



# Good Practice Guide

# Clinical Supply Systems

Data Standards

Functionality and Design

System Interfaces

- Packaged Box (1)
  - Booklet Label (1)
  - Carton (1)
  - Foam (2)
  - Foam (1)
  - Tamper Evident
- Packaged Vial (2)
  - Vial (1)
  - Booklet Label
- Packaged Vial in a Packa

- Packaged Blister Card (1)
- Tamper Evident Seal (1)
- Blister Card (1)
- Packaged Blister Strip (1)
- Film (0)
- Foil (0)

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## Good Practice Guide

# Clinical Supply Systems

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ISBN 978-1-936379-68-2

# Preface

Many biopharmaceutical organizations have numerous internal systems that are used to manage and control clinical studies and investigational medicinal products, or use third party providers to perform at least some of their investigational medicinal product management activities. Currently, there are no standards or guidelines for system functionality that manage investigational medicinal products.

Lack of standards for data and functionality has resulted in varying terminology, data formats, and controls which can often make the selection, use, and/or interfacing of systems challenging. This Guide, the ISPE Good Practice Guide (GPG): Clinical Supply Systems, contains a list of proposed standard data terminology along with frequently used equivalent terms, definitions of the data terms, and data formatting standards.

The Guide also provides a detailed discussion of important areas of clinical supply system functionality touching on key business requirements to assist interested parties in developing customized clinical supply applications or assessing commercial off the shelf systems for implementation. The Guide provides examples and requirements for interfacing clinical supply systems involved in the management of investigational medicinal products with other internal or external systems.

# Acknowledgements

The Guide was produced by a Task Team led by David Riege (Pfizer). The work was supported by the ISPE Investigational Products Community of Practice (IP COP).

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The Team Leads would like to express their grateful thanks to the many individuals and companies from around the world who reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

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# 1 Introduction

## 1.1 Background

A wide variety of computer systems are currently employed by biopharmaceutical organizations and third party service providers to manage Investigational Medicinal Products (IMPs) throughout their life cycle (e.g., planning, manufacturing, label design, packaging and labeling, distribution, Interactive Response Technology (IRT), drug accountability, returns, destruction).

A survey conducted by the ISPE Investigational Products Community of Practice (IP COP) indicates that many of the applications in use are either fully customized applications or Commercial off the Shelf (COTS) applications developed specifically for IMPs, or highly customized COTS applications developed for the management of commercial products.

Most biopharmaceutical organizations utilize multiple third party providers to perform at least some of their IMP management activities. Additionally, most biopharmaceutical organizations have numerous internal systems that are utilized to manage and control clinical studies and IMPs. There is often a significant benefit in interfacing the internal clinical supply chain system with other internal or external systems to maximize process efficiencies, to provide full visibility of inventory and lot genealogy to each individual patient, and to ensure robust quality and regulatory controls of IMPs.

Currently, there are no standards or guidelines for system functionality that manage IMPs. Lack of standards for data and functionality has resulted in varying terminology, data formats, and controls which can often make the selection, use, and/or interfacing of systems challenging.

## 1.2 Scope

This Guide, the ISPE Good Practice Guide (GPG): Clinical Supply Systems, contains a list of proposed standard data terminology, as well as equivalent terms which are frequently used, definitions of the data terms, and data formatting standards.

The Guide also provides a detailed discussion of important areas of clinical supply system functionality touching on key business requirements to assist interested parties in developing customized clinical supply applications and/or assessing COTS systems for implementation. Examples and requirements for interfacing clinical supply systems involved in the management of IMPs with other internal or external systems is provided.

This Guide will be useful for individuals with a foundational background in clinical supplies, who are involved in evaluating or designing clinical supply systems which meet operational, quality and regulatory requirements.

This Guide also may be useful to personnel in smaller biopharmaceutical organizations to assess the systems that their suppliers use to support the clinical supply services they provide. This Guide is also meant to help companies adopt common data standards to make working across company boundaries more seamless.

It is important to note that this document is a Guide. Each company should determine requirements for their systems based on business priorities and their interpretation of current regulatory and quality requirements.

### 1.3 Key Concepts/Terms

This Guide has been written using the proposed standard terms that are listed in Appendix 1. If a term used is unfamiliar when reading the Guide, please refer to Appendix 1 for a definition of the term and commonly used equivalent terms.

**Note:** it is assumed that readers of this Guide will have basic knowledge of the clinical supplies domain. Readers interested in this Guide who may not have full familiarity with the clinical supplies area are encouraged to also refer to the ISPE Training Guide on Clinical Supplies [1].

## 2 Data Standards

### 2.1 Introduction

In order for the data exchange process to function successfully, several points of harmonization should be established with internal or external partners who will exchange information electronically (system-to-system): vocabulary harmonization and data set harmonization.

### 2.2 Metadata

Exchange partners should agree to a standard set of metadata vocabulary. Partners also should agree to either use the same terms or to provide a stable metadata vocabulary for easy mapping.

Exchange partners also should agree to adhere to specified data set formats within the data sets. Where feasible, exchange partners should use any industry standards for data exchange (e.g., flat files, Extensible Markup Language (XML), or Electronic Data Interchange (EDI)).

Frequently used clinical supply system metadata, analogous terms, descriptions, and recommended formats are provided in Appendix 1. Metadata has been logically classified or grouped into the categories listed in Table 2.1.

**Table 2.1: Data Set Classification**

|          |
|----------|
| Material |
| Lot      |
| Depot    |
| Protocol |
| Contact  |
| Address  |
| Shipment |

**Note:** data elements could be used in multiple areas and/or for other purposes.

The metadata listed in Appendix 1 is intended to include data that would typically be found in a supply system and/or shared with other systems.<sup>1</sup> The recommended terms and formats for each data element are provided to assist in designing systems that can easily be interfaced with other systems designed following the same, or similar, standards.

<sup>1</sup> The Metadata list does not include all possible data elements that could be found in a clinical supply system.



## 3 Functionality and Design Considerations

### 3.1 Material Requirements Planning

Although well-established in the commercial sector, formal Materials Requirements Planning (MRP) processes have not traditionally been formally or fully applied in the pharmaceutical Research and Development (R&D) sector for Clinical Supplies. However, some organizations have now adopted and successfully applied several aspects of MRP in the R&D setting.

MRP is a set of techniques used to:

1. Calculate requirements for materials
2. Plan supply orders to meet those requirements

When determining the total requirements for clinical supplies, all individual requirements for a material are compiled as MRP runs at the material level.

#### 3.1.1 *Independent Demand and Dependent Demand*

Demand is typically comprised of the elements:

- How much is needed?
- Where is it needed?
- When is it needed?

Independent demand is not dependent on demand for another material and is forecasted.

Dependent demand is dependent on demand for another material and is derived from the Bill of Material (BOM).

#### 3.1.2 *Demand Forecasting for Kits*

Demand forecasting for kits (clinical finished materials) creates an independent requirement for kits at the distribution centers which supply clinical sites.

#### 3.1.3 *Planning for Kits at a Distribution Center*

Requirements for kits include:

1. Independent requirements (demand forecasts)
2. Inventory management parameters, such as safety stocks

The “Required Use-By-Date” is a key attribute of the requirements for kits and ensures that the associated supply order has only the minimum shelf-life remaining. The minimum shelf-life duration typically includes:

- Transit time from a distribution center to clinical sites
- Storage time at clinical sites
- The use period of the kit by the patient

MRP evaluates any requirements for kits against inventory to determine whether there is a need for kits at a distribution center. Where required, the distribution center creates a requisition (e.g., purchase requisition to buy or order to make) for kits from a packaging facility.

