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Managing the Drug Supply Chain with eProcesses

Electronic solutions can enhance the efficiency of tracking drugs throughout a clinical trial.

For all clinical trials, it is necessary to perform drug accountability, reconciliation, returns, and destruction (ARRD) activities as part of managing the complete drug supply chain. The strict regulatory stance on this area places the onus on biopharmaceutical companies to ensure this process is followed diligently. However, the reality of conducting and fulfilling this requirement can often prove extremely difficult and time consuming for study personnel.

The challenge of ARRD in a clinical trial is that full documentation of the chain of custody for study material from bulk manufacture to eventual collection and destruction must be available, and the

sponsor is held responsible for providing the full evidence of this including any changes to the relevant documentation. However, audit findings (both internal and regulatory) indicate that current ARRD processes do not always provide this level of information in a clear and concise way at study, site, and/or country level.

Drug accountability and reconciliation are painful activities for site and monitor personnel. The current largely paper-based practices mean dealing with disparate and duplicate data sources, making it a highly labor-intensive and time-consuming process. This also makes it difficult to demonstrate the complete chain of custody information for medication units. This article will address the regulatory requirements for a sponsor to produce documentation of its drug accountability, the problems of current processes, and the way forward for the industry.

Drug accountability processes

When studying the problems associated with ARRD, the overall process flow that biopharma-

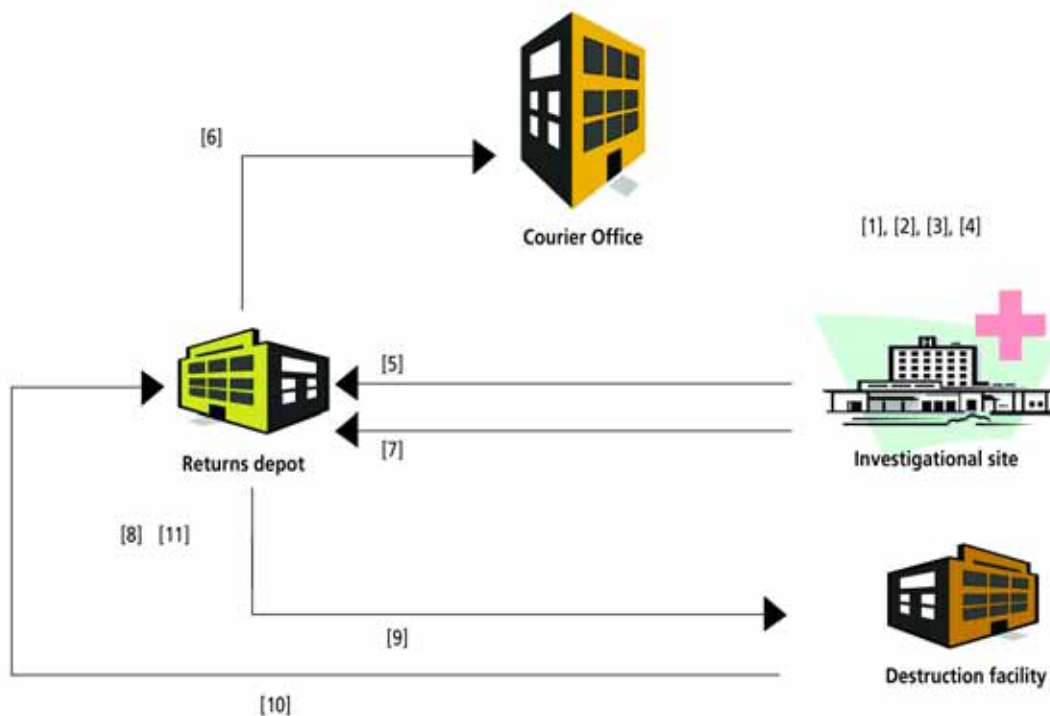
ceutical companies are required to follow must be considered. In order to understand the process itself, it is essential to recognize all four components of accountability, reconciliation, returns, and destruction. Although there remains some degree of variability between sponsors, study protocols, and country practices, the high-level description of the typical process is the same.

