



GOOD PRACTICE GUIDE:

Investigational Medicinal Product Reverse Logistics

*Good Returns and
Reconciliation Practices*

Clinical Trial

Supply Chain

Risk Assessment

GCP/GMP

Product Return

Product Reconciliation

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Investigational Medicinal Product Reverse Logistics

Good Returns and Reconciliation Practices

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Preface

Every year the number of clinical trials conducted across the globe rises in a concerted effort to develop new or improved medicinal products that ultimately improve lives. Each trial is supported by dedicated professionals who work tirelessly to uphold the safety of the medicinal products being tested in the trial and to ensure the safety of those participating in the trial. Armed with regulatory guidance, the pharmaceutical industry has developed standards and best practices in almost every aspect of a trial. Additionally, as the pharmaceutical industry has evolved, medicinal products have changed from primarily single small molecules to include biologics, combination product/devices, and personalized medicines such as cell and gene therapies. With each innovation, the industry has typically established new best practices. Despite this progress however, there is one area that lacks foundational best practices: that of medicinal product accountability, reconciliation, and return for destruction, otherwise known as reverse logistics.

Most current reverse logistics processes lack effective planning, thorough application of risk management, and well-defined roles and responsibilities. This results in inefficient and costly processes that often cause delays in study closure as failure to account for study materials can affect the acceptability of trial data. Establishing better standards is also complicated by gaps in and lack of harmonization between Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), local environmental laws and regulations, and import/export and customs regulations. Regulatory scrutiny exists and failure by a sponsor or investigator to maintain accurate, complete, and current records related to the receipt, use, and disposition of investigational products is frequently cited in findings such as US FDA 483 observations and warning letters.

As the industry continues to expand and regulators continue to modernize laws, reverse logistics will need to gather the needed attention and focus to escape from being the weak link in the clinical supply chain. The *ISPE Good Practice Guide: Investigational Medicinal Product Reverse Logistics – Good Returns and Reconciliation Practices* recommends best practices for consideration to improve reverse logistics processes.

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The Guide was produced by a Task Team made up of:

Neal A. Gordon, PhD	Merck & Co., Inc.	USA
Edward Groleau	PCI Pharma Services	USA
Catherine (Cat) Hall, MS, MBA	endpoint Clinical	USA
Greg Hottell	GSK	USA

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Company affiliations are as of the final draft of the Guide.

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

www.ISPE.org

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Table of Contents

1	Introduction	7
1.1	Purpose and Scope	7
1.2	Key Considerations	7
2	Regulatory Considerations	9
2.1	RRD Requirements	9
2.2	Documentation Requirements	10
3	Industry Trend Considerations	13
3.1	Risk-Based Monitoring and Virtual Monitoring	13
3.2	Depot Monitoring versus CRA Monitoring	13
3.3	Direct-To-Patient Logistics and Decentralized Trials	14
3.4	Technology	14
3.5	Mergers and Acquisitions	15
3.6	Product Type	15
4	Product Considerations	17
4.1	Non-Solid Materials	17
4.2	Devices	17
4.3	Expired Materials	18
4.4	Hazardous Materials	18
4.5	Biologic Materials and Waste	18
4.6	Controlled Substances	19
4.7	Radiolabeled Materials	19
4.8	Materials with Multiple Special Characteristics	19
4.9	Packaging	20
5	Trial Conduct Considerations	21
5.1	Reconciliation Measures	21
5.2	Site Documentation	21
5.3	Objective Compliance Measures	22
5.4	Site Qualification	22
5.5	Retention Policies	22
6	Common RRD Approaches	23
6.1	Centralized: Return Everything to a Sponsor-defined Central Depot	23
6.2	Decentralized: Return Everything to a Local (e.g., In-Country) Destruction Facility	23
6.3	Decentralized: Return Nothing – Reconcile and Destroy at Site	24