The “Required Use-By-Date” is a key attribute of the requisition and ensures that the associated supply order meets the requirement which initiated the requisition. The requisition activates a requirement for kits at a packaging facility with a requirements date that should factor in the:

- Transportation time from the packaging facility to the distribution center
- Goods receipt
- Usage decisions at the distribution center

### **3.1.4 Planning for Kits at the Packaging Facility**

Where a requisition activates a requirement for kits at a packaging facility, MRP can be used to decide whether to “make” or “buy:”

- If “make,” the packaging facility creates a planned order to make the kits.
- If “buy,” the packaging facility creates a requisition (e.g., purchase requisition to buy or order to make) to buy kits from a supplier.

The clinical supply system should provide the capability to assess the planning impact at the packaging facility, distribution centers, and clinical sites for different “Required Use-By-Date” scenarios, e.g.:

- The “Start Date” of a planned order is dependent on the time it takes the packaging facility to make kits, including batch usage decisions.
- The “Release Date” of a requisition (e.g., purchase requisition to buy or order to make) is dependent on the time it takes the supplier to deliver kits to the packaging facility, goods receipt, and batch usage decisions.

The BOM for kits drives dependent demand for component materials (including drug products) at the packaging facility. The requirements for drug products consist of:

1. The dependent demand derived from the BOM for kits
2. Inventory management parameters, such as safety stocks of drug products at the packaging facility

The requirements date is dependent on when the drug product is needed in the packaging process. MRP evaluates the requirements against inventory to determine whether there is a need for drug products at the packaging facility. Where required, the packaging facility creates a requisition (e.g., purchase requisition to buy or order to make) for the drug products. This requisition initiates a requirement for drug products at the manufacturing facility, with a requirements date that factors in:

- Transportation time from the manufacturing facility to the packaging facility
- Goods receipt
- Usage decisions at the packaging facility

### 3.1.5 *Planning for Drug Products at the Drug Products Manufacturing Facility*

The requirements for drug products at the drug products manufacturing facility are determined by the requisition from the packaging facility. Independent requirements for drug products, e.g., for stability testing, are determined within the drug products manufacturing facility. MRP evaluates the requirements against inventory to determine whether there is a need for drug products at the manufacturing facility. Where required, MRP can be used to decide whether to “make” or “buy:”

- If “make,” the manufacturing facility creates a planned order to make the drug product.
- If “buy,” the manufacturing facility creates a requisition (e.g., purchase requisition to buy or order to make) to buy drug product from a supplier.

The clinical supply system should provide the capability to assess the planning impact at the manufacturing facility:

- The “Start Date” of a planned order is dependent on the time it takes the manufacturing facility to make drug product, including batch usage decisions.
- The “Release Date” of a requisition (e.g., purchase requisition to buy or order to make) is dependent on the time it takes the supplier to deliver drug product to the packaging facility, goods receipt, and batch usage decisions.

The BOM for drug products drives dependent demand for component materials (including drug substance) at the drug products manufacturing facility. The requirements for drug substance consist of:

1. The dependent demand derived from the BOM for drug products
2. Inventory management parameters, such as safety stocks of drug substance at the manufacturing facility

The requirements date is dependent on when the drug substance is needed in the drug products manufacturing process. MRP evaluates the requirements against inventory to determine whether there is a need for drug substance at the drug products manufacturing facility.

Where required, the drug products manufacturing facility creates a requisition (e.g., purchase requisition to buy or order to make) for the drug substance. This requisition (e.g., purchase requisition to buy or order to make) initiates a requirement for drug substance at the drug substance manufacturing facility with a requirements date that factors in:

- Transportation time from the drug substance manufacturing facility to the drug products manufacturing facility
- Goods receipt
- Usage decisions at the drug products manufacturing facility

## 3.2 **Drug Product BOMs/Material Masters**

### 3.2.1 *Drug Product Material Masters*

A drug product is a finished dosage form (e.g., tablet, capsule, or solution) that contains an active ingredient (drug substance), usually in association with one or more inactive ingredients. The term also can be used for a finished dosage form which is intended to be used as a placebo and does not contain an active ingredient.

Materials tracked in an inventory management system should be defined using a material master. A material master is a collection of attributes that describe and uniquely identify a material. Each material master should be referenced by a unique material identification (ID).

**Table 3.1: Common Attributes of a Drug Product Material Master**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Material ID                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Material Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Material Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Material Subtype                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Compound Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Generic Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Trade Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Potency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Unit of Measure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Controlled Substance Code                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Storage Temperature                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Storage Restriction                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Version Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Notes:</b><br>1. Material Type is a classification used to group materials. Typical material types include: <ul style="list-style-type: none"> <li>• Dosage Component</li> <li>• Dosage Form</li> <li>• Packaging Component</li> <li>• Packaged Material</li> </ul> 2. Material subtype is a sub-classification used to group materials under a material type. For example, typical material subtypes found under a dosage form material type would be: <ul style="list-style-type: none"> <li>• Capsule</li> <li>• Tablet</li> <li>• Syringe</li> <li>• Vial</li> </ul> |

**Note:** a material master is the clinical supplies definition of the material's composition and key attributes; it does not imply whether or not there is any physical inventory of that material.

### 3.2.2 *Bill of Materials*

The material composition or “recipe” of a dosage form is normally referred to as a BOM. The BOM contains a linked relationship between the material masters of the dosage form and the component materials. The dosage form and each component material should have a material master defined in the clinical supply system. BOMs are usually represented in a tree structure diagram with the dosage form at the top. Each component material is added to the tree structure with the required quantity of that material to make one unit of a single dosage form.

Where component materials or quantities required differ, the formulation of each dosage form will have a specific BOM. For example, a 500 mg tablet of a product will have a different BOM to that of a 250 mg tablet of the same product.

Where MRP or forecasting is used, a planning BOM may be defined early in the drug development process for use during planning. Where the formulation of the dosage form needs to change, the BOM may undergo several changes before creation of the final version used for manufacturing. This could be managed within the clinical supply system by using different statuses.

Only approved final BOMs are used for manufacturing execution.

Examples of how BOMs are used include:

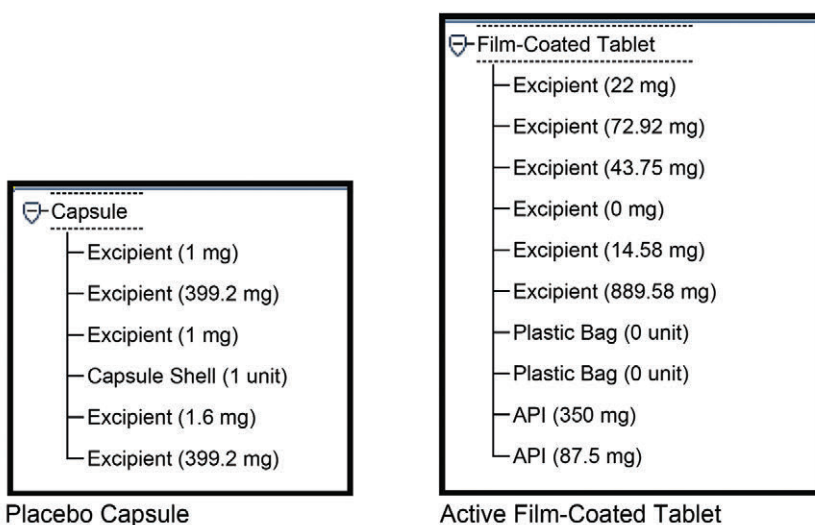
- During manufacture of dosage forms
- To provide material list and quantities
- For calculations of batch sizes
- For verification after dosage form manufacture
- In batch records

**Note:** a BOM is the clinical supply system's definition of the material (dosage form); the existence of a BOM does not imply any physical inventory of that dosage form.

