



Interactive Response Technology





Good Practice Guide

Interactive Response Technology

Disclaimer:

This Guide describes how interactive voice response technology can support various clinical trial activities and leverage cGMP data and information to enhance compliance, efficiency, and patient safety. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

Interactive Response Technology (IRT), commonly referred to as Interactive Voice Response (IVR) or Interactive Web Response (IWR) technology, has been used in the pharmaceutical industry for more than 15 years. The original implementation of this technology was via the telephone and hence the term interactive voice response. Several years after implementation of IVR, the use of web-based technology (interactive web technology) emerged.

The document contains guidance to assist interested parties in using the technology and it describes current industry challenges and expectations when it is used. The document will reflect upon industry wide survey results and compare these results to previous surveys and current trends.

Interactive response technology is a tool that can be used to support multiple business processes and within this Good Practice Guide we will describe how the pharmaceutical industry can apply the technology to support various clinical trial activities. It is a tool that leverages current Good Manufacturing Practice (cGMP) data and information to enhance compliance, efficiency, and patient safety. It is the intent of this document to describe how interactive response technology can be used to support these established cGMP and related Good Clinical Practice (GCP) business processes.

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Table of Contents

1	Introduction	7
1.1	Background	8
1.2	Purpose and Objectives	10
1.3	Scope	11
1.4	Benefits and Challenges	12
1.5	Structure	13
2	Overview of Interactive Response Technology	15
2.1	History	15
2.2	Evolution	15
2.3	Current State of Affairs	15
2.4	Where and When to Use IRT	17
2.5	Managing and Maintaining Data Integrity	17
2.6	Key Concepts	22
3	System-Design and Controls	27
3.1	Validation	27
4	Pooling of Supplies	35
4.1	Considerations When Selecting What Approach to Take	38
5	Warehousing and Distribution	41
5.1	Warehousing	41
5.2	Distribution and Challenges	41
6	Training Considerations	47
6.1	Training of Investigators and Site Personnel	48
6.2	Computer Based Training versus Instructor Led Training	49
7	Monitoring Critical Activities (Risk Considerations)	51
7.1	Verification of Data Transfer Activities	51
7.2	Help Desk Issues	55
7.3	Monitoring Clinical Supplies	56
7.4	Resupply Strategies (Maintaining the Blind)	56
8	Appendix 1 – GCP Considerations	57
9	Appendix 2 – Example UAT Scheme	63
10	Appendix 3 – Frequently Asked Questions: Pooling	67
11	Appendix 4 – Frequently Asked Questions: Removal of Use-by-Dates	71
12	Appendix 5 – Interactive Response Technology Minimal Functional Standards Requirements Checklist	75
13	Appendix 6 – References	79
14	Appendix 7 – Glossary	81
14.1	Acronyms	82
14.2	Definitions	84



1 Introduction

Interactive response technology is becoming a more widespread application which has the potential to make a significant contribution to business processes in the field of clinical trials; however,

- The pharmaceutical industry needs to move beyond what has proven to be effective, compliant, and well accepted for more than 30 years.
- The pharmaceutical industry needs to be engaged to provide confidence and “lessons learned” from personnel who have experimented with the technology for managing investigational medicinal products, information, and regulatory requirements.

This ISPE Good Practice Guide aims to address this challenge to standardize the application and promote the use of interactive response technology in managing investigational medicinal product.

Interactive response technology is usually applied to blind clinical trials, but it also can be used effectively to manage open clinical trials. The use of IRT in open clinical trials presents challenges associated with container selection, dispensing, and confirmation. Interactive Response Technology (IRT), can be applied as Interactive Voice Response (IVR) (telephony) and/or Interactive Web Response (IWR) (Web-based) system. IVR and IWR are sometimes implemented simultaneously.

Based on feedback from the pharmaceutical industry, there is a need for clear guidance on:

- how to use interactive response technology
- how to design and validate interactive response technology
- how to monitor the use and effectiveness of interactive response technology

This Good Practice Guide describes how to design and deploy interactive response technology to manage investigational medicinal product. This Guide establishes minimal functional standards for these systems.

An established understanding and acceptance of interactive response technology is needed within individual pharmaceutical organizations and within regulatory agencies, before global confidence in this technology can be developed.

The challenge here moves from demonstrating confidence and reliability of the technology to influence local regulations to accept the technology and remove the existing manual impositions commonly used to support the regulations (i.e., “use-by-dates” on labels).

This Good Practice Guide is intended to assist in a pharmaceutical industry effort to enhance country regulator knowledge, and acceptance of interactive response technology to support the management of investigational medicinal product; particularly removal of “use-by-dates” from labels and implementing program level pooling worldwide.

1.1 Background

Traditionally, a variety of management tools have been used effectively to record information about investigational medicinal product activities, historical transactions, product specifications, release actions, and stability data. These tools include spreadsheets, project plans, and databases designed specifically to record product specific information. As part of this evolution, regulatory requirements were written to ensure robustness and reliability of these cGMP processes and systems. Although these particular validated systems and processes ensure accurate and retrievable information to support regulatory and operational queries, they provide little support for efficient, real time management and control of clinical trial activities.

Many investigational medicinal products are still packaged conventionally (protocol and patient specific) and most non-US clinical labels still require expiry dates, or “use-by-dates,” to be printed directly on to labels. Through the use of advances in technology or more innovative ways of using current technology:

- Legacy processes can be more effectively managed.
- Processes can be made significantly more efficient.
- Compliance with regulations can be more controlled.
- Risk to patients can be reduced.

A new technological tool which should be considered to achieve this is Interactive Response Technology (IRT).

Interactive Response Technology (IRT), generally referred to as Interactive Voice Response (IVR) or Interactive Web Response (IWR) technology, has been used in the pharmaceutical industry for more than 15 years. IVR and IWR are sometimes implemented simultaneously in an effort to provide back-up options if either system should become unusable (e.g., loss of telephone service or a server is down).

In November, 2007 only 6% of 65 respondents to a survey indicated they had requested approval to use interactive response technology for removal of “use-by-dates” on IMP labels outside the United States. Three years later, in October of 2010, 15% of 40 respondents indicated successful endorsement to use this technology for removal of “use-by-dates.” Notably, 65% of the respondents still had not used the technology for this purpose, indicating a significant need to establish broader awareness and acceptance within the pharmaceutical and regulatory environment.

