A Guide to Working with the Investigational Drug Service

for: Coordinators, Investigators, Data Managers and Business Administrators

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Investigational Drug Service- University of Pennsylvania School of Medicine – Philadelphia, PA

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Introduction

The Investigational Drug Service (IDS) is a RESEARCH PHARMACY. We ONLY work with studies – clinical or non-clinical, medications or devices. We can NOT fill prescriptions for non-study patients and we do NOT carry a full inventory of medications like a traditional pharmacy.

The IDS was established in 1991. In 2001 we asked the School of Medicine for help to maintain our operations. This led to IDS leaving the Health System to become a service center and biomedical core facility. Our 'academic home' is within the Institute for Translational Medicine and Therapeutics. However, **we are self-sustaining through user fees** – we do not receive financial support from either the Health System or the University at this time.

We do not serve patients who are not participating in a study (we can't charge insurance and don't stock many medications), we still operate like a traditional pharmacy in other ways. We are bound by the same state and federal regulations as other pharmacies. That means that we need an actual PRESCRIPTION to dispense a medication. Whether a medication is or isn't already on the market, is irrelevant.

Submitting a New Trial to IDS

Generally the IDS should receive a copy of the protocol BEFORE grant (or contract) submission to sponsor and BEFORE IRB submission. ***Why?***

- IDS is supported by user fees and must abide by federal guidelines and school policies. We can't waive or reduce fees, as the fees we pass on reflect our 'actual cost' of providing the service.
- For more complex trials, or trials which involve manufacturing, packaging or procurement, the IDS needs to consider feasibility and logistical issues and might need to suggest changes.

On our website www.itmat.upenn.edu/ctsa/ids, go to the 'forms' tab and you'll see a 'Protocol Cover Sheet' to use with complete protocols, or a 'Preliminary Cost Estimate' sheet to use when your protocol is still being written.

Pre-Study

Schedule an appointment with IDS if the sponsor wants to see IDS (see Study Sponsors/Monitors below). Even pre-study visits need to be scheduled, so that we can be sure someone is available to meet with your visitors.

IRB Approval and Study Initiation

Once your study is approved to start, contact the IDS to get things started.

1. **When scheduling your SIV, make sure IDS is included** (at least a short visit to cover the medication piece). Someone will begin working on a dispensing procedure before the SIV and this is our opportunity to bring up our questions while the sponsor is here.
2. During the SIV, we'll ask if the sponsor requires separate "hand written" inventory logs. While many sponsors have shifted study coordinator documentation to the computer, some sponsors still use paper. The IDS uses a

state-of-the-art electronic inventory system – and many of our trials do NOT use paper logs. **Be aware that separate "paper" logs may incur additional monthly costs.** There is more information about that below.

3. Ask your business administrator to complete and return the cost estimate worksheet that IDS prepared beforehand. This should be received by the time the study starts.

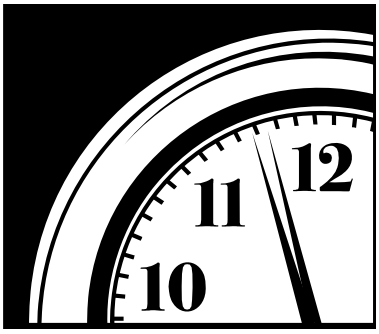
Drug and Supply Purchases:

IDS keeps some general supplies, however most medications and any study-specific supplies are actually **purchased FOR a specific trial and charged back to that study account** when we make the purchase.

We rarely purchase 'everything' at once –most things expire and may be difficult to return (and even harder to get any 'credit' back). If we can purchase in small quantities we will – and then we'll just buy more along the way as the supply is used. We can buy most things that a sponsor may want, but sometimes we can only buy a 'case' or 'box' (not 1 or 2 pieces). We shop around for the lowest price when possible, but we have no control over the price that vendors are charging for something at the time we buy it. If we enter a price in our cost estimate worksheet, it's guidance for putting together your budget – it's never a 'quote' or 'firm price' for something we haven't bought yet.

While the Study is Active and Recruiting

- **<u>Prescriptions need to be sent to IDS in advance</u>** – not when the patient arrives. For things like baseline or randomization visits, or when the sponsor does not allow an IVRS call prior to the visit, you should either send the prescription in advance (IDS will still wait for the IVRS or a phone call before preparing the dose) or if not possible, send an email (PennIDS@) or fax to IDS in advance so that we know there's a patient scheduled.
- If you have an **upcoming monitor visit**, time in IDS needs to be scheduled in advance (see below).



What about Trials that Require 24/7 Access?

Whenever possible, we prefer to manage all of the preparation and dispensing entirely through IDS. This way we can ensure things are done accurately and documented completely. If the study has a long 'window' for enrollment, or if there is a large enough study population to permit enrollment just on weekdays, that is always preferable.

When this isn't possible, the IDS may involve the inpatient pharmacy at HUP, which is open 24/7. There are additional costs with this, sometimes significant, as well as additional time to plan and set up. Because there is such a large number of people in the HUP pharmacy – and guaranteed most of them will not be familiar with the study when your patient enrolls – we keep things as simple and straightforward as possible – this may involve preparing 'starter kits', pre-packaging doses or pre-printing labels, etc. The IDS maintains all the records and replenishes supplies the next weekday when something has been used.