### 3.2.3 Single Level BOM

Where none of the component materials of a dosage form have a BOM, a single level structure may be sufficient for the BOM. The relationship shown in Figure 3.1 includes the higher level dosage form and each of the component materials with the required quantity.

**Figure 3.1: Single Level BOM**

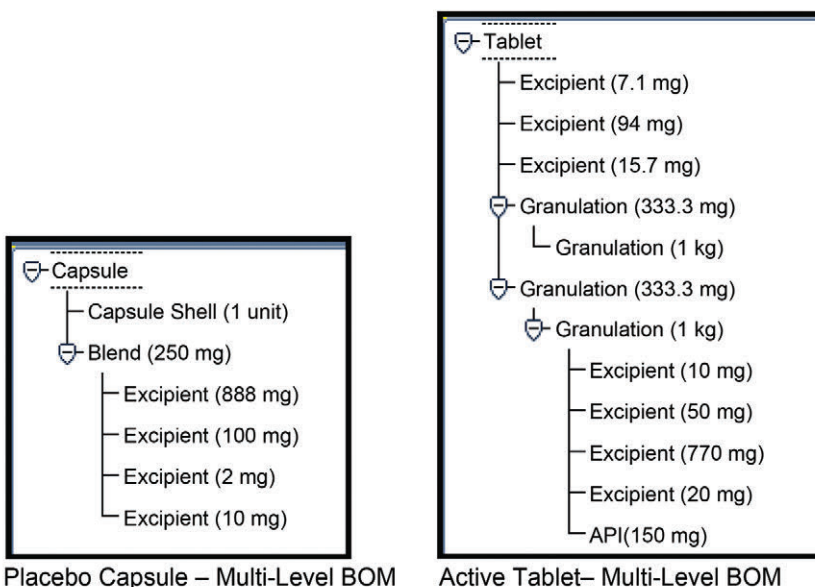


**Note for Figure 3.1:** combination products may have more than one Active Pharmaceutical Ingredient (API) in a single BOM.

### 3.2.4 Multi-Level BOM

A dosage form that contains other dosage forms, which are called “intermediates,” requires a multi-level BOM. The structure should contain the component materials for each of the dosage forms with their required quantities (see Figure 3.8).

**Figure 3.2: Multi-Level BOM**



Multi-Level BOMs can be defined as either “Top Down” or “Bottom Up.”

- A “Top Down” definition starts with the top level dosage form and associates each component material and quantity, including the intermediate and its BOM.
- A “Bottom Up” design defines each intermediate dosage form independently with its own BOM. The top level dosage form definition includes the BOMs for each intermediate.

The “Bottom Up” definition allows intermediate BOMs to be maintained and referenced independently from the BOM for the top level dosage form. The intermediate BOMs also can be manufactured and tracked in inventory.

An intermediate BOM for a “Bottom Up” definition can be used in several top level dosage form BOMs.

### 3.2.5 Equivalent Materials

Clinical supply systems may allow materials of the same material type and subtype to be set as “equivalent.” Where the specifications of these materials are very similar and meet all requirements set by the quality organization to be used interchangeably, they may be designated as “equivalent” within the system.

A specific material can be designated within a BOM, but at the time of fulfillment an equivalent material can be used. This allows flexibility of materials without modifying the BOM. Where an equivalent material is used during the fulfillment process (rather than the material that is specified within the BOM), the system should indicate the equivalent material ID used, but the master BOM is not altered.

Reasons for making materials equivalent include:

- Insufficient quantities of the original material

- Discontinued materials
- Lot usage preference
- Retest date constraints
- Supplier material identifier changes

### 3.3 Packaging BOMs/Material Masters

#### 3.3.1 *Packaging Material Masters*

Packaging is the placing of dosage form into dispensable units. It can be divided into primary and secondary packaging. Primary packaging refers to filling bulk dosage form into bottles, syringes, or blister strips to make an individual dispensing unit. Secondary packaging covers finishing primary packaging using boxes or cartons and then labeling.

Materials used in packaging (including labels) and packaged materials that are tracked in an inventory management system are defined using material masters.

Two types of materials are frequently referenced in packaging:

1. Packaging materials – those materials used to package clinical supplies (e.g., bottle, cap, carton, or desiccant).
2. Packaged materials – materials that have gone through a packaging process (i.e., the primary packaged kit or secondary finished kit).

Packaged materials have taken the component materials to a new state and are identified with a new unique material master. Where a packaged material that has been primary packaged is further packaged into secondary packaging, a new packaged material is created and identified with a new unique material master.

**Table 3.2: Common Attributes of Packaging Material Masters**

|                      |
|----------------------|
| Material ID          |
| Material Description |
| Material Type        |
| Material Subtype     |
| Storage Temperature  |
| Storage Restriction  |
| Transport Condition  |
| Version Number       |

Typical packaging material subtypes include: blister card, bottle, cap, carton, desiccant, tamper evident seals, foil, and film.

**Table 3.3: Common Attributes of Packaged Material Masters**

|                               |
|-------------------------------|
| Material ID                   |
| Material Description          |
| Material Type                 |
| Material Subtype              |
| Storage Temperature           |
| Storage Restriction           |
| Kit Group Material ID         |
| Kit Group Blinded Description |
| Kit Type Open Description     |
| Blister Coordinate            |
| Version Number                |

Typical packaged material subtypes include: packaged blister card, packaged bottle, packaged box, packaged pump, packaged syringe, packaged vial, and packaged kit.

### 3.3.2 **Bill of Materials**

The material composition of a packaged material is normally referred to as a Bill of Material (BOM) or as a kit design. It contains a linked relationship between the material masters of the packaged material and the component materials. The packaged material and each component material should have a material master defined in the clinical supply system. BOMs are usually represented in a tree structure diagram with the packaged material at the top. Each component material is added to the tree structure with the required quantity of that material to define the packaged material.

Typically, for an open study each treatment or kit type has a unique BOM.

The system should allow users to create two descriptions for each kit type in the BOM:

1. A blinded description
2. An open description

Blinded descriptions should be displayed on system screens and printed on reports accessed by users with blinded roles (e.g., study team personnel). The open description should be displayed on system screens and printed on reports accessed by users with unblinded roles, e.g., packaging personnel.

When creating packaging requests using a multi- kit type BOM, the clinical supply system should allow the user to define how many of each kit type to prepare in each lot. Where specific kit types in the BOM are not needed, the clinical supply system should allow users not to prepare them.

#### 3.3.2.1 **Blinded Supplies**

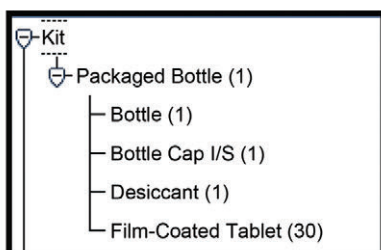
For blinded supplies, each treatment or kit type may be created as an individual BOM. The clinical supply system should provide a mechanism to group the blinded kits together so that they share attributes important to maintain the blind. Alternatively, blinded kits could be created within one BOM to group them.

The BOM for blinded kits should contain the same components (except the dosage form, in order to maintain the blind), whether created within the same BOM or in separate BOMs that are grouped.