The fundamental goal of drug accountability is to know at all times the exact status and location of all medications throughout the entire supply chain. The ARRD process should effectively begin with the manufacture of the study drug. This process then follows the drug's entire lifecycle through packaging, shipment, dispensation, return, reconciliation, and, ultimately, destruction. Existing processes at manufacturing sites mean that this element of ARRD is

highly visible, as this is within the sponsor's direct control. However, once the drugs are shipped, the process becomes much more difficult to manage as information starts to appear in a number of formats from different sources, as detailed in Figure 1.

In general, investigative sites are required to maintain an inventory of supplies received and returned—a “master supplies log” and a “subject dispensation log” to record individual medication given to and returned by each patient (see Figure 2). These two documents are typically the key informational repositories of site-based drug accountability, although additional sponsor and/or site specific documentation may also be used. Subject returns may be captured simply as the return of the pack dispensed, or more frequently, by capturing the quantity of medication returned.

The Many Steps of Managing Drug Status Throughout the Supply Chain



- [1] Log medication received at site
- [2] Investigator/Pharmacist log dispensation
- [3] Capture subject returns
- [4] CRA: consolidate returns/unused medication

- [5] Notify depot of returns to be collected
- [6] Contact courier to arrange collection
- [7] Collect returns and ship to depot
- [8] Log arrival of shipment at depot.

- Verify content of shipment. Consolidate into shipment for destruction
- [9] Ship to destruction facility
- [10] Return destruction certificate
- [11] Log destruction certificate against medication packs

Figure 1. Keeping track of a drug's status from packaging to destruction is the essence of drug accountability.

Sponsors need to take both European and U.S. regulations (GCP/GMP) into consideration at the inception of every clinical research study.

The next step of drug reconciliation is typically performed by a monitor who verifies and reconciles all of the received, utilized, and recovered medication for each site according to the sponsor's written procedures. This entails checking the site documentation and physically verifying quantities and status of all relevant materials. Additionally, monitors will often coordinate the return of drugs from the site to an appropriate destination, which in most cases is a local depot. This may include other supplies that are no longer useable or necessary, such as damaged or expired medication.

Next, return shipments are sent to a designated depot accompanied by a document detailing quantities, individual contents, and format of medication. A unique identifier is assigned to each shipment, and very often this is the only tracking device to link the shipment received at the depot

with the individual medication packs sent from the site.

Upon receipt of a returns consignment, the depot must clearly identify the supplies, store them in an appropriately controlled area, and maintain inventory records. In approximately 20% of cases, the depot is required by sponsors to undertake a further reconciliation activity verifying received contents matched against those shown in the shipment documentation.

Finally, the returned materials must be destroyed. Returned supplies are generally stored at the depot until enough have accumulated to warrant sending a large shipment to the final destruction facility. At destruction, a certificate must be issued, and the study sponsor must link the information back to the individual medication units to prove both the identities and quantities of destroyed material.

Throughout the entire process, if any discrepancies are identified they must be investigated, explained, and resolved.

Drug accountability regulations

Good manufacturing/clinical and distribution practices mandate that ARRD procedures must be implemented in all investigational clinical trials. There are both European¹ and U.S.^{2,4} regulations that sponsors need to take into consider-

Medication Dispensation/Return Logs Ensure Drug Accountability at Investigative Sites

Site No. 014	Subject No. 00019	Subject Initials BNH	PROTOCOL NUMBER: [REDACTED]	
			VISIT 3	
Medication Bottle No.	Date Tablets dispensed (dd/mmm/yyyy)	Date Tablets returned (dd/mmm/yyyy)	No. of Tablets Returned	If discrepancy between number of tablets returned and expected returned number indicate reason for discrepancy
00613	10 MAY 2005	15 JUN 2005	08	Patient forgot to take medication on a number of occasions
Investigator's Signature [REDACTED]			Date 09 JUN 2005	

Figure 2. Investigative sites must maintain a master supplies log and a subject dispensation log to record individual medication given to and returned by each patient.

ation at the inception of every study.

According to the European Commission's Good Manufacturing practices guide Annex 13¹: "The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for."

FDA regulations²⁻⁴ also state that the investigator is responsible for the proper and secure physical storage and recordkeeping of investigational agents. More specifically, the regulations state that the investigator must:

- Maintain a careful record of the receipt, use, and final disposition of all investigational agents received using the Drug Accountability Record Form
- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent
- Return any unused investigational agents at the completion of the study or upon notification that an agent is being withdrawn.

The intent of these drug accountability procedures is to assist the investigator in making certain that drugs are used only for patients enrolled in an approved protocol.