For pooling of supplies, it seems that interactive response technology has seen a wider application. Approximately 53% of 34 respondents to the 2010 survey indicated interactive response technology was used routinely for pooling of supplies and the remaining 47% indicated it was used by exception (expensive supplies or limited inventory). Although this technology has been in general use for several years, the industry is just now experiencing an increase in its application.

Organizations that use the interactive response technology more frequently, quickly realize the benefits it brings to:

- business efficiencies
- increased compliance
- increased patient safety

These benefits were further substantiated in a Failure Mode and Effects Analysis (FMEA). This analysis report can be found in the ISPE/PDA White Paper: “Use of Interactive Voice Response or Web Systems to Manage IMP Retest Dates” (Reference 1, Appendix 6). In particular, the Failure Mode and Effects Analysis (FMEA) results reflect a significant increase in patient safety when using the interactive response technology.

Expiration Date Management

Industry practice for managing updates to clinical supply “use-by-dates” normally requires a physical update to the Investigational Medicinal Product (IMP) label if outside the United States and the following should be determined:

- which resources will be available to conduct the physical updates
- how the updates will be verified and documented
- what training requirements may also be needed

Inherent in each of these activities are processes that are highly susceptible to errors even for experienced personnel. As updates at the site level may require use of non-GMP experienced personnel, the potential for error is increased. Common errors encountered during these updates include:

- labeling incorrect containers
- inadvertently breaking the blind
- incomplete updates (not all containers updated)
- errors in documentation
- obscuring critical label content

The use of interactive response technology can eliminate many manual activities, reduces risk, and can significantly improve patient safety.

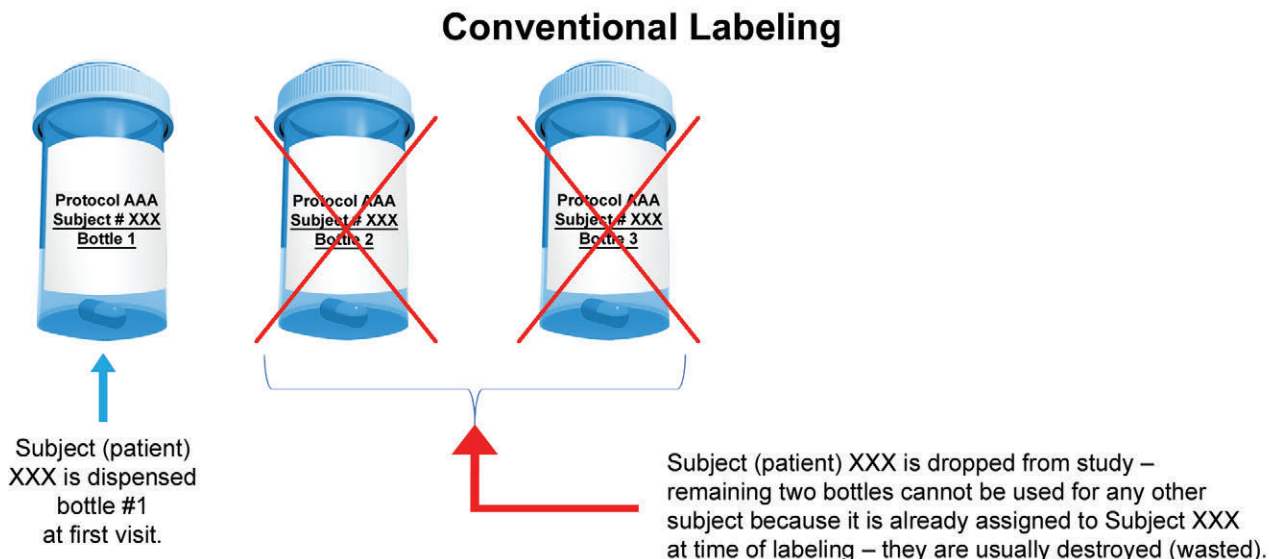
Conventional Packaging versus Pooling

For the purposes of this Guide, conventional packaging (or non-IRT) is defined as the use of protocol and subject specific packaging and labeling.

Example

In this scenario, each container is labeled with the protocol number and the subject or randomization number. If protocol #AAA requires a subject to receive three bottles of medication, each of the three bottles would be labeled with protocol AAA, subject number XXX, bottle #1, subject number XXX, bottle #2, and subject number XXX, bottle #3. Should this patient be dropped from the clinical study for any reason after receiving only bottle #1, the remaining containers cannot be used for another patient. This is because they have already been pre-assigned to a subject that has already entered the study and subsequently dropped. In essence, these supplies are wasted (see Figure 1.1).

Figure 1.1: Conventional Packaging



Alternatively, when using interactive response technology, each container is made to be unique using randomly assigned container numbers that are only linked to a patient at the time of dispensing or at time of distribution. These containers can be packaged with unique container numbers at either a protocol level or a program level. For more specific information on how these processes work, see Chapter 4 of this Guide.

1.2 Purpose and Objectives

The pharmaceutical industry needs to:

- meet expectations to operate in a lean and cost effective way
- meet patient expectations
- comply with global regulations
- ensure patient safety (primary obligation)

Ensuring the safety of patients has to be given priority when designing and implementing new business efficiencies. This Guide aims to show how interactive response technology can increase the ability to meet these expectations.

Use of Interactive Response Technology (IRT) is an example of how technology can improve both business efficiencies and patient safety. Interactive response technology can be applied in a new way to processes that require strict cGMP adherence and to variable global regulations that require strict compliance. A methodical approach should be used when considering the use of interactive response technology to manage these challenges. This approach should:

- Generate awareness of the technical capabilities of interactive response technology.
- Educate users of this technology.
- Establish global confidence in its capabilities.
- Standardize critical functionality ensuring full compliance with all regulations and enhance patient safety.

Interactive response technology can provide a single standardized approach to meeting global regulatory expectations and patient safety.

Standardization of the design of interactive response technology and its application to key clinical trial activities, such as “use-by-date” and pooling management, could have a significant impact on the global acceptance of this technology.

Technology can be a significant factor in the capability of a clinical supply organization to improve efficiency and cost of investigational medicinal product; although technology also can introduce further complexity.

For example, without standardization, systems used could have varying levels of functionality and robustness. This would make it difficult for inspectors and auditors to evaluate effectiveness. It also can mask the true benefits of what the technology can provide.

Understanding any complexities in the interactive response technology in advance of implementation can help to ensure a successful outcome and compliance with regulatory requirements.