7	Quality Considerations	25
7.1	GMP or GCP	25
7.2	QMS Jurisdiction	25
7.3	Setting Policy	27
7.4	Setting Standard Operating Procedures	28
7.5	Protocol and Pharmacy Manuals	29
7.6	Defining RACI	30
7.7	Change Management	30
7.8	Documentation	31
7.9	Due Diligence Investigations	32
7.10	Metrics and Quality Thresholds	32
7.11	Managing Discrepancies	33
7.12	Resolution of Discrepancies	39
8	Logistics Considerations	43
8.1	Return Exports	43
8.2	Direct-to-Patient	43
8.3	RRD Process Exemptions	44
8.4	Transfer of Ownership	44
9	Technology Considerations	45
9.1	Use of IRT For RRD	46
9.2	Use of Technology Pitfalls	46
10	Timeline Considerations	47
11	Appendix 1 – References	49
12	Appendix 2 – Glossary	51
12.1	Acronyms and Abbreviations	51
12.2	Definitions	52

1 Introduction

Reverse logistics is the process of planning, implementing, and controlling the efficient and effective inbound flow and storage of secondary goods and related information for the purpose of recovering value or proper disposal. Within the pharmaceutical industry, this is often referred to as Returns, Reconciliation, and Destruction (RRD). While sponsors spend a great amount of time and effort ensuring the security of putting investigational products into the hands of patients, often less energy is spent accounting for used and unused products within a trial. With an increased focus on how falsified products are entering the market, regulators have turned their attention to this portion of the supply chain, re-invigorating the industry to complete the final steps of an investigational product's journey, the one to its destruction.

1.1 Purpose and Scope

RRD processes are often clouded with uncertainty as they fall across the Good Clinical Practices (GCP)/Good Manufacturing Practices (GMP) boundaries. While regulatory guidelines (for example, US FDA CFRs [1], EU Annex 13 [2], and ICH E6 [3]) mention RRD, they fail to provide with any certainty who owns what, lacking best practices to guide decisions. The purpose of this *ISPE Good Practice Guide: Investigational Medicinal Product Reverse Logistics – Good Returns and Reconciliation Practices* is to provide further clarity from across the industry on what best practices exist, what nuances can be important to understand, and where the first standards in RRD can be relied on by the industry and health authorities. By far, just establishing clear RRD policies and procedures represents a best practice within the industry, and this Guide recommends areas for consideration to address within such documents.

This Guide primarily focuses on Investigational Medicinal Products (IMP) and does not cover diagnostics, ancillary or laboratory supplies. Although the general principles may be applied to all of these areas, the authors recognize that there are also key differences that may not be addressed. This Guide uses the general assumption of working with solid-dosage forms, as they form the majority of experience in the industry; however, alternative dosage forms and their special considerations are addressed in Chapter 4. In addition, this Guide primarily focuses on sponsor-supplied materials rather than site-sourced materials, which are more of an extension of the commercial supply chain rather than the clinical supply chain, while recognizing that it is a gray area.

1.2 Key Considerations

This Guide is structured to denote several key areas of consideration that are commonly taken into account when creating and implementing RRD policies and procedures. It is not intended to cover every scenario and it is assumed that the use of this Guide is accompanied by a risk-based approach in its application.

Every sponsor has different interpretations regarding regulations, and thus it is important to refer to your company's position and policies related to IMP RRD. Additionally, while references to key regulatory documents are provided, this Guide is not intended to be an extensive or in-depth analysis of the regulations, and users must recognize that regulations are always subject to change. Finally, the definitions within this Guide are based on collective best practice and have not been directly endorsed by any regulatory agency.

2 Regulatory Considerations

This chapter of the Guide references some but not all applicable regulatory guidances and laws regarding RRD expectations.

2.1 RRD Requirements

The primary regulations and guidance documents within the industry that have been historically in effect and refer to RRD include:

- ICH E6 Guideline for Good Clinical Practice [8]
- US FDA Code of Federal Regulations (CFR) [2, 3]
- EU Clinical Trial Directive (EC) No. 2001/20/EC [4]

Each portrays language for the need to retrieve product from subjects for accountability by the investigator, and that the sponsor must ensure the return and destruction of IMP. While on one hand this seems quite straight forward, one area that has often caused confusion is that these regulations apply the law to unused product. It is this use of the term “unused” that has often been an area defined differently within the industry.