### 3.3.3 Single Level BOM

If the packaged material has no component packaged materials and is the dispensable unit, a single level BOM may be sufficient for the BOM. The relationship shown in Figure 3.3 includes the packaged material and each of the component materials with the required quantity.

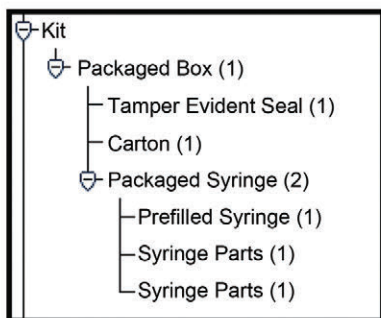
Figure 3.3: Single Level BOM



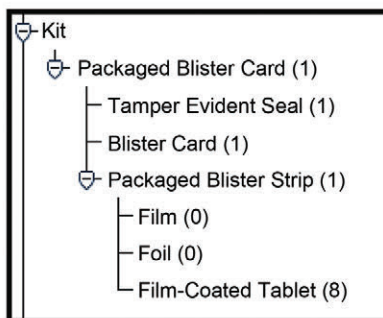
### 3.3.4 Multi-Level BOM

A packaged material that contains other packaged materials or is not the dispensable unit requires a multi-level BOM. The structure should contain the component materials for each packaged material with their required quantities (see Figure 3.4).

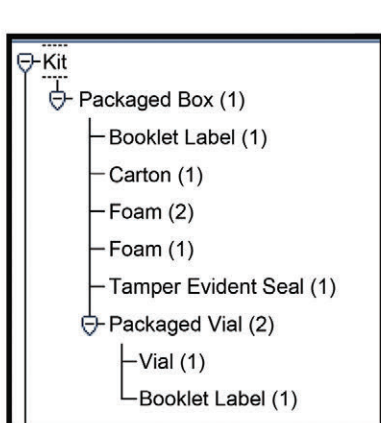
Figure 3.4: Multi-Level BOM



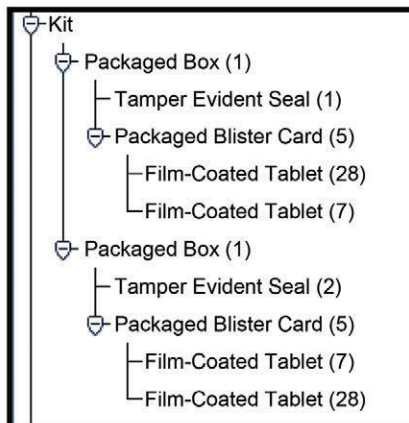
Packaged Syringe in a Packaged Box



Packaged Blister Strip in a Blister Card



Packaged Vial in a Packaged Box



Blinded Kit Structure with Two Treatments

Packaged material multi-level BOMs can be defined as either “Top Down” or “Bottom Up.”

- A “Top Down” design starts with the top level packaged material and associates each component material and quantity, including the intermediate packaged materials and their BOMs.
- A “Bottom Up” definition defines each intermediate packaged material independently with its own BOM. The top level packaged material definition includes each of the BOMs for each intermediate.

The “Bottom Up” definition allows the intermediate BOMs to be maintained and referenced independently from the top level packaged material. The intermediate BOMs can also be packaged and tracked in inventory.

An intermediate BOM for a “Bottom Up” definition can be used in several top level packaged material BOMs.

### **3.3.5 *Equivalent Materials***

Functionality to support definition of equivalent packaged supplies can be beneficial (similarly as for drug product), see Section 3.2.5 of this Guide.

### **3.3.6 *How BOMs Are Used***

BOMs are used:

- During manufacture of packaged materials
- To provide material lists and quantities
- For calculations of batch sizes
- For verification after the material packaging
- In batch records

## **3.4 Inventory Management**

Activities tracked in systems include the receipt of material through to the removal of that material. Some activities are tracked at the lot level while others can be tracked at a container level. Systems should manage existing material and once consumed or removed, the activity history should continue to be available for viewing.

The first entry of material into the system can be the result of a receiving operation or the fulfillment of a manufacturing or packaging execution.

### **3.4.1 *Receiving***

Systems may assign a unique lot number to the batch of material upon receipt. The supplier lot number may be captured for reference in another field during the receipt.

**Table 3.4: Fields Commonly Entered During a Receive Activity**

|                            |
|----------------------------|
| Material ID                |
| Supplier Material ID       |
| Supplier Lot Number        |
| Quantity                   |
| Unit of Measure            |
| Number of Containers       |
| Quality Status             |
| Manufacture Date           |
| Retest                     |
| Location to Store Material |

System conversions should allow material to be processed using multiple units of measure. For example, tablets or capsules could be received with a count (unit) or a weight (grams, kilograms, etc.). The system should be able to make the conversion between the two if a conversion formula is identified for the material master. The formula can be contained within the material master for the material.

Material can be stored in logical containers each with a unique identifier. A receipt that contains ten drums should have ten logical containers created during the receipt. A system's containers may be driven by a specific labeling requirement rather than a physical size or shape requirement. For example, the drums do not have to be a container type of drum in the system as long as the label design for the chosen container contains the information required for drums. Labels for containers that contain basic information about the container and the material can be printed. The system should support bar-coding the container ID on the container label to allow for material management using scanners for entry.

Restrictions may be setup to control the material allowed into a container. Containers usually contain a single lot of a single material, but multiple lots may need to be placed into a single container. Multiple lots or multiple materials should be allowed into a container with specific controls set.

Systems should allow setting of a default quality status for the receipt. It should be set up at a material type or material subtype level and automatically populate for the lot as it is received. Usually materials from a trusted source that do not come in contact with the drug may have the default status of "Released," while other materials will default to a quarantine type of status and require an upgrade before they can be used for manufacture or packaging.

Systems should guide users to locations with storage conditions matching the material being received. Where storage conditions are set up for materials and locations, systems should check for compatibility when moving the material. Systems may display only locations matching the storage condition of the material for selection. There should be an override of the check to allow selection of other locations. For example, refrigerated material should be in refrigerated locations, but there may be a need to place the material in a controlled room temperature location for a short time during processing.

The details of the receipt activity are written to a log or journal file. It contains the receipt action, who performed the receipt, and when the receipt was performed.

### **3.4.2 Fulfillment of a Drug Product Manufacturing Execution or Packaging Execution**

Upon completion or fulfillment of a manufacturing or packaging execution the quantity of the resultant material will be “received” into the system. If the system assigned a request number when the request was created, the request number should become the lot number once the material is in the system.

Information should continue to be available after a fulfillment.

### **3.4.3 Material Movement**

The movement of material to different locations should be tracked within a system. Barcodes on container labels and locations allow the use of barcode scanners to enter information to reduce data entry during movement. As a material is moved from one location to another systems typically accept the receipt of material into the new location. Storage condition checking can occur during material movement.

If active identification such as Radio Frequency Identification (RFID) is used, the system should have sensors that read the information about material and automatically register the movement as it passes or enters monitored areas and locations. This reduces the need for manual entry of material movement.

The details of material movement activities also should be written to the journal file. It contains the material movement action, who performed the material movement, and when the material movement was performed.

### **3.4.4 Adjustment**

Quantities of materials change as they are processed. Automatic adjustments occur when materials are consumed during manufacturing or packaging execution. Manual changes to a quantity also should be allowed, e.g., when cycle counting or other activities reveal that the quantity listed by the system does not match the actual quantity in a container and an adjustment is needed.

