

**Using An Interactive Voice System or Interactive Web Technology to
Manage IMP Retest Dates in Lieu of Placing Retest Dates on IMP labels**

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Table of Contents

- 1.0 Scope
- 2.0 Introduction
- 3.0 Glossary
- 4.0 Use of an Interactive Voice Response or Interactive Web
Technology to Manage IMP Retest Dates
 - 4.1 Background
 - 4.2 Risk Assessment
 - 4.3 Cover Memo for CTA/IMPD Filing
 - 4.4 Capabilities and Essential Functions of IVR/IWR System
(Flow Diagram)
 - 4.5 Conclusion
- 5.0 References
- 6.0 Attachments
 - Attachment 1: Retest Dates – IMP Risk Areas Identified
 - Attachment 2: Risk Assessment
 - Attachment 3: Cover Memo
 - Attachment 4: Flow Diagram

1.0 Scope

This document describes, for Investigational Medicinal Products (IMP), how an IVR or IWR system can be utilized to efficiently and effectively manage retest dating in a manner that helps to ensure patient safety.

2.0 Introduction

It is current practice within the Pharmaceutical Industry to manage dating of Investigational Medicinal Products (IMPs) by placing "expiration" and/or "retest" dates on IMP labels when used in EU/EEA studies. Most IMP supplies are research materials which are in various stages of development and are intended for eventual commercialization. In the development lifecycle for these compounds stability programs run concurrently with Clinical Trials. It is common for the "retest dates" to be extended beyond the initial assigned date based on evolving data. In general, "expiration dates" cannot be extended. Managing retest date updates for IMPs that are in use at study sites is costly, labor intensive and, based on the specific process used to update existing IMP labels, can introduce some risk.

In accordance with Clinical Trials Directive 2001/20 and GMP Directive 2003/94 and as detailed in Annex 13, Rules Governing Medicinal Products in the European Community, Volume IV, the period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity must be provided on the IMP label "unless its absence can be justified, e.g. use of a centralized electronic randomization system".

The objective of this paper is to provide guidance on how one might employ Interactive Voice Response (IVR) and/or Interactive Web Response (IWR) technology to support retest date management of IMPs, remain in compliance with the "Directives" and maintain patient safety.

This paper does not imply that permission has been granted by EU/EEA Competent Authorities to eliminate "expiration" and "retest" dates on IMP labels for trials in all EU countries. It is intended to provide guidance and clarity on how one might successfully apply the use of IVR/IWR technology in lieu of also having retest dates on IMP labels and comply with the Directives and ensure patient safety. The ability to take this approach must be confirmed for each trial via the registration process.

3.0 Definitions (As used in this document)

- 1) **Expiration Date:** Date assigned to a product, usually commercial, that is definitive and usually not extended.
- 2) **Retest Date:** A date assigned to an IMP that defines the time frame by which the IMP must be used unless there is sufficient stability data that will support an extension. Non-commercial IMP retest dates are often extended based on the expanding generation of additional stability data.
- 3) **Use-By-Date:** Synonymous with "Retest Date".
- 4) **Manual Relabeling Process:** The process of creating, approving and issuance of labels (IMP or auxiliary labels) for the purpose of updating "retest" dates currently on IMP containers at warehouses, depots or clinical study sites.
- 5) **Sponsor Company**
The Pharmaceutical Company having responsibility for the affected clinical study.
- 6) **Competent Authority**
---obtain from the Directives or from EU colleague
- 7) **IVR:** Computerized Technology which combines the use of databases and telephones to input, retrieve and manage IMP specific information for uses including subject randomization assignment, IMP assignment and dispensing.
- 8) **IWR:** Computerized Technology which combines the use of databases and the Web to input, retrieve and manage IMP specific information for uses including subject randomization assignment, IMP assignment and dispensing.

4.0 Use of Interactive Voice Response or Interactive Web Technology to Manage IMP Retest Dates

4.1 Background

The International Society of Pharmaceutical Engineers Investigational Products Community of Practice (ISPE IP-COP) partnered with the Parenteral Drug Association (PDA) Clinical Trial Interest Group (CTM IG) in an effort to describe an efficient, effective and compliant process for using Interactive Voice or Interactive Web Technology in fulfilling the requirements of the EU/EEA Directives in managing "expiration" and/or "retest" dates .