Regulatory bodies conduct audits for various reasons but always ultimately to ensure the safety of research participants and to guarantee the accuracy and integrity of the clinical data collected. Clinical Investigators are well aware of the possible consequences of a negative regulatory inspection. At worst, this might result in disqualification from research and possible jail sentencing. More likely, disciplinary actions range from a figurative slap on the wrist to restrictions that limit participation in future projects.⁵ The FDA Web site lists many warning letters specifically mentioning drug accountability violations.⁶ These letters include warnings on aspects such as incomplete or inaccurate dispensing records, failure to maintain adequate drug inventory, and the unavailability of drug distribution records. Many of these issues could have been prevented by proper drug accountability procedures and regular checks during monitoring visits.

Electronic ARR: Complete Control of the Supply Chain

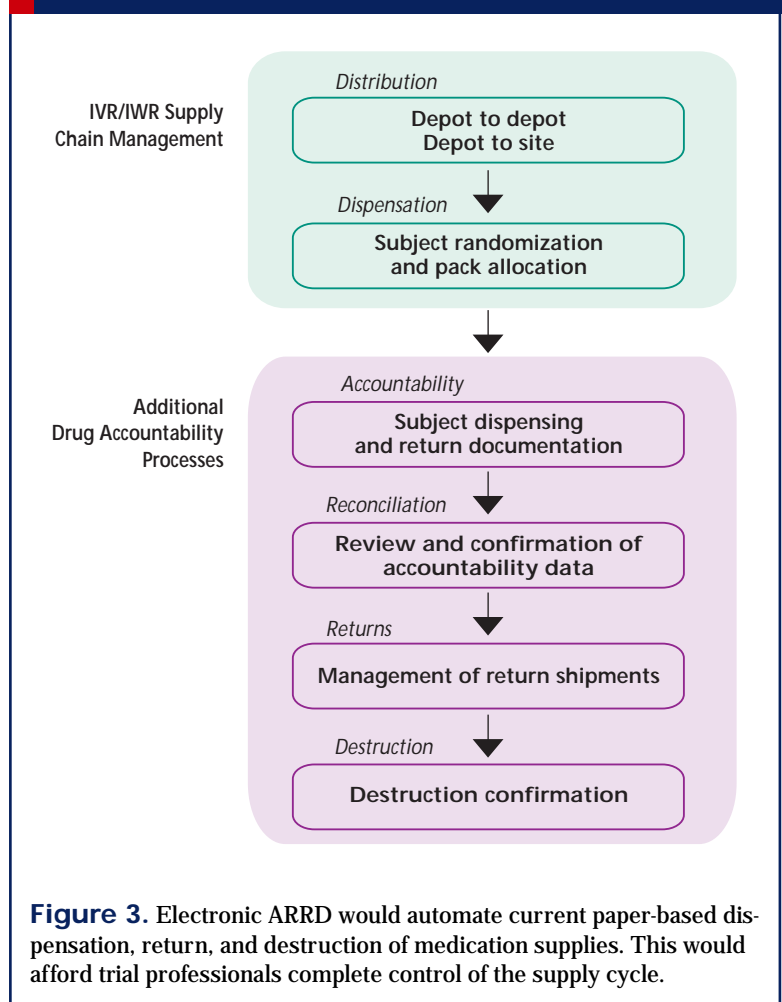


Figure 3. Electronic ARR would automate current paper-based dispensation, return, and destruction of medication supplies. This would afford trial professionals complete control of the supply cycle.

Problems with traditional methods

While many clinical processes are progressing into the electronic age in an effort to make them faster, more efficient, and more accurate, the ARR process has lagged behind. Most clinical sponsors address the ARR regulations by relying heavily on inefficient manual paper-based systems with information coming from a number of sources in a variety of formats including, for example, electronic shipment files, emails, paper forms, and handwritten notes. This paper-based process makes it difficult to access information detailing the complete chain of custody for individual units of medication through a trial's lifecycle. Aggregate-level transparency frequently—particularly study or batch-level—is very poor, making it extremely difficult to obtain a holistic snapshot of the overall supply status. Mistakes are common due to multiple locations and formats of the same data, leaving studies vulnerable to audit findings.