Usually systems allow increasing and decreasing quantities for composite materials, but only allow decreasing quantities for discrete materials. There is a relationship between a discrete material and a randomization number. The decrease of discrete material usually requires selection of specific discrete numbers rather than entering a quantity to reduce.

The details of the adjustment activity are also written to the journal file. It contains the adjustment action, who performed the adjustment, and when the adjustment was performed.

### **3.4.5 Restock/Reorder Point Notification**

Systems that provide full management of materials should provide a mechanism to notify users when it is time to restock. Reorder points can be entered for a material and when the available quantity of that material drops below the value specified a notification is generated. This functionality is an inventory management activity and not related to material requirements planning or forecasting.

### **3.4.6 Retest Notification**

Material management systems may provide notification when the retest dates are approaching. A time frame before the expiration of the date is entered at a material master level and a notification is generated when the date of a material enters that time frame. Systems may allow the quality status of material that has reached the retest or expiry date to be downgraded automatically.

### 3.4.7 **Material Allocation**

The process of associating material to a specific manufacturing, packaging, or shipping request is called material allocation. Systems may remove the material from the “available” quantity of the material. Allocation is considered a hard stop as it does not allow any other activity to use the material.

### 3.4.8 **Material Reservation**

Material reservation usually notes that material is to be used for an activity, but does not remove it from the “available” quantity of the material. A reservation may notify users that the material is reserved, but continue to allow use of the material.

### 3.4.9 **Viewing Material**

Screens for viewing material and location information may be searchable by selection of specific fields to allow easy finding and viewing of materials.

**Table 3.5: Common Searchable Fields**

|                    |
|--------------------|
| Lot Number         |
| Vendor Lot Number  |
| Container ID       |
| Quantity Status    |
| Warehouse          |
| Warehouse Location |

Searchable fields are normally used for viewing, sorting, and filtering. Basic information about the material and its location can be augmented with more detailed information about a specific lot or information at the material master level.

The journal of activity and lot genealogy also can be displayed for materials. As activities occur against material they are written to a journal. Displaying that journal allows viewing of the history of the material as it is processed through the system. It contains the trail of what activities were performed against the material, who performed the activity, and when the activity was performed.

Fields captured in journals (but not limited to) are shown in Table 3.6.

**Table 3.6: Common Journal Fields**

|                                                             |
|-------------------------------------------------------------|
| Activity (Receipt, Move, Ship, Quality Status Change, etc.) |
| Material Identifier                                         |
| Lot Number                                                  |
| Quantity of Activity                                        |
| User ID of Person Performing Activity                       |
| Date and Time of Activity                                   |

If component materials are consumed into a new material through a manufacturing or packaging execution the journal also will contain the lot genealogy of the material. Lot genealogy displays usually allow looking both forward and backward for a material to see where it has been used in further processing and the components and lots used to create the material.

Fields captured and displayed for lot genealogy can include those listed in Table 3.7.

**Table 3.7: Common Lot Genealogy Fields**

|                                |
|--------------------------------|
| Parent Lot Number              |
| Parent Material ID             |
| Parent Material Description    |
| Component Lot Number           |
| Component Material ID          |
| Component Material Description |
| Component Vendor Lot Number    |
| Component Quantity             |
| Component Unit of Measure      |

### 3.5 Drug Product Manufacturing Execution

As the physical activities of drug product manufacturing are planned and completed, corresponding electronic transactions also should be completed. Clinical supply systems may track drug product manufacturing in two steps:

1. The creation of a request for manufacture
2. A fulfillment of that request

#### 3.5.1 *Request for Manufacture*

The request for manufacture should be entered in the planning phase and may initially require only a few pieces of information, e.g.:

- What to make?
- Where to make it?
- How much to make?

A tracking number is assigned to the request during its creation. This is not considered an actual lot or batch number, as there is no physical inventory at this time. Upon fulfillment of the request for manufacture, inventory is created and the request number may become the lot or batch number.

Clinical supply systems use the BOM of a drug product to identify the component materials and to calculate the total quantity of those materials required to make the requested quantity of the drug product. Available inventory of the materials may be displayed and may allow allocation of specific lots of component materials to the manufacturing request.

If the BOM contains multiple levels, the clinical supply system may allow users to break each level into a separate job to allow the jobs to be fulfilled at different times or manufactured at different locations.

The initial request for manufacture may be updated as planning progresses and more information is obtained: more precise quantities and various dates may be entered, e.g.:

- Start by Date
- Release by Date
- Manufacture by Date

Multiple approvals may be required to finalize the request for manufacture and prepare for the fulfillment process.

### 3.5.2 **Fulfillment**

When the details of the manufacturing process are available via paper batch documentation the request to manufacture can be fulfilled. This creates a new batch of drug product in the inventory and consumes the lots of component materials from the inventory.

Actual lot numbers and quantities of component materials used in the manufacturing process should be entered during the fulfillment process. Materials that were damaged or wasted during the manufacturing process also may be entered so that they are removed from the inventory. Where a clinical supply system utilizes an electronic batch record, data needed to fulfill the batch may be collected during the manufacturing process.

Where a material does not exist in the inventory, clinical supply systems may provide “lots on the fly” to allow creation of the lots at the time of the fulfillment. For example, this concept may apply to filtered water provided by the manufacturing facility which does not exist in the inventory, but which needs to be reflected in the lot genealogy of the manufactured material. In this case, an automatic receive and consume are executed by the system.

Jobs are generally fulfilled from the bottom up (in a multilevel BOM) in order to create any intermediate materials needed in higher job steps and result in the top level drug product.

The clinical supply system may perform several checks against material attributes, e.g., for quality status and retest/ expiry dates, and limit the material that is allowed to be used during the fulfillment. Clinical supply systems may allow setting up of a consumption quality status by material subtype and then check that materials are at that status or higher before allowing them to be selected. The system also may require a sufficient quantity to be entered as defined by the BOM.

## 3.6 **Lot Genealogy**

As materials are processed through a clinical supply system and are consumed to become different materials, their path is captured. Following an excipient into an intermediate drug product and that intermediate into a final drug product is achieved using the lot genealogy. Typically, full lot genealogy from “cradle to grave” is tracked forward from the receipt of raw materials manufactured into drug product, through packaging and shipping. Full lot genealogy is the tracking forward and backward from any point in the life cycle.

Lot genealogy can be used to locate materials in the event of a recall. It shows which materials are still in a warehouse and which materials have been shipped. An inventory display can be used to identify the location in the warehouse which holds the materials in question.

### 3.7 Kit Identification

The type of kit (e.g., active drug or placebo) can be determined via attributes on the kit label, by its description (if an open description), or by a unique serial ID that can be traced to the kit's contents. Kit labels may include:

- Blind or Open Descriptions
- Serialization

#### 3.7.1 Description on Label: Blind or Open

Supplies are defined as “blind” or “open” based by the description on the kit label, e.g.,

- 10 mg Trimycin Kit (Open Description)
- 10 mg or Placebo Trimycin Kit (Blind Description)

The contents of a kit with a blind description on the label cannot be determined by the description. Labels with blind descriptions should include a unique serialized ID which can be traced back to the kit's contents via a serialized kit list, which defines the treatment contained within that Kit (see Figure 3.5).

Where a kit label does not have a unique serialized ID, the kit label should contain an open description to allow one kit to be distinguished from another and to allow the contents of each kit's to be determined.

#### 3.7.2 Serialization on Label: Unique Kit ID, Subject ID/Visit ID, or No ID

Clinical supplies may be labeled with a unique serialized identifier (Kit ID or Subject ID/Visit ID) or no serialized identifier.