A Team of eleven (11) representatives from ISPE IP-COP and the PDA CTM IG was formed to define the issues, determine the level of industry use of IVR/IWR technology to meet requirements of EU/EEA Directives and to understand reasons for any resistance that may have been encountered within the sponsoring organization or from the Competent Authorities.

To begin, a survey was provided to approximately 140 attendees at the 2007 Annual ISPE Meeting representing approximately 60 IMP related professional organizations which included Pharmaceutical companies, IMP Service Providers and Universities. Sixty five responses were received and summarized.

The survey requested feedback from each company with regard to how they manage IMP "retest" dating, the extent to which they used IVR/IWR technology to manage the IMP updates and how successful they have been in eliminating placement of "re-test" dates on IMP materials.

Survey Highlights :

- We received a total of sixty-five responses to the survey. It was not possible to determine how many companies may have had more than 1 representative responding to the survey.

Always update by some means of over labeling	73%
- Do not always update	13% (1 response- "always replace supplies")
- No response to the question	14%
Have obtained approval to eliminate "retest dates" from IMP labels	6%
- Have never received approval	65%
- No response to the question	29%
Have estimated cost impact of "relabeling"	7% (1 respondent indicated \$1500.00 per site for relabeling effort; another \$25,000 per effort- not clear on scope of work in either case)
- Have never estimated the costs	67%
- No response to the question	26%

In addition to the survey, we interviewed colleagues from two major Pharmaceutical Companies within the EU who were successful in obtaining approval from Competent Authorities to eliminate "expiration" and "retest" dates from IMP labels by using IVRS technology. Each company indicated the scope of their program encompassed multiple EU/EEA countries. A small number of countries requested further clarification and discussion on the proposed process, but no country denied use of the process.

Conclusions from the survey and interviews suggests that an opportunity to improve IMP "retest date" management exists and precedent, albeit small, has been set. It was also clear that there is a substantial

need to increase awareness on the capabilities of IVR/IWR technology and its ability to manage IMPs in full compliance with Directives and assurance of patient safety.

In general, most reluctance appeared to come from within sponsor organizations and less from the Authorities. The survey and follow-on discussions suggest that Quality and Regulatory departments within the sponsor company may have limited knowledge or awareness of the IVR/IWR capabilities and how it can be used to effectively manage the IMP "expiration" and "retest" date process. This lack of awareness may further perpetuate reluctance to defend the process when queried by the Authorities. In these cases, there is an increased need for awareness and this paper will provide the essential substrate that one could use to increase their organizational awareness .

To assist in generating greater awareness of IVR/IWR capabilities and to provide guidance on its use for IMP management, the following attachments have been created:

- 1) IMP Risk Areas
- 2) Risk Assessment Summary
- 3) Cover memo for submission to CTA or IMPD
- 4) Flow Diagram describing the capabilities and essential functions of an IVR/IWR system used to manage IMP "Review Dates"

4.2 Risk Assessment

The flow diagram seen in attachment #1 outlines the critical steps in managing IMP retest dates. It further identifies the particular areas that represent some risk when data and logic are entered into an IVR system or when manual label updates are performed.

The Failure Mode and Effect Analysis (FMEA) approach was used to assign values to the risks associated with the manual process versus the process of using IVR or IWR technology. We measured 3 categories:

- 1) "Probability" of an event occurring (scale of 0 = not possible to 5 = likely)
- 2) "Severity" that an event might have on patient safety (scale of 1 = minor impact and 5 = major impact)
- 3) "Detectability" of an undesirable event (1 = readily detectable and 5 = non-detectable)

Eight (8) potential failure modes (or Risks) were assessed:

- 1) Obscuring critical label text when applying new expiry/ retest date labels
- 2) New dating labels applied such that two dates are visible
- 3) The wrong IMP being re-labeled
- 4) Label reconciliation issues
- 5) Incorrect data in IVR system
- 6) Incorrect IVR system logic utilized
- 7) IVR/IWR System becomes unavailable for use
- 8) Personnel at site don't follow established process and dispense expired materials

In summary, although there are risks associated with utilizing either approach, with appropriate controls in place, the use of an IVR/IWR system for managing expiry/retest dates presents an overall lower risk (see attachment #2).

4.3 Cover Memo For CTA/IMPD Filing

Annex 13 states that the period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity must be provided on the IMP label "unless its absence can be justified, e.g., use of a centralized electronic randomization system".