The dictionary contributes to the confusion by including different definitions for *unused*: *not being used*, which can mean a) not having been used before and/or b) available for use in the future [7]. Each of these concepts translates into two different perspectives when it comes to unused IMP. In a patient centric view, unused translates to IMP available for use by a subject or as available for human exposure. On the other hand, in a trial centric view, unused translates to IMP that has not been assigned to a subject and is available for use in the trial.

Often when it cannot be determined which to adopt, the regulations are consulted for clues as to which was intended to be adopted. Considering the ICH E6 Guidelines [3], Section 5.14.4 states:

“The sponsor should: ... (b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial). (c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim). (d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.”

If a patient centric definition is applied, available for use by a subject or for human exposure, then in order to maintain a system for the disposition and documentation of the unused IMP, a sponsor would need to record any IMP not consumed by the patient that is a risk of further human exposure. In fact, for many years within the industry the practice of counting every unit returned by a patient has often been in place. As early products were often small molecule solid-dosage forms found to be safe in healthy volunteers, this was not an issue; but as products have evolved to forms not easily or not available for further handling, such as cytotoxic compounds, counting every unit is not always feasible.

Given that ICH E6 [3] was revised in 2016 and retains this same language, it may either be interpreted to mean they approve of the historic practice to count every dose or that they always intended for organizations to adopt the trial centric definition: that IMP is unused when it has not been assigned to a subject and is available for use in the trial.

On the other hand, other regulations such as CFR 312.59 [8] contain:

“The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug.”

This points back toward the patient centric definition. This may be why the authors have seen a movement by regulators to now suggest that while “unused” may be historically stated, the regulation should apply more generally.

Many sponsors and suppliers have noted that regulatory inspectors often provide observations citing return of used/unused to indicate that they expect all IMP to be returned and destroyed by the sponsor. Additionally, within the Frequently Asked Questions (FAQ) on ICH Guidelines the Czech Republic [9] answers the question:

“Is the disposal of leftover medicinal products from studies indeed up to the sponsor?”

“Yes, it is. The sponsor is responsible for the conduct of the clinical trial, responsible for providing the investigational medicinal products, and therefore also for their disposal, be it the disposal of leftover investigational medicinal products or unused complete packs.”

This wider scope of what is subject to return and destruction is also reflected within the more recent EU Clinical Trial Regulation No. 536/2014 [10], where the term “unused” has been removed, and the regulation no longer makes a distinction that reverse logistics should only apply to one form of product, but rather all forms of medicinal products provided within a trial.

For these latter reasons, the authors of this Guide have found that best practice is to define a clear scope within RRD policies and procedures regarding any IMP provided to the site by the sponsor and address any risk-based considerations needed within such policies and procedures.

2.2 Documentation Requirements

A common misconception is that the regulations do not provide much direction around what documentation is required as proof of RRD processes or the use of an alternative disposition process. They are, however, clear in a few areas that generally apply to clinical trials as a whole. Within ICH E6 Section 8.4 [3], it describes documents required after the completion or termination of a trial to include records that have the purpose to document:

“the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor”

And:

“of destruction of unused investigational products by sponsor or at site...(if destroyed at [destruction site])”

Additionally, CFR 312.57 [8] states:

“A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.”

EU Annex 13 Guidelines [2] states:

“When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.”

The more recent EU regulation [10] further adopted this language:

“The relevant information regarding the traceability, storage, return and destruction of medicinal products referred to in paragraph 1 shall be contained in the application dossier.”

“The protocol shall at least include: (t) a description of the arrangements for tracing, storing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product in accordance with Article 51.”

Additionally, several local authorities provide more guidance, such as in South Africa, their Guidance on Good Manufacturing Practice (GMP) [11] states:

“Ideally the destruction company signs a receipt detailing drug per participant and the total quantity. This should also be documented on a certificate.”