Where supplies are intended to be managed (assigned to subjects) by an IRT system, a unique Kit ID should be included on each kit's label. A Kit ID also may be included on supply labels for tracking purposes when supplies are not managed by an IRT system.

Supplies labeled with Kit IDs and managed by an IRT system are flexible. They can be assigned to any subject or visit that is eligible for the particular treatment the kit contains. The IRT system assigns kits to subjects based on the subject's treatment group and predefined rules programmed into the IRT system's dosing/visit schedule (see the ISPE Good Practice Guide on Interactive Response Technology [2]). Depending on the study design, the IRT system supplies with Kit IDs on labels may have either an open or blind description of the kit's contents on the label.

Subject IDs (and, normally, visit IDs) are typically only printed on supply labels with blind descriptions when the supplies are not managed by an IRT system.<sup>2</sup> Kits labeled with Subject IDs have the disadvantage that they are not commutable to other subjects in the study (i.e., if a given subject drops out during the study, any remaining kits labeled for that subject are wasted). Kits prepared with subject IDs, however, may be employed for:

- Short duration blind studies
- Low dropout studies
- Where waste is not of great concern
- And/or the timing or expense to set-up an IRT system is an obstacle

<sup>2</sup> Historically, labeling with subject IDs was a commonly used way of preparing blind supplies before the advent of IRT systems.

Kits can be produced with no serialization ID on the label. In this case, the kit should be labeled with an open description so that its contents can be directly identified.

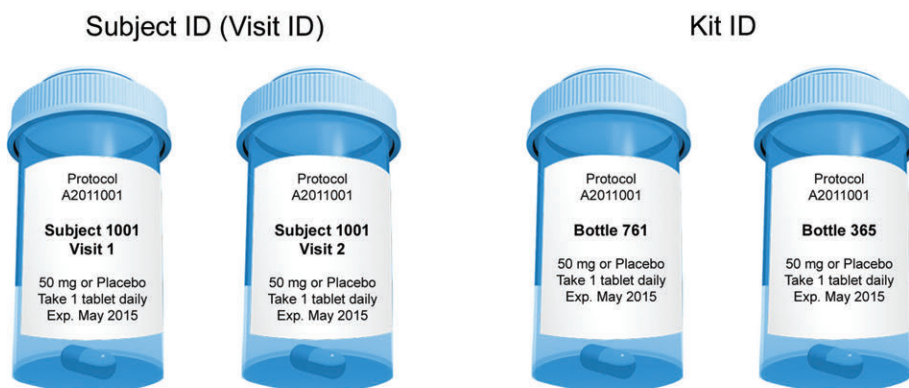
Table 3.8 summarizes four common types of packaging types characterized by serialization and description.

**Table 3.8: Four Common Types of Packaging Types Characterized by Serialization and Description**

| Serialization On Label | Description on Label | Other IDs on Label         | Supply Assignment to Subject                                                           |
|------------------------|----------------------|----------------------------|----------------------------------------------------------------------------------------|
| Kit ID                 | Blind                | Optionally Confirmation ID | Supplies are assigned to subjects using an IRT system                                  |
| Kit ID                 | Open                 | None                       | Supplies may be assigned to subjects using an IRT system or manually assigned (no IRT) |
| Subject ID             | Blind                | Optionally Visit ID        | Supplies are manually assigned to the subject allocated the subject ID at enrollment.  |
| No ID                  | Open                 | None                       | Supplies are manually assigned to the subject                                          |

Figure 3.5 shows examples of blinded supplies labeled with Subject versus Kit IDs.

**Figure 3.5: Blinded Supplies Labeled with Subject versus Kit IDs**



### 3.7.3 System Requirements for Kit Identifiers

For each lot of IMP, the system should be able to determine whether the supplies are serialized. Where the kits are serialized, the system should be able to determine whether they are serialized with a Kit ID or a Subject ID/Visit ID.

Based on the Serialization Type (Kit ID, Subject ID/Visit ID, no ID), the system should be able to vary the format, headers, and content of system screens and documents such as pick lists, shipping invoices, etc.

For each lot of IMP, the system should allow users to specify whether the label description on the kits being produced is blind or open. When the label description is blind, the system should:

- Capture both a blind and open description for each kit.
- Display/print blind kit descriptions on any screens viewed by blind users or on documents produced for blind users.
- Display/print the open description (instead of the blind description) on system screens/reports to unblinded users.

- Ensure that all kit types within blinded packaged lot containing a mix of kit types (e.g., both active and placebo kits) are labeled with the same blind descriptions, same lot number, same retest date, same storage condition.

Note: systems may assign a different lot number to each kit type when prepared, and then assign an overarching packaged lot number to the grouping of blinded kit type lots. Alternatively, systems may assign the same packaged lot number to all individual kit types with a different job number for each kit type. Either approach is acceptable as long as the lot number representing the grouping of the blinded kit types corresponds to what is printed on the label.

## 3.8 Subject Randomization

Subject randomization falls into two categories:

1. Static
2. Adaptive (Dynamic)

### 3.8.1 Static Subject Randomization

Static subject randomization files are created in advance of a study, typically by a biostatistician. Static subject randomization files are either loaded into the packaging and labeling system (where subject IDs are to be printed on study supply labels) or into the IRT system to assign subject IDs to patients.

A basic static subject randomization file contains a listing of subject IDs; each associated with a particular Treatment Group (also referred to as an “arm”). Randomization of subject IDs to treatment groups occurs within each block (or quantity of subject IDs). Each block is given a sequential ID. Treatment Group assignments to Subject IDs within a given block may be made in equal or unequal ratios.

Figure 3.6 shows an example of a basic subject randomization with a block size of six, where each six subject IDs have been randomized to an equal number of treatment groups (2A:2B:2C) within each block.

**Figure 3.6: Example of a Basic Subject Randomization**

| Subject ID | Block ID | Treatment Group ID | Treatment Description  | Group |
|------------|----------|--------------------|------------------------|-------|
| 1001       | 1        | C                  | Placebo Treatment      |       |
| 1002       |          | A                  | Active 50 mg Treatment |       |
| 1003       |          | A                  | Active 50 mg Treatment |       |
| 1004       |          | B                  | Active 25 mg Treatment |       |
| 1005       |          | C                  | Placebo Treatment      |       |
| 1006       |          | B                  | Active 25 mg Treatment |       |
| 1007       | 2        | B                  | Active 25 mg Treatment |       |
| 1008       |          | A                  | Active 50 mg Treatment |       |
| 1009       |          | C                  | Placebo Treatment      |       |
| 1010       |          | B                  | Active 25 mg Treatment |       |
| 1011       |          | A                  | Active 50 mg Treatment |       |
| 1012       |          | C                  | Placebo Treatment      |       |
| 1013       | 3        | B                  | Active 25 mg Treatment |       |
| 1014       |          | A                  | Active 50 mg Treatment |       |
| 1015       |          | B                  | Active 25 mg Treatment |       |
| 1016       |          | C                  | Placebo Treatment      |       |
| 1017       |          | A                  | Active 50 mg Treatment |       |
| 1018       |          | C                  | Placebo Treatment      |       |
| 1019       | 4        | A                  | Active 50 mg Treatment |       |
| 1020       |          | B                  | Active 25 mg Treatment |       |
| 1021       |          | C                  | Placebo Treatment      |       |
| 1022       |          | A                  | Active 50 mg Treatment |       |
| 1023       |          | B                  | Active 25 mg Treatment |       |
| 1024       |          | C                  | Placebo Treatment      |       |
| 1025       | 5        | C                  | Placebo Treatment      |       |
| 1026       |          | B                  | Active 25 mg Treatment |       |
| 1027       |          | A                  | Active 50 mg Treatment |       |
| 1028       |          | B                  | Active 25 mg Treatment |       |
| 1029       |          | A                  | Active 50 mg Treatment |       |
| 1030       |          | C                  | Placebo Treatment      |       |

Table 3.9 shows key attributes of a static subject randomization.