When a Pharmaceutical Company intends to use IVR/IWR technology to manage the IMP dating process, a memo of intent ("Cover Memo") indicating there will be no "Review Date" or "Expiry Date" on the IMP label and describing the system that will be used to manage the process in compliance with Annex 13, should be filed with each CTA.

A "Sample" memo (see attachment #3) has been created as guidance to the sponsor company when filing to the CTA and/or IMPD. The memo explains the intent to eliminate "Retest Dates" and "Expiration Dates" on IMP labels, identifies the technology (IVR/IWR) that will be used to manage the process, it provides detail on critical functionality that should be provided to ensure the appropriate level of control and patient safety and it indicates that the appropriate level of QP controls will remain in place.

Filing the memo to the CTA does not guarantee that the Competent Authorities will accept it without question. It may require further clarification and justification prior to specific country approval. The sponsoring company should therefore, establish a contingency plan for how to address country specific concerns without delaying other participating countries.

4.4 Capabilities and Essential Functions of IVR/IWR System (Flow Diagram)

IVR/IWR technology can be designed and implemented with very limited or very complex functionality. For this reason, one cannot simply assume that use of IVR/IWR technology in general, will support full compliance with the Directives. Therefore, it is important to define the functionality that will be used specifically to ensure the appropriate controls are in place. One very critical functionality is the ability to prohibit dispensing of a IMP container that is beyond the established "expiration" and/or "retest" date.

The "Cover Memo" (example #3) in conjunction with the Flow Diagrams (see examples 4A and 4B) and the risk assessment define the critical functionality of IVR/IWR and the required controls to be considered when managing IMP "expiration" and/or "retest" dates. The "Flow Diagram" provides additional reference to the capabilities and can be modified to fit the needs of any IMP organization or IVR/IWR system. However, any change must ensure that the appropriate levels of control remain in place that assure compliance with the Directives and prevent dispensing and consumption of expired IMPs.

4.5 Conclusion

Technology continues to evolve and its use in the management of Clinical Trials is growing rapidly. With the ever increasing demand to rapidly provide quality medicines to patients around the world at reasonable costs we must move away from the traditional, more laborious and often more risky processes toward processes that are more automated, less costly and less risky. The use of IVR/IWR technology is a move in the right direction and it begins to address some of these needs. Not only does this technology provide greater efficiency to the IMP process, depending on its application, it can also reduce risk and increase patient safety. If IVR/IWR technology is not available, however, a manual re-stickering process can be successfully utilized when adequate controls are in place (e.g., SOPs, Training).

IVR/IWR technology can be designed to meet specific needs of the sponsor company and can provide either very simple functionality or very complex functionality. The sponsor company must make the appropriate decision on functionality based on the desired outcome and systems expectation.

Annex 13 allows an alternative means, using IVR/IWR, to manage IMP "expiry" and "retest" dates. When using the IVR/IWR technology to fully support IMP "expiry" and "retest" dates, and thus not add this information directly onto the IMP label, the sponsor must ensure the proper functionality is designed in the system(s) and is functional in a way that ensures compliance with applicable Directives and, as always, ensure patient safety.

Precedent has been set, allowing use of the IVR/IWR technology to manage "expiry" and "retest" dates for IMPs. For whatever reason, be it a lack of experience in the IVR/IWR technology, lack of awareness on its applicability to IMP "expiry" and "retest" date management, cost associated with the design and application of

the technology or perhaps lack of confidence in their system's capability when queried by the Authorities, the industry hasn't yet taken full advantage of this opportunity.