The purpose of this document is to provide guidance to the pharmaceutical industry on how to:

- successfully implement an interactive response technology to manage key clinical trial activities; particularly expiry date management and program pooling
- ensure robustness of the technology; contributing to its effectiveness and reliability
- communicate and foster a standardized, industry wide approach to critical functionality of interactive response technology when used in managing investigational medicinal product

Although interactive response technology can support many activities, standardization of critical functionalities supporting use-by-date management and clinical trial supply dispensing is considered crucial to its successful adoption.

1.3 Scope

The Guide suggests interactive response technology design considerations to ensure development of industry wide standards. It covers the application of these design considerations and standards when used in managing pooled supplies and removal of “use-by-dates” from investigational medicinal product labels. Use of industry wide standards will allow study site auditors and local regulators to apply a more harmonized approach to evaluating effectiveness of the systems and help to improve their confidence in its ability to more effectively manage investigational medicinal product.

This Guide also considers:

- interactive response technology benefits
- key concepts, roles, and responsibilities
- system fundamentals
- considerations for in-house versus vendor managed interactive response technology systems
- regulatory requirements
- quality controls

- systems validation requirements
- warehousing
- distribution
- importation considerations
- training
- monitoring of critical activities and associated risks

This Guide does not cover processes related to determining which phases of clinical program to apply IRT, use of IRT to manage study enrolment parameters, or the use and benefits of booklet labels in conjunction with interactive response technology.

1.4 Benefits and Challenges

Interactive response technology can provide benefits associated with process improvements and other activities. For example, interactive response technology can contribute to the business actions, including:

- standardization in a global approach to managing critical clinical trial activities
- consistency in managing dispensing activities at the study site
- contribute to more effective management of drug accountability at the study site level and at the end of the clinical trial
- more effectively manage site inventories
- instantaneously stopping of dispensing of any product to a study subject should that action be required
- allowing packaging configurations, such as protocol and program level pooling, that conserve materials and reduce cost
- greater flexibility in the ability to initiate more studies simultaneously
- more efficient product recall process

From a safety and compliance perspective, interactive response technology has significant advantages over current clinical trial processes. These safety advantages are most prominent in the management of clinical supply “use-by-dates” and the process used to update clinical trial labels when “use-by-dates” change. From a quality perspective, interactive response technology can enforce greater controls over data and as a result greater confidence in the integrity of that data.

Challenges in the implementation of IRT include:

- lack of experience at the study site level
- lack of standardized approaches to the design and use of the technology
- lack of knowledge on what countries will accept this technology

- historical issues associated with improper design and implementation

These challenges need to be addressed before there can be global acceptance of interactive response technology.

For further information on how interactive response technology can bring benefits to an organization, see Section 2.6 of this Guide.

1.5 Structure

This Guide covers topics that start with the fundamentals of interactive response technology for those who have limited experience and moves toward greater detail and concepts for those who have a more expanded experience.

The first two chapters of this Guide, the Introduction and the Overview of IRT, provide a general understanding of the background and benefits of the use of interactive response technology for readers with limited experience in interactive response technology.

The chapters covering “Managing and Maintaining Data Integrity” and “Key Concepts” will provide background information that reveals how interactive response technology utilizes existing cGMP/GCP data and effectively retains the integrity of previously established “Tried and True” systems and controls. These sections provide diagrammatic depictions of how this data is used by interactive response technology currently and why it retains the quality controls and integrity previously established.

The Guide also provides information relating to the various uses of interactive response technology, validation considerations, training, risk factors, and Good Clinical Practice (GCP) considerations.

The Guide also points to other sources of reference material to further support or explain a particular concept.

2 Overview of Interactive Response Technology

2.1 History

Examples of interactive response technology can be found in aspects outside of the pharmaceutical industry, e.g., tele-banking, ordering tickets, and answering services for large complex organizations. Use of interactive response technology in supporting pharmaceutical clinical trial activities is a reasonable extension to earlier uses and the technology can be leveraged to support business efficiencies, industry wide “green” efforts, and specifically, increase controls over patient safety.

2.2 Evolution

For more than 30 years, management of clinical trial materials has relied on spreadsheets to track activities, and databases to record cGMP/GCP transactional data. These systems have proved to be “tried and true” with respect to conformance to global regulatory requirements and in meeting critical business record keeping requirements. In general, these tools remain the primary tools in use.

As technology continues to progress, and it becomes more robust and globally available, its function capabilities and application are being used more extensively to enhance accuracy, consistency, and efficiency in the pharmaceutical industry. One such technology is Interactive Response Technology (IRT).

2.3 Current State of Affairs

Interactive response technology experience within the pharmaceutical industry is variable, ranging from no knowledge on how this technology works to using it routinely to manage Investigational Medicinal Products (IMPs). In an October 2010 survey, 57% of 74 respondents indicated that interactive response technology was used in some way to manage investigational medicinal product; however, 43% indicated the technology was not used at all.

Remaining challenges are being addressed and with increased use of the interactive response technology, increased level of understanding, training, and standardization there should be greater acceptance within the industry.

Pharmaceutical organizations that see the value in interactive response technology may continue to be reluctant to implement to its full capability due to a lack of a comprehensive understanding and concerns over regulatory inquiries and audits. While understandable, the pharmaceutical industry needs to work together and build an environment of trust and confidence in the use of modern technology. This Guide is an effort to start generating that trust and confidence in IRT.

2.3.1 Clinical Site Perspective

Technology in the Investigational Medicinal Product (IMP) business usually focuses on cGMP processes and activities and as a result, may exclude a focus on downstream impact of Good Clinical Practice (GCP) and investigator or site related activities. However, many of the more significant advantages and controls of interactive response technology are at the GCP/site level and for this reason we have incorporated a specific GCP section in this Good Practice Guide.

In addition to the GCP functional attributes of an interactive response technology, some study site specific logistical considerations also should be considered. To obtain a better understanding of study site specific benefits and challenges of using an IRT system an industry wide survey was issued. More than 200 study sites from all around the world responded to this survey. The results of the survey can be found on the ISPE Web Site (www.ispe.org).

In summary, the following conclusions were made as a result of the survey:

- There is still a lack of full understanding, and therefore, acceptance of interactive response technology use in IMP processes.
- Training of all involved parties is of critical importance to successful use and long term acceptance of IRT.
- No real technological reason was provided as a reason for not using IRT and multiple benefits from interactive response technology were cited – suggesting acceptance of new and emerging technology in the management of IMP processes.

2.3.2 Significance of GCP Compliance

Fundamental GCP activities associated with interactive response technology should be taken into consideration when implementing the technology.