In summary, these regulatory references identify the need for a certificate of destruction that should include details (e.g., lot and quantity) of what IMP was returned and destroyed, and should also provide a direct link to how the same IMP was shipped and dispensed within the trial.

Despite these multiple points of definition within the regulations and by authorities, it is often the case that certificates of destruction are not available with the applicable data due to the lack of a consistent process and system that can provide full traceability of IMP from manufacture to site, to patient, back to site, and then to destruction. In many cases documentation may be missing certain details such as the lot number, quantity, or date; however, this may be due to reasonable circumstances that the regulations do not address. For example, a certificate of destruction may not provide for lot and quantity for any pre-filled syringes disposed of in a sharps container.

This Guide recommends the use of policy and procedure to describe how regulatory requirements are met and where risk-based consideration may justify where they are not met. For example, where data is not available, or when a local regulation needs to be applied, it is important to incorporate appropriate flexibility in RRD procedures.

Finally, as with all clinical trial documentation, ALCOA+ principles should be applied regardless of whether the documentation is paper-based or electronic.

3 Industry Trend Considerations

This chapter addresses some trends within the industry that are influencing or are likely to influence RRD procedures.

3.1 Risk-Based Monitoring and Virtual Monitoring

There have been many changes within the pharmaceutical industry that have impacted reverse logistics, and like other change factors they present the opportunity to evaluate old processes not often subject to review and renewal. One of the key changes in clinical trials that has begun to influence RRD procedures is risk-based monitoring and virtual monitoring. In a traditional returns process, a Clinical Research Associate (CRA) monitor is typically present to physically examine the investigational materials and verify, on behalf of the sponsor, that the site has conducted drug accountability correctly. The CRA also has been engaged in preparing materials for on-site destruction or for return to a sponsor for destruction.

When risk-based monitoring or virtual monitoring is employed, CRA monitors are conducting either less on-site visits or none at all, which has created a challenge to these physical inspection processes. In the case of less on-site monitoring, sites are expected to store large amounts of returned IMP, which they may or may not have the storage capacity to do. If the CRA must visit the site to do returns, the value of risk-based monitoring, to reduce visits, is diminished. It is best practice to take the RRD process into consideration when employing these monitoring practices and evaluate alternative disposition allowances to ensure sites are not burdened with excessive storage requirements.

3.2 Depot Monitoring versus CRA Monitoring

Historically, IMP management at a site has been subject to physical verification of the supply by a CRA monitor rather than a review of site documentation. However, ICH E6 5.18.4 [3] describes a monitor's responsibilities:

“ensure that the trial is conducted and documented properly by carrying out...[activities that include verifying] the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.”

Similarly, the regulation states that a monitor is to verify:

“that the investigator is enrolling only eligible subjects.”

If one can verify a patient was properly enrolled by review of documents, then one can infer that they may verify an IMP was handled appropriately through document review as well. Therefore, examination of only the documentation held by the site can be interpreted to apply to RRD just as it is for other clinical trial oversight conducted by a CRA monitor. None the less, it is still a common approach that when it comes to IMP, the CRA monitor physically examines the products.

ICH E6 [3] however does not dictate who may act as a “monitor;” thus, the industry has begun to establish that either a CRA or destruction depot might be delegated by a sponsor to verify that IMP returns are controlled and documented.

In support of the depot acting as monitor, not only is a destruction depot better trained to appropriately handle IMP during the RRD process, but eliminating the CRA from RRD often reduces transcriptional-type errors commonly found when CRAs are inserted between the site and the destruction depot. Thus, it is becoming a common practice in RRD for the depot to act as a “monitor” per ICH E6 [3] and a best practice in cases where the CRA monitor is less available or not available to act in the capacity to monitor RRD.

3.3 Direct-to-Patient Logistics and Decentralized Trials

Another factor impacting RRD process is the growth of direct-to-patient logistics and the introduction of Decentralized Virtual (siteless) Trials (DCT) and hybrid trials. In these cases, a site may not handle the investigational products at all, but rather the return of materials is handled by a subject through direct-to-patient logistics. In these cases, often only a destruction facility/depot has the opportunity to verify the control and documentation of the return and hence act as “monitor.”