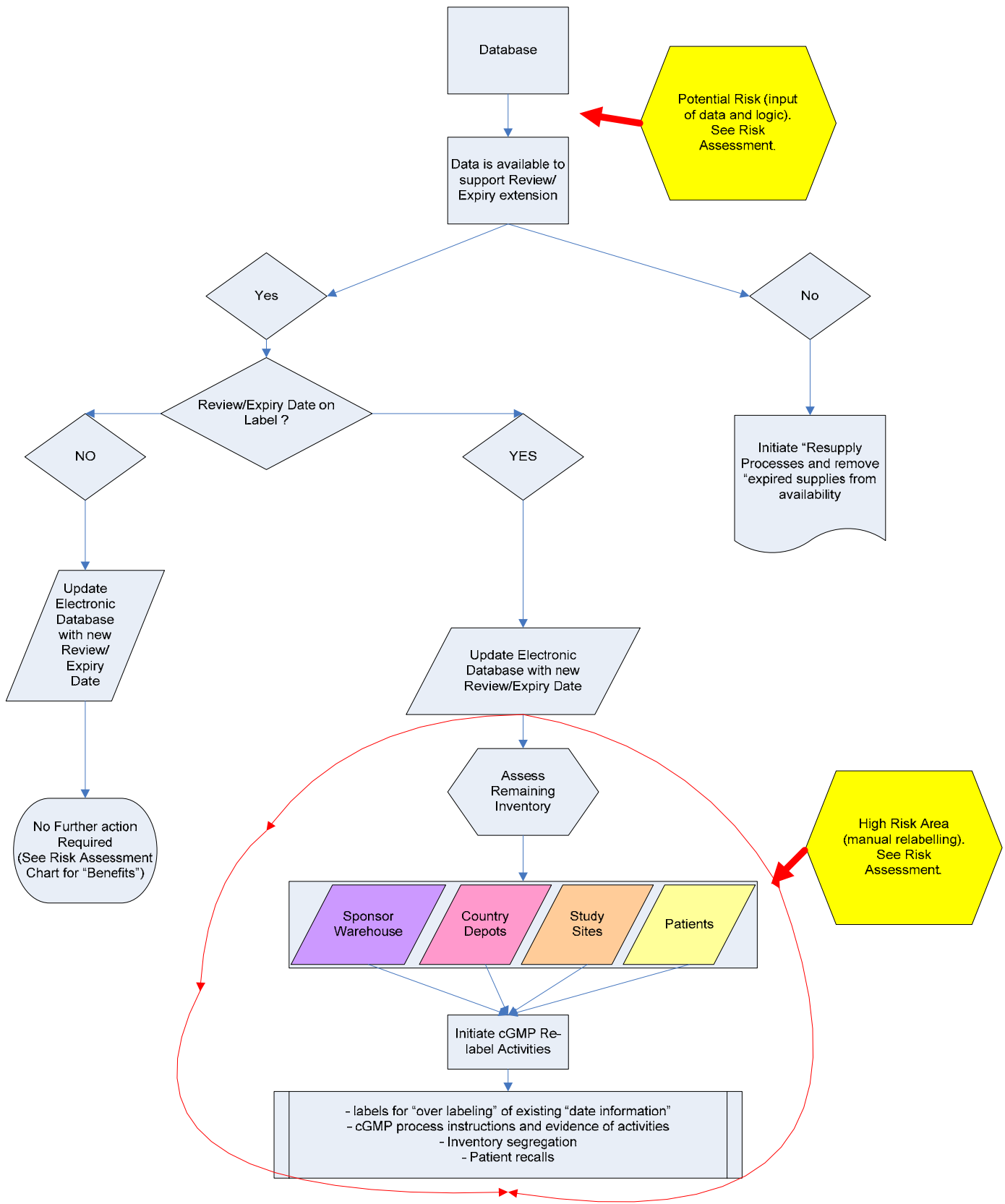
Effective use of the IVR/IWR technology has been demonstrated on numerous occasions within the Pharmaceutical Industry and more routine use of these systems seems appropriate today.

It is hoped that this paper will provide the right level of guidance and resource to allow us all to expand the use of technology in the management of IMPs and meet the ever growing obligations that we as Health Care Professionals have in meeting the needs of our patients around the world.