GCP compliance, while not routinely considered a responsibility of the clinical supplies organization (it is usually considered the responsibility of the clinical organization) is a significant component to ensuring patient safety and study integrity.

IRT is a tool that can help manage both cGMP related activities and the GCP activities as well. It is not the intent of this Guide to provide comprehensive detail on all GCP aspects that IRT provides; however, the following GCP activities should be considered:

Site Dispensing Record

The IRT system can be functionally programmed to define and force adherence to subject inclusion and exclusion criteria prior to determining acceptability for study enrolment and subsequent dispensing of study drug. This functionality captures the decisions made during the life cycle of the study and maintains a dispensing record for all enrolled subjects. The detail of this information is limited only to what is programmed as system functionality.

Dispensing Confirmations

Figure 2.1: IRT Dispensing Single Protocol-Multi Center

Protocol: A123654

Center 1001 – Web Enty # 1 and 3

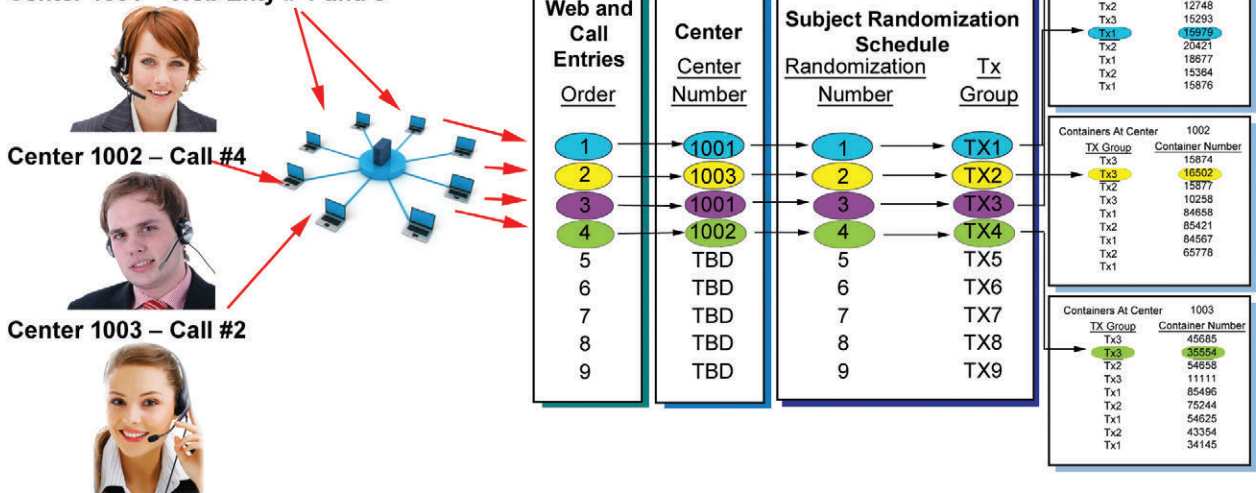


Figure 2.1 depicts a process for assigning containers/kits to study subjects. A significant percentage of study sites may not have a standard process for “verification” of dispensing containers to study subjects. In this context, verification is considered as the initial selection of the container identified by the IRT system, and then a second check to confirm that the correct container has been selected prior to providing it to the study subject. This “verification” step can occur as a manual second check process (by an independent site representative) or by the IRT system itself. The associated documentation and approvals should be retained by the site. Interactive response technology can be programmed to allow a second verification step prior to dispensing if desired. In the interest of patient safety, this capability should be incorporated into the IRT system.¹

Drug Accountability

At the end of each study, drug accountability should be performed; how much was received, dispensed, consumed, and returned. This is usually a manual process and may be captured on spread sheets with little or no industry standards. Several spreadsheets are usually compiled manually and can be error prone. Use of IRT can significantly streamline, standardize, and automate this process.

2.4 Where and When to Use IRT

Once effective industry standards have been established and the ability of IRT to manage investigational medicinal product effectively is generally understood and accepted, more information will be available; therefore, determining when to use interactive response technology should become easier.

It is usual to use the technology for:

- blind studies
- studies with expensive products
- studies with complex dosing schemes (those that might require complex blister cards or multiple containers)
- studies where supplies are limited, but multiple studies are required to support New Drug Application (NDA) and/or Abbreviated New Drug Application (ANDA) approval

2.5 Managing and Maintaining Data Integrity

Interactive response technology can initially appear complex, but understanding how the system works is helpful in understanding its capabilities for ensuring data integrity and cGMP/GCP quality control.

Interactive response technology is a software tool that uses existing information previously generated and contained within the existing “tried and true” systems. The database system and information is the same as that usually described to demonstrate compliance of operations during internal and external audits and should be consistent with ISPE GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures (Reference 2, Appendix 6).

How Interactive Response Technology Uses this Data

In general, clinical supply systems have at least two major components to their structure:

- “Inventory Database” – which records the standard attributes pertaining to a unique lot (or batch) of material.
- “Inventory Transaction Files” – which capture all transactions associated with a product recorded in the inventory database.

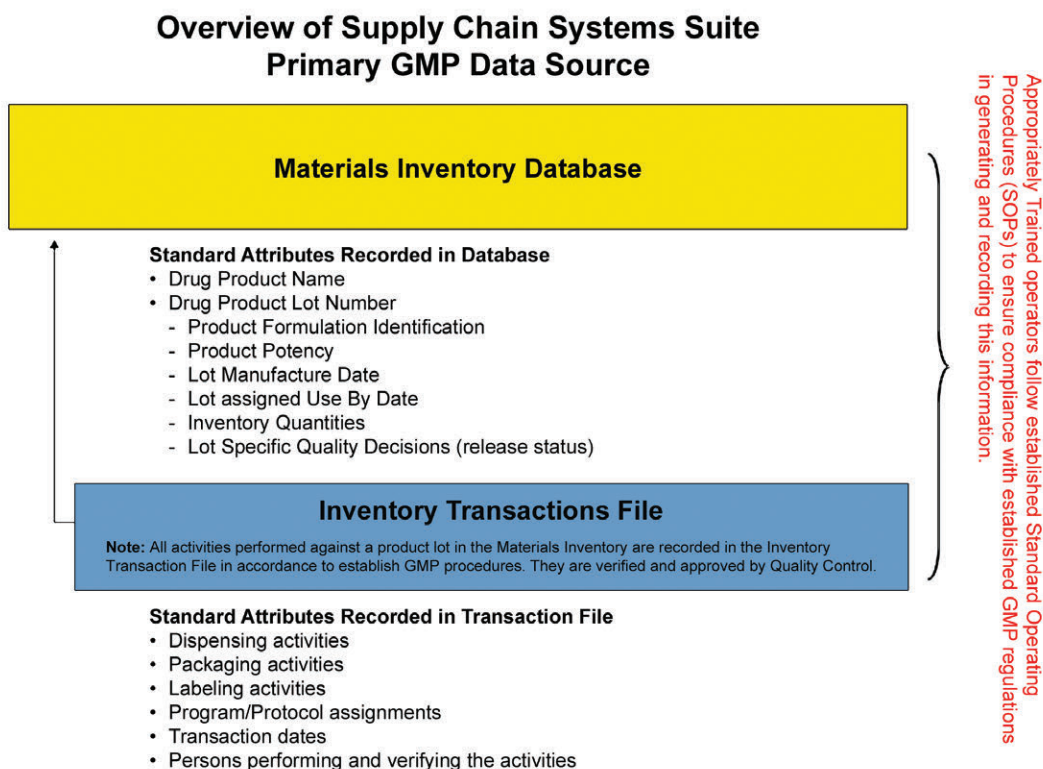
¹ There may be benefit in making this capability an industry standard.