The use of a courier to accept returns directly from a patient must include alternate ways of conducting drug accountability, which is the responsibility of the site. Just like returns, it is also often the case that drug accountability is verified by physical examination of the investigational products. The increased use of patient diaries and drug compliance technologies augment drug accountability data and provide more robust data regarding a patient's compliance to product-dosing requirements as well as being more efficient and reflective of the subject's conduct during the trial. In these cases, the investigator is measuring accountability through these methods and is physically removed from handling the IMP. The authors have found that eliminating the site and the CRA from RRD processes provides for a more efficient and accurate process by limiting the opportunity for materials to be lost or miscounted, and reducing transcriptional errors because the return goes directly from the patient to a facility trained to handle the IMP.

3.4 Technology

As stated earlier, the regulations cite the need to maintain a system regarding everything from shipment to final disposition of IMP. Historically, when an end-to-end clinical trial supply chain was paper-based or a combination of paper and technology, making the connection from first shipment to destruction has been difficult. However, as the industry has progressed, the prominent use of technology across the lifecycle of the trial has provided such a system for full traceability. Even with Direct-to-Patient (DTP) logistics, where certain details of a shipment must be withheld from sponsor line of sight with clear separation of data accompanied by data encryption, the risk of the patient's personal information being revealed can be well mitigated and still adequately provide for sponsor oversight.

Technology in general has helped to reshape RRD and, in some cases, has helped to bring standardization to many parts of the overall process. However, the transition from paper to electronic systems, like many transitions within the pharmaceutical industry, has been slow and is still incomplete. This is largely due to the inconsistencies between each company's expectations and requirements of how sites conduct and document drug accountability that then must be reconciled. Once moved to electronic form, standardization typically ensues, and consistency can be gained.

In large part, drug accountability, reconciliation, and returns have been adopted within clinical Interactive Response Technology (IRT) Systems and follow a common set of steps for the site to enter what was received back from a subject, a CRA monitor to verify these entries, and then to either identify the IMP as destroyed on-site or generate a shipment back to the sponsor destruction facility/depot where final verification and destruction is recorded. In many cases however the use of the IRT is duplicitous to other site procedures and documentation or to alternate site electronic systems that govern the traceability of any medication per local and/or national pharmaceutical laws. The small gains in standards are already at risk however as organizations move to risk-based monitoring, DTP logistics, and decentralized trials where the standards cannot be applied.

Additionally, as the use of interactive compliance technologies is more widely adopted, the industry will find additional ways to better understand accountability through digital means and determine what IMP was not used in the trial and was returned for destruction, allowing for more robust traceability of the IMP. As electronic systems within and bordering clinical trials further integrate, it is likely that once disparate systems will help resolve issues and augment communication across the various parties involved in the process and jointly influence the industry toward a more defined standard. The ability for a sponsor to understand an IMP's cradle-to-grave journey (from manufacture to destruction) through highly integrated systems will shift focus from document reconciliation to data analytics.

3.5 Mergers and Acquisitions

Another element that has a tremendous influence toward a universal RRD process is the prevalence within the industry for joint ventures, mergers, and acquisitions. There is no better force within the industry to help align practices and procedures than those that occur from having to adopt an ongoing program from another company. The chance to better understand how it was done by another company, especially a younger one that approached the problem from a fresh perspective, can often introduce a level of innovation and sense of continual improvement to more dated approaches.

3.6 Product Type

Finally, it should be noted that the change in the type of products used in clinical trials may have the greatest impact yet on the RRD process. Practices founded on solid-dosage forms handled and stored at room temperature in bottles and blisters are difficult to apply to cold chain liquid products stored in multi-use vials or single-dose syringes, and even more difficult to apply to cell and gene therapy products and other products considered hazardous waste. In cases where physical inspection of materials is challenging or impossible, the RRD process will continue to move away from historic physical inspection to more modern electronic traceability procedures.