheme will differ based upon the method of randomization and distribution of the drug supply.

Single randomization is often used when the randomization method is not centralized (i.e., an IVR or Web-based system is not used) and randomization must take place at each site. In this scenario, the randomization scheme and the kit list are created together as a 'single' list (Table 4.3). The kits are often numbered sequentially and the treatment in each kit corresponds to the sequence of treatment assignments in the randomization scheme.

Table 4.3: Example of a Single Randomization

Patient	Block	Treatment	Kit Number
1	1	Active	101
2	1	Placebo	102
3	1	Placebo	103
4	1	Active	104
5	2	Placebo	105
6	2	Active	106
7	2	Placebo	107
8	2	Active	108

In single randomization, the assignment of a kit to a patient is fixed at the point of packaging. For example, in Figure 4.3, the first patient will receive kit 101, the third patient will receive kit 103, and so on. The primary benefit of a single randomization is that each site may simply pick the lowest numbered kit for each patient and the randomization scheme will be followed. The downside of single randomization is that the kits must be used in a fixed order, which limits flexibility in the distribution process.

When the randomization method is centralized (e.g., IVR, Web-based enrollment), double randomization is often used as it increases the efficiency of study drug distribution. As the name implies, double randomization involves the use of two independent lists, a randomization scheme, and a kit list. Prior to the start of the trial, the randomization scheme is created independently from the kit list. In this scheme (Table 4.4), only the treatment assignments are included. It is important to note there is nothing in the scheme pertaining to kit number.

Table 4.4: Double Randomization - Randomization Scheme

Site	Block	Treatment
101	1	Active
101	1	Placebo
101	1	Placebo
101	1	Active
101	2	Placebo
101	2	Active
101	2	Placebo
101	2	Active

The kit list is then created which associates a kit number to a treatment type. Sequence is often included in the list to assist with the packaging process. In this example, the kit numbers are three-digit random numbers. Kits may be packaged and shipped in any order as long as the inventory shipped to each site is tracked.

Table 4.5: Double Randomization – Kit List

Sequence	Kit Number	Treatment
1	223	Active
2	345	Active
3	125	Active
4	462	Active
5	241	Placebo
6	234	Placebo
7	352	Placebo
8	113	Placebo

- D. So, if the kit list and the randomization scheme are two independent lists, how is a patient assigned a kit number? The central randomization program (e.g., IVR or web-based system) utilizes information from the randomization scheme (i.e., to which treatment is the next patient randomized) and the information about which kits are in inventory at a site to determine which kit number to assign. The following is an example of how the first two patients at site 101 and 102 would be randomized to a kit number.