Accountability and reconciliation are viewed as the most difficult aspects of the ARR process to maintain, and this



An electronic ARRД system could create a complete and compliant audit trail that can be maintained throughout the return cycle.

could be facilitated by an electronic solution to track and reconcile materials throughout their entire lifecycle. For example, Michael Grabo, PhD, F. Hoffman-La Roche Ltd., Pharmaceutical Division, Pharmaceutical Development Operations, states:

“Drug accountability and reconciliation are painful activities where the site and monitoring personnel really bear the brunt of the manual process. The largely paper-based documentation which is often disparate and duplicate means people spend many frustrating hours accounting for and reconciling investigational drugs throughout the duration of the trial. As we are continuously trying to find ways to work smarter and more efficiently, this is clearly an area that will benefit enormously from an electronic solution.”

Electronic solutions to ARRД

Certain electronic solutions can assist with aspects of the ARRД process. For example, interactive voice and Web response (IVR/IWR) systems are already used to control the distribution of drug from depot to site and allocation to a subject.⁷ Some clinical trial management systems (CTMS) and drug supply management systems (DSMS) provide the ability to track certain elements of drug accountability. However, key

Key ARRД Benefits

An electronic ARRД solution promises to offer a number of key benefits:

- Full visibility of the chain of custody for the investigational medicinal product
- Centralized management of the ARRД process
- Reduced or eliminated dependence upon a paper trail
- Enhanced demonstration of regulatory compliance and reduced audit findings
- Rapid end-of-study completion of ARRД documentation and reporting.

stakeholders, such as site and depot personnel, rarely enter information directly into CTMS or DSMS databases—so these systems serve as a second record of data currently recorded elsewhere and do not make drug accountability quicker or more reliable.

IVR/IWR medication management solutions provide full control of one direction of the clinical supply chain—from central storage depot to subject allocation.⁷ An electronic ARRД solution would, therefore, be a logical extension—taking into account the remaining steps of recording the physical dispensation to subjects, receipt of their returned supplies, return of used/unusable medication held at site to appropriate depots, and the ultimate destruction of supplies (Figure 3). Because current users of IVR/IWR solutions include study site personnel, site pharmacists, monitors, and depot personnel, extension of these solutions provides a real opportunity to eliminate or limit the paper-based activities and centrally provide complete visibility of the entire ARRД process. This would provide sponsors with total custodial control and traceability of the entire supply chain from manufacturing to destruction.

The desirable properties of an electronic solution for ARRД are detailed below.

Real-time data visibility, reporting, and error-checking. An electronic system should allow sponsor personnel to have instant access to supply information and be capable of reporting summary-level, aggregate information based on a wide range of variables as well as granular, custodial tracking of individual medication units from creation to destruction. An ARRД solution must also incorporate edit checks to limit any unnecessary errors and provide functionality to flag and manage the resolution of reconciliation discrepancies. Enabling the user to provide reasons for discrepancies found would be an essential property.

Quick and simple use. A solution should complement the working practices and processes followed by the end-users. Solutions should provide an easy-to-use environment with no limitations. A Web-based application is likely to enable most of the functionality requirements, but should be designed with end-user performance and convenience in mind.

Remote monitoring features. Monitors should be able to perform their activities at sites with and without direct connection to the application. At some sites, obtaining access to the Web may be problematic; so the application must be able to enable CRAs to undergo their activities while limiting the requirement to rekey data when in the office. Many modern CTMS solutions include offline working for monitors, and this type of functionality would be attractive for an ARRД solution.

Integration with other eClinical solutions. Integration with other eClinical solutions is important to prevent duplication of data and activities. Integrations that might prove valuable for an ARRД solution would include those with IVR/IWR systems, CTMS, and DSMS applications.

Full audit trail and rights management. An electronic ARRД

system could create a complete and compliant audit trail that can be maintained throughout the return cycle. Like an EDC solution, it will be vital to accurately authenticate each user and to record the user, time, and date against all entries made. The ability to change data should require documented reason for change, with previous records retained within the audit trail. Access rights will be important to ensure specific user-types retain responsibility for key activities.

Conclusion

Using an electronic ARRD solution to reconcile and track the destruction of unused clinical materials provides numerous benefits including full visibility of chain of custody for investigational and medicinal products, centralized management of processes, and reduction in paperwork and errors. In combination with IVR/IWR this allows sponsors to implement an integrated IT approach from the decision to begin a study through enrollment and randomization of the first patient, right through to the destruction of the last drug unit.

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