5.0 References

1. Good Manufacturing Practices, ANNEX 13, Manufacture of Investigational Medicinal Products, July 2003; Revision 1

ATTACHMENT 1 - Critical Steps in Managing IMP Retest Date Updates



No.	Risk (Failure Mode)	Cause	Impact	Patient Severity	Probability (Manual)	Ability to Detect (manual)	Comments	Controls (Manual)	Probability (IVR/IWR)	Ability to Detect (IVR/IWR)	Comments	Controls (IVR/IWR System)	RPN (Manual)	RPN (IVR/IWR)	
1	Obscuring critical label text when applying new "use by date"	Improper placement of the auxiliary label	Utilize incorrect CT materials	5	2	1		SOP and training should be available to ensure medical personnel apply auxiliary labels properly.	0	0	No auxiliary label required for IVR managed "use by dates"		10	0	
			CT material unavailable to patients due to labelling issues	3	2	1			0	0			6	0	
			Need to destroy or rework CT materials	1	1	1			0	0			1	0	
2	New dating labels applied such that two dates are visible	Improper placement of the auxiliary label.	CT material unavailable to patients due to labelling issues	3	2	1		SOP and training should be available to ensure medical personnel apply auxiliary labels properly.	0	0	No auxiliary label required for IVR/IWR managed dates		6	0	
			Need to destroy or rework CT materials	1	1	1			0	0			1	0	
3	Wrong CT materials re-labelled	Auxiliary label placed into incorrect containers. Improper relabeling process described or followed	Outdated materials utilized in clinical trials	3	1	3		SOP and training should be available to ensure medical personnel apply auxiliary labels properly.	0	0	No auxiliary label required for IVR/IWR managed dates		9	0	
4	Labelling reconciliation issues	Improper number of auxiliary labels prepared, incorrect number of containers updated, improper containers updated.	Investigation, impact assessment and deviation reporting required	1	3	1		SOP and training should be available to ensure medical personnel apply auxiliary labels properly.	0	0	No auxiliary label required for IVR/IWR managed dates		3	0	
			CT material unavailable to patients due to labelling issues	3	3	1			0	0			9	0	
5	Incorrect data in the system (external database or IVR/IWR system - includes initial data or updates)	Human error in data entry, ineffective procedures or processes, ineffective change control.	Outdated materials shipped to the site and/or dispensed at the site	3	2	2		SOPs and proper training should be established. Data entry verified by a second person (since this is critical data).	2	2	If data is manually entered into the IVR/IWR module it has same probability as manual entry into underlying database(s). Using IVR/IWR technology, it is more likely that the error will be found early because if the wrong lot is updated, it would impact another study dispensing algorithm and it would be captured at next dispensing.	SOPs and proper training should be established. Data entry verified by a second person (since this is critical data).	12	12	
			Outdated materials dispensed at the site	3	0	0	Note: Interface not applicable to manual process.		1	2	The computer interface is validated. These inconsistencies should be identified and resolved during the validation process.	Robust validation protocol should be in place to ensure the accuracy and integrity of any data transfer.	0	6	
6	Incorrect software logic used to assign "use by date"	Incorrect dispensing logic and/or dosing algorithm designed into system.	Outdated materials dispensed/utilized in clinical trials	3	0	0	Note: This issue not applicable to manual process.		1	2	Likely to be picked up by the CTM representative during shipping or during the CTM resupply process. Current database (non IVR/IWR) will have correct dating and won't match the IVR/IWR dispensing schedule.	Robust validation protocol should be in place to ensure accuracy of the logic around expiry calculation and use determination. Provide option for "dispensing agent" to obtain a dispensing report for each container dispensed. The report would have the current assigned "use by date"	0	6	
7	IVR/IWR System becomes unavailable for use	Phone or Internet service unavailable at clinical site	CT materials may not be able to be dispensed (severity depends if volunteers or patients are involved and the indication)	3	1	1	For blinded trials, the risk is the same if the retest date is on the label, or not, since dispensing cannot be performed without the IVR/IWR system, or backup	HELP desk resources available. Can utilize an IVR system if the IWR system is down, and visa versa. A backup system can be established - e.g. FAX or e-mail with appropriate QC processes employed.	1	1		HELP desk resources available. Can utilize an IVR system if the IWR system is down, and visa versa. A backup system can be established - e.g. FAX or e-mail with appropriate QC processes employed.	3	3	
			CT materials may not be able to be dispensed (severity depends if volunteers or patients are involved and the indication)	3	1	1	For blinded trials, the risk is the same if the retest date is on the label, or not, since dispensing cannot be performed without the IVR/IWR system, or backup	IVR/IWR system providers have redundancies and recovery processes in place. Can utilize an IVR system if the IWR system is down, and visa versa. A backup system can be established - e.g. FAX or e-mail with appropriate QC processes employed. Also can query the vendor databases for lot and expiry info.	1	1		IVR/IWR system providers have redundancies and recovery processes in place. Can utilize an IVR system if the IWR system is down, and visa versa. A backup system can be established - e.g. FAX or e-mail with appropriate QC processes employed. Can also query the vendor databases for lot and expiry info.	3	3	
8	Personnel at the clinical site accidentally dispense expired materials	Lack of adherence to SOPs and/or protocol intent.	Outdated materials utilized in clinical trials	3	1	1	Use by date will be on each CT material and be visible unless label applied incorrectly	Training, and periodic site audits/inspections.	2	1	IVR/IWR system will not allow expired materials to be dispensed. Dates not visible on supplies at home (clinicians must control)	Follow protocol design and assignments from IVR/IWR system.	3	6	
Key: Probability Scale: 0 - Not possible 1 - Unlikely 2 - Remote 3 - Moderate possibility 4 - Probable 5 - Likely Severity Scale: 1 - Minor impact on patient safety 2 - Moderate impact on patient safety 3 - Major impact on patient safety Detectability Scale: 1 - Readily detectable 2 - Likely to detect 3 - Somewhat detectable 4 - Not likely to detect 5 - Not detectable													Totals	66	36