These attributes capture pre-defined activities associated with a particular lot (or batch) of material for historical purposes and lot genealogy. See Figure 2.2 which shows some of the more standard (not comprehensive) attributes in use.

Note: clinical supply inventory systems may be built differently and may not use the same terminology, but conceptually they function in the same manner and all should have the appropriate quality control gates, processes, and standards built in. If the system is validated and has been in use for several years and has withstood the test of both internal and external audits, it is likely to be a robust system on which to leverage the interactive response technology.

Figure 2.2 (Example #1) is a conceptual view of key attributes of an established inventory and transaction database, which explains how the data points are connected.

Figure 2.2: Example #1



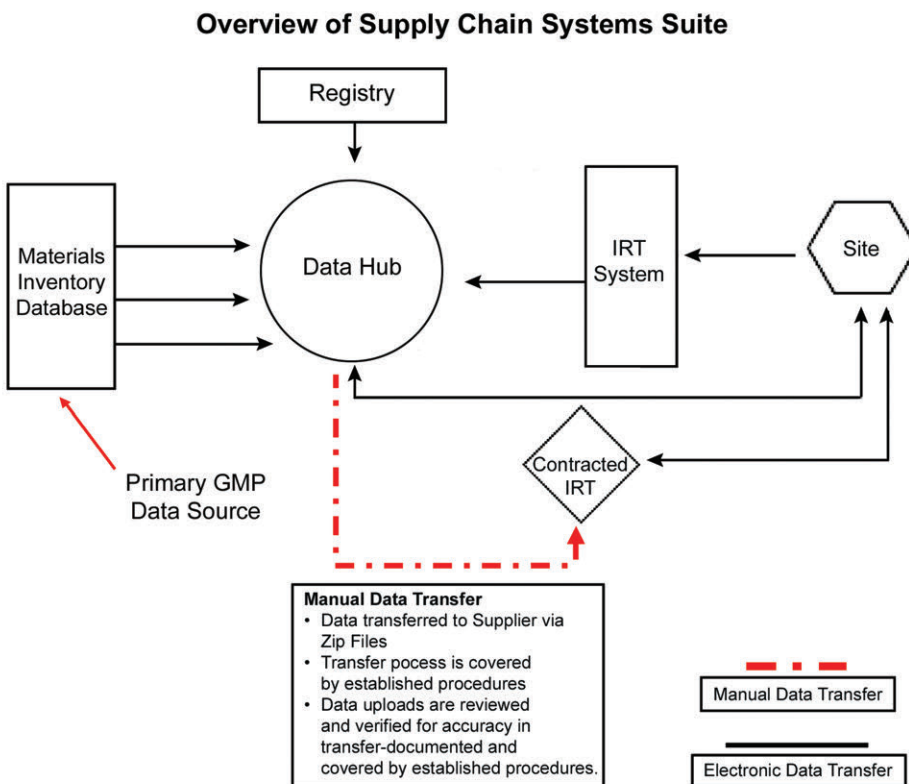
Many interactive response technology systems are built to interface directly with a clinical supply database where data is accessed in a seamless way. IRT systems may have been built in-house for some pharmaceutical organizations and managed by internal operations. Systems may have been built as standalone systems where key product information, normally found within the clinical supply database, has to be manually imported into the system. External systems may be used by pharmaceutical organizations that have no internal systems or where internal systems may not have the required functional capabilities.

- In either scenario, the concept of using data that exists within “tried and true” inventory database systems is the same.
- How the data is accessed and shared can vary.

For those systems that are not directly interfaced to the inventory database, a procedure should be in place to ensure that all migrated information was transferred accurately. Having a direct interface to the inventory system using seamless electronic transfer of data is considered to be the optimal and lowest risk approach for executing this process.

Figure 2.3 (Example #2) indicates a general method on how data might be accessed or migrated into an interactive response technology system.

Figure 2.3: Example #2



Key points from Example #2:

- Data is taken from a primary cGMP source, such as the inventory database.
- Interactive response technology uses this data to conduct pre-defined transactions at the study site.
- Data can be transferred electronically or manually between sponsor and suppliers who provide the IRT services.
- In-house and supplier systems interface directly with sites to perform pre-defined transactions prescribed by the sponsor.
- Manual data transfer requires secure and controlled processes that should be managed with appropriate procedures.

This is how interactive response technology uses our existing cGMP data and how this data can be leveraged through direct interfacing or manual transfer (uploading) into stand alone IRT systems. Once the data is in the interactive response technology system, how key data elements are linked together to complete critical transactions need to be understood, e.g.,

- distribution
- site inventory management
- dispensing to a subject

- expiry date management
- drug accountability

(See also Figure 2.1 which explains how the data points are connected.)

For full lot genealogy, the active drug substance and its ingredients should be integrated into the inventory system. For the purposes of this Guide; however, it is assumed that the inventory system initiates at the bulk drug product stage. Figure 2.4 (Example #3) depicts those key attributes that are usually found in clinical supply inventory systems (the primary cGMP data source).

Prior to production of the study labels, randomization codes are produced:

- Randomization codes are usually generated by a biostatistics group to assign study subjects to a particular treatment group within a clinical study. This randomization may also be referred to as “subject randomizations.”
- The biostatistics group may assign subjects to either a placebo group or an active group. In more complex studies, this assignment can include multiple treatment groups.