**Table 3.9: Key Attributes of a Static Subject Randomization**

| Attribute                   | Description                                                                                                                                                                                                                                                                                                  |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Subject (Randomization) ID  | Unique value for each randomized subject within a protocol.<br><br>Where a study does not use an IRT system, it may be printed on each kit label.<br><br>Where a study does use an IRT system, the subject ID should be allocated to each subject using the IRT system randomization function.               |
| Block                       | A defined number of subject IDs across which Treatment Groups can be randomly allocated according to a predefined ratio.<br><br>Full blocks of Subject IDs may be pre-assigned to each study site to ensure that each site achieves a similar distribution (or balance) of subjects in each treatment group. |
| Block Size                  | The number of subject IDs included in each block. For example: Block Size of 6 means there 6 Subject IDs each Block.                                                                                                                                                                                         |
| Block ID                    | A unique ID assigned to each block of subject IDs.                                                                                                                                                                                                                                                           |
| Treatment Group Code        | A unique code assigned to each Treatment Group.                                                                                                                                                                                                                                                              |
| Treatment Group Description | Description for each Treatment Group.                                                                                                                                                                                                                                                                        |

In the case where the static randomization file is loaded into an IRT system, subject IDs are typically allocated to subjects at randomization in one of two ways:

1. Site based randomization
2. Central randomization

#### 3.8.1.1 Site Based Static Randomization

Subject randomization IDs are pre-allocated to each site (typically by block) from a master list. When a subject presents for randomization, the next available subject ID in the block should be allocated to the subject.

When a full block of subject IDs has been assigned at a site, another block (or blocks) of subject IDs should be allocated to the site from the master list.

A (balanced) distribution of subjects across treatment groups at every site can be maintained by using site based randomization.

#### 3.8.1.2 Central Randomization

In central randomization, the next available subject ID is retrieved from a central list which is shared by all the sites in the study (or region or other grouping). Assignment of subject IDs to subjects at a site moving down the list is on a “first come first serve” basis. Using central randomization, it is not possible to maintain a similar (balanced) distribution of subjects in each treatment group at a single site.

Static subject randomization files that are used in the packaging and labeling system (when subject IDs are printed on supply labels) also may include other information such as Visit ID, Cohort<sup>3</sup>, etc.). Conversely, the packaging and labeling system may contain the ability to model visits for a study and integrate visit IDs into the subject randomization file that has been created externally and uploaded into the system. The advantage of modeling visits is that additional variables beyond the visit ID to be printed on labels (that may differ by visit) can be included in the visit model.

### 3.8.1.3 Stratified Randomization

Stratified randomization is also often applied to ensure approximate balance subjects in treatment groups by selected prognostic variables or other patient factors such as age, sex, weight, condition severity, etc. Stratification randomization simply means having separate block randomization list for each characteristic or combination of characteristics (i.e., stratum). An IRT system is used to collect data to determine which stratum the subject is matched to and then selects the next available randomization from a static list that has been assigned to that stratum.

### 3.8.2 Adaptive (Dynamic) Subject Randomization

Static randomization methods described above involve applying randomization allocation sequences that have been defined before the start of the trial.

In contrast, adaptive (dynamic) randomization assigns subjects to treatment groups based on the characteristics of the subject being randomized and previous treatment assignments for other subjects already randomized. In this case, it is not necessary to have a randomization list for each stratum. An IRT system is used to collect data to determine the characteristics or which stratum the subject is matched to and then “dynamically” assigns the subject to an appropriate treatment group based on a predefined algorithm.

### 3.8.3 System Requirements for Packaging and Labeling Systems

- Ability to create static subject randomization (optional)
- Ability to upload static subject randomization files created outside the supply system
- Ability to model visits for each subject ID and define other visit based variables beyond visit ID to print on labels along with the subject ID
- Ability to allocate a subset of “unused” subject IDs from the randomization list to a packaging request
- Ability to create package requests for replacement kits when a subject ID-labeled kit expires or is damaged or lost

### 3.8.4 System Requirements for IRT Systems

- Ability to upload static subject randomization files
- Ability to allocate subject randomization IDs to sites (site based or central)
- Support ability to program adaptive (dynamic) randomization schemes
- Encryption of randomization assignments at the database level to prevent unauthorized access and interpretation

## 3.9 Kit Lists (Randomized or Sequential)

A kit list contains a listing of Kit IDs. Each Kit ID is associated with a specific kit type (treatment) (e.g., active 10 mg kit, placebo kit).

Where a kit list supports a blinded study, Kit IDs should be randomly assigned across all kit types (e.g., Kit IDs 1, 2, 5, 6... should be assigned to active kits, and Kit IDs 3, 4, 7, 8... should be assigned to placebo kits).

<sup>3</sup> For the purposes of this Guide, cohort is a group of people who share a common characteristic or experience within a defined period (e.g., date range they are born, are exposed to a drug or vaccine or pollutant, or undergo a certain medical procedure.)

Where a kit list supports an open study, Kit IDs may be sequentially assigned to each kit type (e.g., 10 mg kit may be assigned IDs 1-1000, 20 mg kit may be assigned IDs of 1001 to 2000).

Figure 3.7 shows an example of a portion of a randomized kit list used for blinded supplies (also referred to as a “kit or container randomization.”)