Attachment 3 - Template for Submission Letter

<Date>

<Addressee Name> Formatted *as per Company Policy*

<Title>

<Division>

<Address 1>

<Address 2>

<Address 3>

Note: *This text is intended for use in either CTA and/or IMPD submissions. The text could also be used to amend existing CTA's when required. The information is intended to be used to insert into the appropriate document and in the proper company format.*

RE: <Relevant CTA/IMPD reference information>

General Correspondence: Intent to use established technology to manage expiration dating of clinical trial materials (IMP) for referenced program, in lieu of placing expiration dates on IMP labels.

In accordance with Clinical Trials Directive 2001/20 and GMP Directive 2003/94 and as detailed in Annex 13, Rules Governing Medicinal Products in the European Community, Volume IV, the period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity must be provided on the IMP label "unless its absence can be justified, e.g., use of a centralized electronic randomization system". For the above referenced clinical trial, an established technology will be used to manage IMP dispensing in accordance with defined "use by dates" and elimination of the expiry date on the IMP label can be justified. With the use of this system we will ensure integrity of the IMP and safety of the patient.

Technology in use: Interactive Voice Response (IVR) / Interactive Web Response (IWR)

Key Functional Attributes of the "Technology in Use"

1. **Clinical Site Inventory Control**

- Verification of IMP receipt at the study site
- Establish and monitor site inventory
- Monitor assigned "use period" for each IMP container

2. **Patient specific dispensing**

- Identify IMP container to be dispensed to each study subject based on established randomization code.
- Links the container directly to the study subject
- Evaluates "use period" prior to dispensing to ensure study subject will consume IMP within established "use period"
 - Is it within established date
 - Will the study subject consume contents before IMP reaches established "use period"

3. **Full product accountability to the patient and container level**

- Location and status of each IMP container is known and accountable
- Inventory of IMP supplies that have reached their defined "use period" are localized to the study site or depots-- no "expired" supplies in use by study subjects.
- Capability for comprehensive product recall if required