The purpose of the randomization code is to ensure a statistically randomized assignment of subjects within the study. Clinical supply professionals are usually familiar with randomization codes.

With the use of IRT, a second randomization code is introduced and this is commonly referred to as the “container randomization.” It is this randomization code that assigns a predetermined, unique number for each of the study containers. For example:

- If a subject is intended to receive 4 containers of medication in a blinded study, and there are 100 study subjects (50 on active and 50 on placebo), 400 containers will be required for the study (100 subjects × 4 containers/subject = 400 containers). Of the 400 containers, 200 will be assigned to placebo subjects and 200 will be assigned to active subjects. The container randomization will generate 400 unique container codes, usually in a randomized sequence.

This segmentation of placebo subjects and active subjects is an important step in the label generation and printing process. It allows the labels to be printed by treatment group and supports the cGMP requirement of bringing only the labels associated with the containers to be labeled into a packaging room.

Where the container numbers need to be sequential and non-randomized is usually where interactive response technology is used to support open label studies (where blinding is not required). When blinding is required; however, the container numbers are usually randomized and not sequentially assigned.

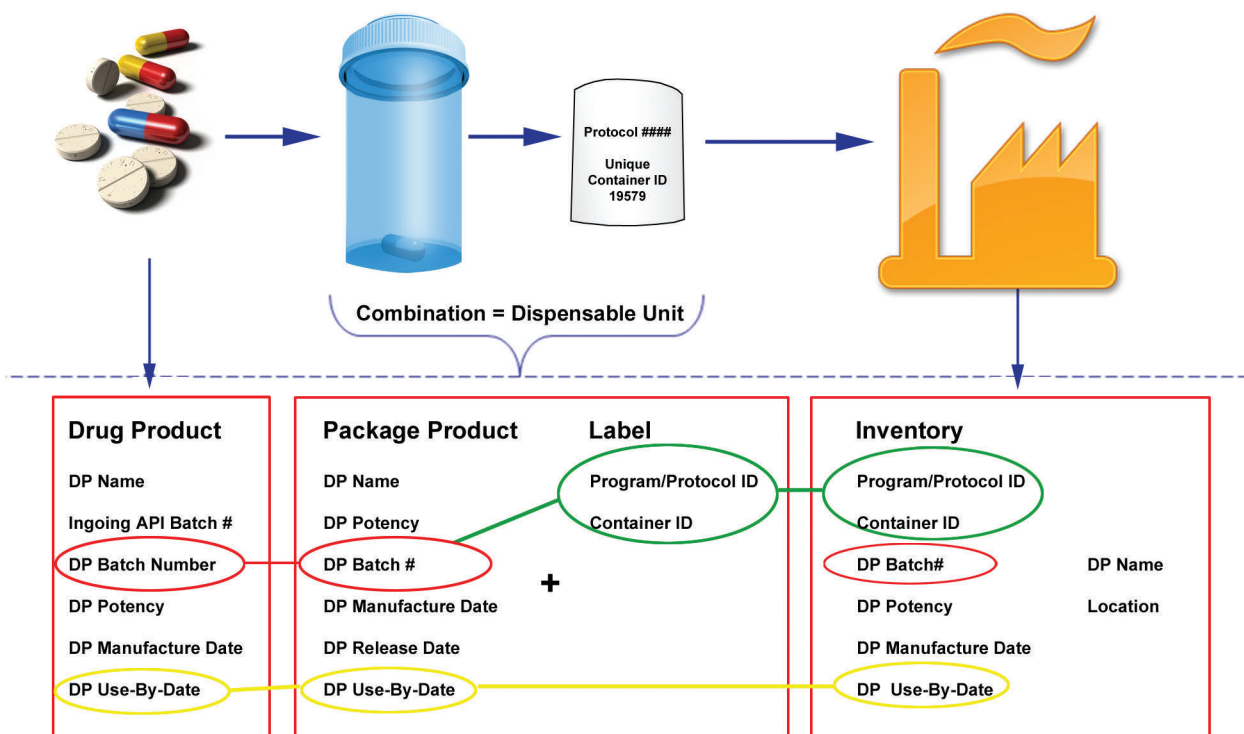
Once the container numbers are generated, the study labels can be produced. The unique container number is printed on the label and the label is affixed to the appropriate container of drug product (placebo or active in this case) for which it is intended. The bottle filling and labeling process follows the standard cGMP process, and ultimately, the container is released by the appropriate quality authority (Quality Assurance (QA) or Qualified Person (QP)).

The scenario described in Figure 2.4 (Example #3) captures the recording of steps from receiving bulk drug product into inventory, the packaging and labeling of this drug product into a “dispensable unit” and then movement to inventory to await shipment to a study site.

(Release actions and appropriate quality (QA and QP) endorsements are intentionally not captured in this diagram.)

Figure 2.4: Example #3

Standard Database Attributes – Linking the Data



Example #3 is intended to show how key data points are linked between normal clinical supply activities.

- Information contained within the Drug Product box is usually recorded in the clinical supply “Inventory database.”
- Information regarding Packaged Product, Label, and Inventory is usually contained within the “Transaction Data Base.”

Two of the four data points, Drug Product (DP) Batch number, and Drug Product (DP) “Use by date” are common to both databases and serve as the links for lot genealogy and product traceability.