**Figure 3.7: Portion of a Randomized Kit List for Blinded Supplies**

| Kit ID | Position Sequence ID | Usage Sequence ID | Block ID | Confirmation ID | Treatment Code | Treatment Description | Kit Type Part # |
|--------|----------------------|-------------------|----------|-----------------|----------------|-----------------------|-----------------|
| 10015  | 1                    | 10001             | 1        | 49135           | A              | 50 mg Active Kit      | PB123456        |
| 10003  | 2                    | 20001             | 1        | 21385           | B              | 25 mg Active Kit      | PB549234        |
| 10001  | 3                    | 10002             | 1        | 91321           | A              | 50 mg Active Kit      | PB123456        |
| 10017  | 4                    | 30002             | 1        | 71341           | C              | Placebo Kit           | PB924612        |
| 10020  | 5                    | 30001             | 1        | 49140           | C              | Placebo Kit           | PB924612        |
| 10027  | 6                    | 20002             | 1        | 81409           | B              | 25 mg Active Kit      | PB549234        |
| 10010  | 7                    | 20003             | 2        | 49130           | B              | 25 mg Active Kit      | PB549234        |
| 10024  | 8                    | 10003             | 2        | 31406           | A              | 50 mg Active Kit      | PB123456        |
| 10013  | 9                    | 30003             | 2        | 81395           | C              | Placebo Kit           | PB924612        |
| 10021  | 10                   | 20004             | 2        | 31403           | B              | 25 mg Active Kit      | PB549234        |
| 10005  | 11                   | 10004             | 2        | 71329           | A              | 50 mg Active Kit      | PB123456        |
| 10025  | 12                   | 30004             | 2        | 49145           | C              | Placebo Kit           | PB924612        |
| 10014  | 13                   | 30006             | 3        | 31396           | C              | Placebo Kit           | PB924612        |
| 10004  | 14                   | 30005             | 3        | 49124           | C              | Placebo Kit           | PB924612        |
| 10007  | 15                   | 20005             | 3        | 49127           | B              | 25 mg Active Kit      | PB549234        |
| 10016  | 16                   | 10006             | 3        | 49136           | A              | 50 mg Active Kit      | PB123456        |
| 10028  | 17                   | 10005             | 3        | 21410           | A              | 50 mg Active Kit      | PB123456        |
| 10029  | 18                   | 20006             | 3        | 21411           | B              | 25 mg Active Kit      | PB549234        |
| 10008  | 19                   | 30007             | 4        | 81390           | C              | Placebo Kit           | PB924612        |
| 10011  | 20                   | 10008             | 4        | 81393           | A              | 50 mg Active Kit      | PB123456        |
| 10026  | 21                   | 20007             | 4        | 91346           | B              | 25 mg Active Kit      | PB549234        |
| 10012  | 22                   | 10007             | 4        | 91332           | A              | 50 mg Active Kit      | PB123456        |
| 10019  | 23                   | 30008             | 4        | 71343           | C              | Placebo Kit           | PB924612        |
| 10002  | 24                   | 20008             | 4        | 49122           | B              | 25 mg Active Kit      | PB549234        |
| 10023  | 25                   | 10009             | 5        | 21405           | A              | 50 mg Active Kit      | PB123456        |
| 10009  | 26                   | 20010             | 5        | 21391           | B              | 25 mg Active Kit      | PB549234        |
| 10030  | 27                   | 30010             | 5        | 61412           | C              | Placebo Kit           | PB924612        |
| 10018  | 28                   | 20009             | 5        | 21400           | B              | 25 mg Active Kit      | PB549234        |
| 10022  | 29                   | 10010             | 5        | 71346           | A              | 50 mg Active Kit      | PB123456        |
| 10006  | 30                   | 30009             | 5        | 21388           | C              | Placebo Kit           | PB924612        |

Table 3.10 provides further information on the values (headers) in the example kit randomization (see Figure 3.7).

**Table 3.10: Explanation of Kit Randomization Attributes**

| Attribute            | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kit ID               | <ul style="list-style-type: none"> <li>Unique value for each kit within a protocol (or group of protocols when pooling)</li> <li>For blinded kits – randomized across all kit types</li> <li>For open kits – may be a sequential number</li> <li>Printed on each kit label</li> <li>IRT system notifies investigators to select an appropriate kit for assignment to a subject based on its kit IDs</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Position Sequence ID | <ul style="list-style-type: none"> <li>A unique sequential number for each kit in the randomized list, applied <b>across all kit types</b> in the randomization list (e.g., active and placebo kits, sequence number 1 to 2000)</li> <li>Determines the order in which kits are stored and shipped if being shipped by a depot that is <b>blinded</b></li> <li>Kit types are placed in warehouse storage containers in the order of the position sequence number (i.e., each storage container will have a mix of all kit types in the container)</li> <li>Not printed on a kit label, but is printed on shipment pick lists</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                            |
| Usage Sequence ID    | <ul style="list-style-type: none"> <li>A unique sequential number for each kit in the randomized list, applied <b>within each kit type</b> in the randomization list (e.g., active kits = sequence 1 = 1000, and placebo kits = sequence number 1001 to 2000)</li> <li>Determines the order in which kits are stored and shipped if being shipped by a Depot that is <b>unblinded</b></li> <li>Each kit type is placed in warehouse storage containers in the order of its usage sequence number (i.e., each storage container will have only one kit type; kit types are segregated by storage container)</li> <li>Not printed on a kit label, but is printed on shipment pick lists</li> </ul> <p><b>Note:</b> it is usually acceptable for a kit list to have only one type of sequence number (either position or usage). However, where there is a combination of blinded and unblinded depots supporting a study, having both a usage and position sequence number within the kit list can provide improved flexibility.</p> |
| Block ID             | <ul style="list-style-type: none"> <li>An ID assigned to each group of kits that are randomized</li> <li>Randomization logic will, typically, first randomly assign kit IDs to a block ID and then randomly assign treatment codes to each kit ID within the block, according to defined ratios</li> </ul> <p>For example:</p> <ul style="list-style-type: none"> <li>A block size of 6 corresponds to 6 kit IDs per block. If there are three treatment codes (3 Kit Types) A, B, C, treatment ratios within each block could be defined as: <ul style="list-style-type: none"> <li>Balanced (i.e., 2:2:2)</li> <li>Unbalanced (e.g., 1:1:4 resulting in 4 times more treatment C kits in the list)</li> </ul> </li> <li>Block ID is a statistical value used when creating a kit randomization, but is not normally used afterwards to manage actual kits</li> </ul>                                                                                                                                                             |
| Confirmation ID      | <ul style="list-style-type: none"> <li>A unique ID for each Kit ID</li> <li>When used, both the confirmation ID and the kit ID are printed on a kit label</li> <li>Clinical supply system notifies investigators to assign a specific kit ID to a subject</li> <li>Investigator selects the kit labeled with the assigned kit ID, and then enters the unique confirmation ID listed on the label (to confirm they have selected the correct kit)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

**Table 3.10: Explanation of Kit Randomization Attributes** (continued)

| Attribute                                | Description                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treatment Code (Dosage Code or Kit Type) | <ul style="list-style-type: none"> <li>A unique code assigned to each treatment (treatment = kit type)</li> </ul> <p><b>Note:</b> “Treatment” is not the same as “Treatment Group.” For example, a subject in an active treatment group could receive different treatments (e.g., a placebo kit on the first visit and then an active kit on subsequent visits).</p> |
| Treatment Code Description               | <ul style="list-style-type: none"> <li>Unblinded description for each treatment (or kit type)</li> </ul>                                                                                                                                                                                                                                                             |
| Kit Type Material Part Number            | <ul style="list-style-type: none"> <li>Part number for the BOM for each kit type</li> </ul>                                                                                                                                                                                                                                                                          |

**Example Kit Randomization for Blinded Supplies**

A kit randomization for blinded supplies may be created “logically” as follows:<sup>4</sup>

**Inputs**

1. Define the total number of Kit IDs to randomize into the list, e.g., 30000
2. Define the starting Kit ID, e.g., 10001
3. *Optional: define the starting confirmation number ID, e.g., 10001*
4. Define the starting position sequence ID (record number), e.g., 1
5. Define the starting usage sequence number for each treatment type, e.g., 10001 (50 mg), 20001 (25 mg), 30001 (25 mg)

**Creation**

1. Assign a sequential position number for each record in the list, e.g., 1 to 30000
  2. Randomly allocate Kit IDs (10001 to 40000) across the entire list
  3. Randomly allocate a confirmation number for each Kit IDs across the entire list
  4. Define a block size (number of Kit IDs in a group) e.g., 6 kits/block.
  5. Assign a sequential block ID sequentially to each block of Kit IDs, e.g., 1 to 500
  6. Define the ratio of treatment types to allocate to each position in each block, e.g., 2-placebo: 2-25 mg: 2-50 mg.
- Note:** where more kits of than one treatment type are needed, ratios of treatment types do not need to be even.
7. Define the range of blocks to assign treatment types to, e.g., 1-x

**Note:** some blocks can be left “open” with no treatment types allocated. This is considered a best practice as it allows the future allocation of treatment types in ratios different to those used initially, where more kits of one treatment type need to be produced as a study progresses.

<sup>4</sup> The exact sequence of steps may differ.