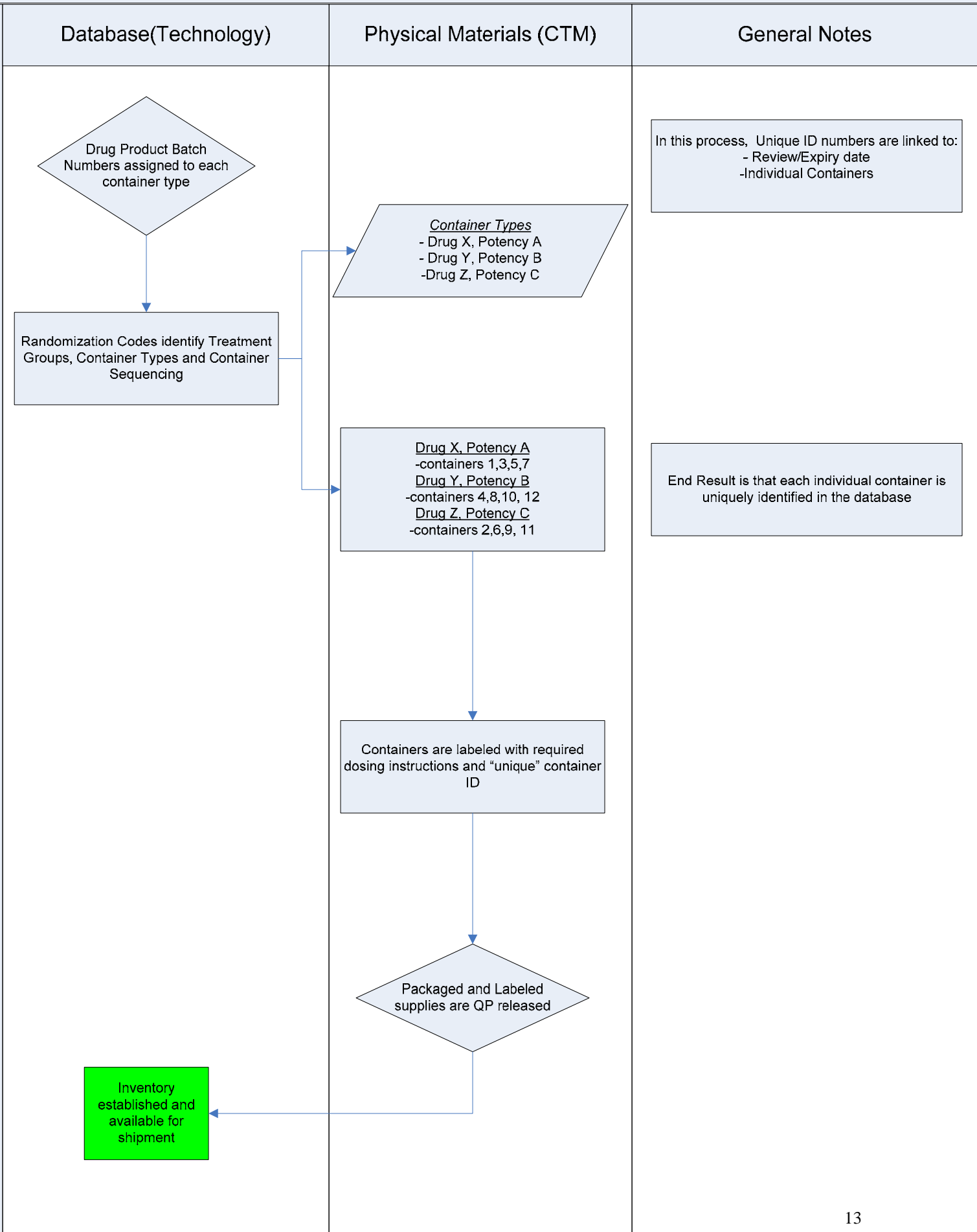
4. **Oversight of the "Technology in Use"**

- Quality components of the "Technology in Use" will be compliant with applicable policies and procedures
- The Qualified Person (QP) will have oversight of and execute all applicable GMP responsibilities

5. **Process Procedures**

- There are established procedures in place to manage the IVR/IWR system
- Procedures describe roles and responsibilities of involved parties
- The procedures will cover critical activities defined in sections 1-4 above to ensure integrity of the IMP and safety of the patient

ATTACHMENT 4A - Process Review for IVR Supplies- Expiry tracking



ATTACHMENT 4B - Process Review for IVR Supplies- Expiry tracking

Database(Technology)

Physical Materials (CTM)

General Notes

Request/Authorization to ship supplies to Investigator/site is received.

Received CTM are verified by investigator against invoice and confirmed via telephony or web system

Site inventory is established and active within database- dispensing can be initiated

Dispensing agent accesses telephony or web system to obtain patient specific container ID information

Container ID Based on-
Established Site inventory
Patient Dosing vs container Quantity
Consumption prior to established review/ expiry date

Site inventory adjusted post dispensing and container linked to subject to whom it was dispensed.

Full lot generology is electronically available and expiry tracking is electronically monitored at the subject, site and inventory level

Requested containers are removed from inventory and shipped to requested investigator

Dispensing Agent retrieves identified container form inventory and verifies via telephony or web system

Dispenses to study subject

Request specifies the Investigator, Site Address and unique container Ids to be shipped

Unique containers are now associated to a specific Investigator and Site

Unique containers are now linked to a single patient or subject

If Expiry date is insufficient to allow full consumption of container contents prior to expiry, the system will not dispense

Full capability to stop dispensing and to perform recalls at the patient/subject level