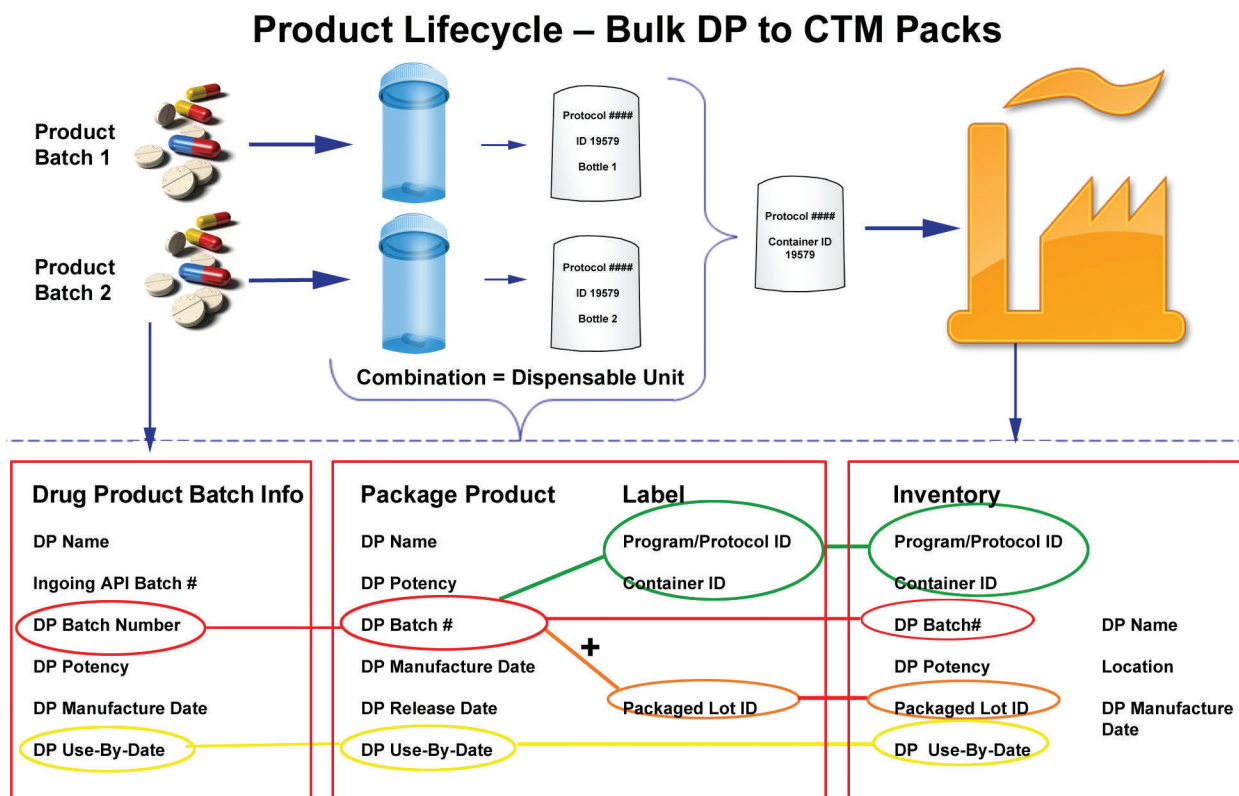
Note:

- Drug Product (DP) Batch number may also be referred to as “Lot Number”
- Drug Product (DP) “Use by Date” also may be referred to as “Expiry Date”

Once a product is labeled for a clinical study a “dispensable unit” is created. This “dispensable unit” can be either a single container for a given subject (see Figure 2.4 (Example #3)) or a kit containing multiple containers for a subject (see Figure 2.5 (Example #4)).

For each dispensable unit, the associated label has unique identifying information, such as program code or protocol number, and a container/kit identification (ID) number. Upon completion of the labeling activity, an entry is made in the “transaction database” that links the program or protocol and container/kit ID with the drug product lot that went into those containers. This is a critical linkage because interactive response technology uses the label information (program code or protocol number and container ID) to make decisions on container assignments at the subject (patient) level when managing “use-by-dates” and pooling of investigational medicinal products.

Figure 2.5: Example # 4



At this point, released materials are at a warehouse waiting for shipment to a study site and assignment to a study subject.

Prior to shipment of materials to a study site, the appropriate regulatory endorsements should be in place to ensure that supplies can be shipped to that particular site.

Note: This Guide does not discuss these regulatory requirements, but assumes that these requirements and processes are well established within the pharmaceutical organization.

The processes outlined in the Figures 2.2 to 2.5, explain how data is linked from drug product, through labeling, and then through release to the depot and/or study site. This information will be used as the foundation for build discussions of the concepts of “pooling” and managing “use-by-dates.”

2.6 Key Concepts

2.6.1 Role of the Quality Organization

The support of internal departments (e.g., Clinical Research, Clinical Packaging, Regulatory, Informatics, and Quality) from within organizations is needed to ensure success of the initiative described in this Guide. The approval and commitment of Quality Units and the Qualified Persons (QPs) is considered to be particularly important.

The quality role is a significant interface to external auditors and inspectors. Acceptance of IRT within an organization may be less likely where there is lack of understanding in how interactive response technology:

- functions

- ensures appropriate control of critical cGMP and GCP parameters
- ensures patient safety

The Quality Organization should be engaged at the onset of an interactive response technology deployment strategy and a clear overview of the system should be prepared. Fundamental elements that should be understood include:

- cGMP data controls
- change control process
- data transfer and verification (between internal and external providers)
- system interfaces (multiple operating systems)
- user training
- system availability (business continuity plans)
- help desk support
- adherence to protocol design parameters

Complete endorsement by the quality organization should be obtained for the interactive response technology implementation strategy before proceeding with an implementation.

Interactive response technology can provide a single standardized approach to meeting global regulatory expectations and patient safety.

Standardization in the design of interactive response technology and its application to key clinical trial activities, such as “use-by-date” and pooling management, could have a significant impact on the global acceptance of this technology.

Technology can be a significant factor in the capability of a clinical supply organization to improve efficiency and reduce the cost of investigational medicinal product; although technology also can introduce further complexity. For example, without standardization, systems used could have varying levels of functionality and robustness. This would make it difficult for inspectors and auditors to evaluate effectiveness. It also can mask the true benefits of what the technology can provide.

Understanding any complexities in the interactive response technology in advance of implementation can help to ensure a successful outcome and compliance with regulatory requirements.

2.6.2 “Use-By-Date” (Expiry) Management

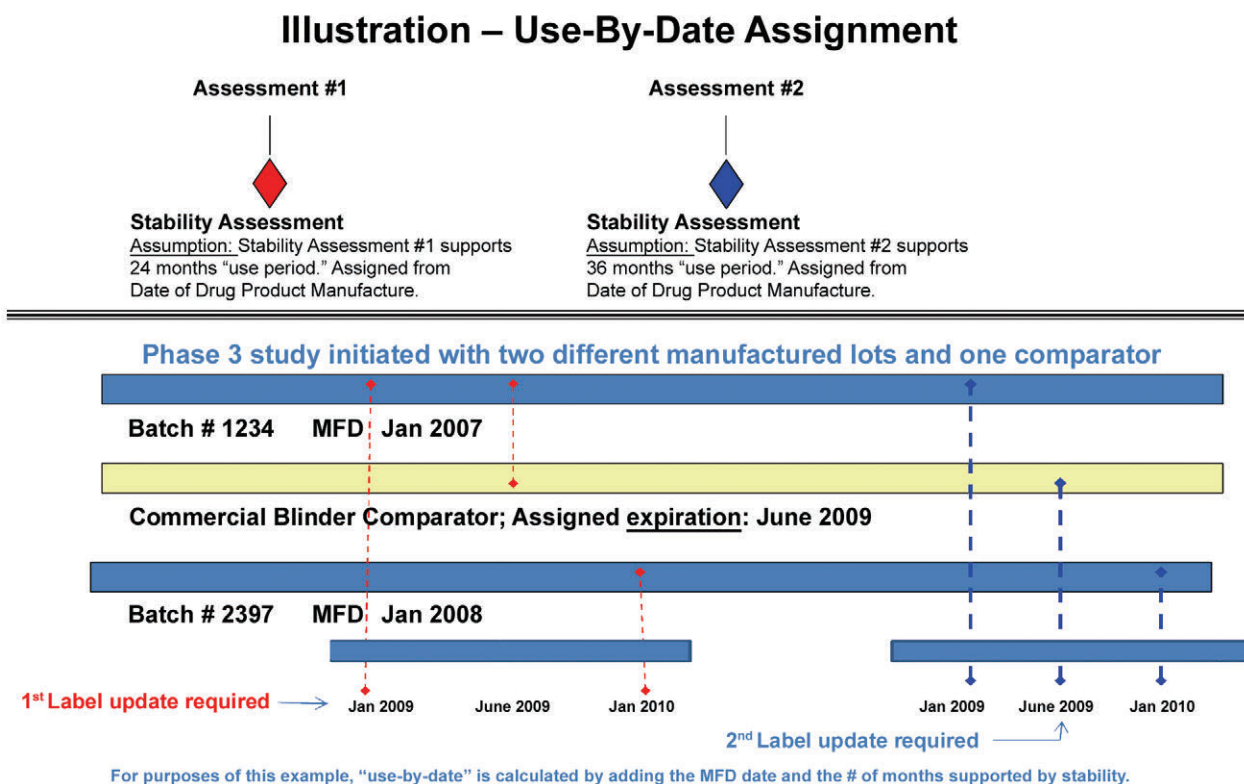
Effective management of investigational medicinal product is a significant requirement to ensure that patients do **not** receive supplies that have:

- expired
- are scheduled to expire prior to consumption of the medication

An understanding of the complexities and risks associated with this commonly applied industry practice for use-by-date management is helpful in understanding the benefits that interactive response technology can provide in this process.

Normally in a clinical study multiple batches of product are required. Each of these products has its own assigned “use-by-date.” To ensure blinding, the labels of all products within a study must look alike and if a “use-by-date” is required, it must be the same on each label. In these situations, it is usual to use the most restrictive date of all batches and assign that date to the Clinical Trial Material (CTM) label. Figure 2.6 (Example #5) illustrates how the process works.

Figure 2.6: Example #5



In Figure 2.6, there are three batches (or lots) of material in the study:

- two investigational products (likely an active and a placebo)
- a comparative agent (i.e., comparator product)

Each product has its own unique batch number and assigned “use-by-date.”

The two investigational products may have their assigned “use-by-dates” extended if supporting stability data exists. For the comparator product, there is an actual assigned “expiration date” which is usually not extended beyond the commercially assigned date.

In this illustrated example provided in Figure 2.6, the study is a blinded study run outside the United States, and the label (in most cases) must have a “use-by-date” on the label. At the time of initiation, the most restrictive date of January 2009 would be selected as the “use-by-date” applied to the IMP label (product batch number 1234).

As January 2009 approaches, information is received that the study is still active and an extension of the “use-by-date” for batch number 1234 is requested. Upon review of the stability data, it is concluded that the product is stable for 36 months (an additional 12 months from original date) and can be extended to January 2010.

When the “use-by-dates” of other batches in the study are considered, it is determined that the commercial blinded comparator now has the most restrictive date of June 2009. This is the new date that must now be applied to the IMP label within the study and all IMP labels will require an update or to be replaced.

To comply with the current requirements for label updates, a strategy should be developed to ensure that the labels of each container located in various locations around the world (sites, warehouses, and depots) are appropriately updated.

The alternative to updating the labels is replacement of supplies within the study.

Depending on the location of the affected supplies, finding personnel experienced in cGMP labeling process that could perform label update activities is improbable. In addition, it is not usually feasible to recall all of the affected containers to a central location for remediation.

A written plan complete with instructions, verification sign off requirements, and the new auxiliary labels, should be prepared and forwarded to each location having supplies that require the update. The containers should then be updated as instructed; the resulting product is released for use, and then made available for dispensing.

As the study progresses, the June 2009 date of the commercial blinded comparator approaches and the process starts again.

Each cycle of updates introduces risk, i.e.:

- that the containers are improperly updated by non-experienced personnel
- that critical label information is over labeled
- that (in some cases) the containers never get updated

Each of these issues presents safety and compliance risks that can be avoided through use of technology such as interactive response technology.

The way in which the process for assignment and ongoing evaluation of the assigned “use-by-date” is managed should not change when using interactive response technology. How the process is managed will remain dependent upon previously established processes; however, use of interactive response technology introduces a greater level of control that does not exist in routinely used label update processes.

Use of interactive response technology introduces a greater level of control to the patient level, e.g.:

- Interactive response can and should be programmed so that a container will not be selected for dispensing if the container contents will not be consumed by the patient prior to reaching the current assigned “use-by-date.” This functionality can be introduced using interactive response technology and this Guide recommends that it should be a standard practice applied by the industry.

Comparing this capability to the conventional process used where the label has a “use-by-date” displayed on it:

- Each site must have established reliable practices, process and/or Standard Operating Procedures (SOPs) that define what to do when a container has reached or is about to reach, the assigned “use-by-date.” Prior to each dispensing, the container must be manually evaluated to ensure that it can be dispensed and will be consumed prior to reaching the assigned date. As a manual activity, this presents room for error and the busier a site gets, the more likely these manual processes will introduce error. In this case, patients could get expired supplies and this can go undetected for substantial time periods.

- With the use of interactive response technology, coupled with site processes and procedures, the chance of patients consuming expired materials is significantly reduced and could be eliminated.

2.6.3 Pooling of Supplies

Pooling of supplies is a process where the use of interactive response technology and unique labeling practices allows greater flexibility and commutability of investigational medicinal products.

A more detailed explanation of the pooling concept can be found in Chapter 4 of this Guide.