When the Last Patient is Off Treatment

- **Inform IDS right away**. For some studies we may be ordering supplies, buying drug or manufacturing or packaging based on expiration or previous use. We won't know not to do that, unless you tell us enrollment is complete.
- **The study closeout visit needs to be scheduled** just like with a regular monitoring visit.
- We'll ask the monitor if IDS files must stay on-site (eg. if a 'final' closeout visit hasn't taken place yet). If they're <u>not</u> needed, we'll ship the records to archives in 2-3 months.
- For investigator-initiated trials, a separate closeout might not be needed – we just need to determine the fate of remaining drug/supplies, as well as (for blinded trials) who should receive the list of treatment assignments.

Study Sponsors/Monitors

The IDS sees study monitors frequently – often 3 to 5 visits in a single day! The information below is intended to help these visits run smoothly.

Scheduling Visits

ALL visits must be scheduled in advance. The IDS maintains a master visit calendar. **Either YOU or your MONITOR can request a visit directly using our scheduling app** (see link below). Your request will go in as a 'tentative' appointment until IDS 'accepts' it. You'll receive an e-mail link back, to use if you need to change or cancel the appointment later.

https://www.med.upenn.edu/apps/ids/scheduler

ALL IDS staff participate in all trials, we do not assign a 'specific' person to one trial. Some monitors may be used to dealing with one person when they visit small pharmacies (or sites without a pharmacy). We discourage that here as it keeps the rest of our staff out of the loop. We use a team approach for all trials. One person may attend the SIV and prepare written instructions for the rest of the staff, but once that's done, everyone is involved.

The IDS handles several sponsor visits every day and the master calendar is used both to ensure that each visitor has a dedicated time (and use of the auditor room) and to give our staff time to pull records in advance so that the visitor can begin working right away.

The IDS has a dedicated 'audit room' which can accommodate one visit (2 monitors) at a time. This room includes:

- Photocopier
- Telephone (local numbers only)
- Wireless (guest) internet
- Shipping supplies – tape, boxes, pouches, etc

For larger groups or SIV's, a small conference room is available.

If your monitor is running late (or early), call IDS before coming down. If another monitor is here at that time, we might need to look for another open time later in the day.

Shipping Information to Provide to Sponsor

Make sure that shipments go to the following address:

University of Pennsylvania
Investigational Drug Service
3600 Spruce St
Ground Floor – Maloney Building
Philadelphia, PA 19104
215-349-8817

The only exception to this is controlled substances when the sponsor must use the exact address on the DEA registration. The IDS currently shares HUP's DEA pharmacy registration, which carries the main address for HUP. When possible, in these situations (a) the IDS should be alerted in advance when a shipment is coming and (b) "c/o Investigational Drug Service" or an IDS staff member's name should be on the shipping label – this way either the UPS or FedEx driver may be able to intercept it and bring it directly to IDS, or if not, someone in the HUP pharmacy will see that the package is meant for IDS and can hold it for us to pick up that day.

Inventory Records

IDS uses an electronic inventory system for all medications and supplies. This system is in compliance with 21CFR11 and is integrated with other functions, such as labeling, billing, patient profiles, etc. The system eliminates math errors, maintains a complete audit trail of changes and is easily accessible for years after 'paper' records have been archived.

Many of our trials do NOT use separate hand-written (paper) logs, however some study sponsors (or monitors) have not yet moved away from these. At the SIV, we inquire about the need for paper logs – and many sponsors are fine not using them. However, we have had situations where the sponsor authorizes electronic logs and then the study monitor at a later visit requests otherwise. For this reason, we present the sponsor with a simple form to document either the decision to accept electronic logs, or confirmation that the sponsor is aware that paper logs incur additional costs.

For sponsors that insist on hand-written logs, there are additional monthly costs (average $5 to $10 per months. This covers the additional cost of recording every transaction in multiple locations, verifying that entries in both records match, as well as performing monthly inventory audits against two separate sets of records.

IVRS/IWRS

If the sponsor uses IVRS or IWRS to register drug shipments or assign treatments to subjects, make sure that **2 OR MORE user accounts** have been requested for IDS. IF the sponsor permits sharing of an account across IDS staff, then one account is acceptable. However, most sponsors prefer 'one user per account' – so IDS must have AT LEAST TWO separate user accounts.

Temperature Monitoring

IDS uses an electronic wireless sensor grid to monitor temperature in each refrigerator, freezer and in several room-temperature locations. The system is accurate to 2 decimal places, collects readings every few minutes throughout the day (24/7/365) and delivers rapid alerts by telephone and e-mail. Each device carries a battery backup. Sensors are calibrated annually by an outside testing company (certificates are available in a binder for monitors to view if necessary). Per department policy, IDS does NOT maintain separate sponsor-specific temperature logs. Special requests by sponsors are passed on to the study account at an hourly labor rate.

Temperature reports are generated 'on demand' and the monitor can keep the copy. The report is in graph form, with the actual high, low, mean, median and standard deviation for that period. While a report of each individual reading is feasible, it's not practical as it can take hundreds of pages to print (there are hundreds of readings each day) so we strongly discourage that. The graph report should contain all the information the monitor needs.

Drug Returns

Medications returned by study participants, need to go back to IDS promptly to be logged in and then stored securely in quarantine. The IDS logs returns under the patient's electronic profile. If the sponsor mandates separate hand-written logs, the IDS may need to transcribe the return information onto those logs as well.

IDS staff can't process returns "stat" – typically they are processed throughout the week as time allows, then the returns are stored in quarantine to await further instruction from the monitor or sponsor. For investigator-initiated trials, the IDS will not routinely save all returns except on request, however they do all need to be logged

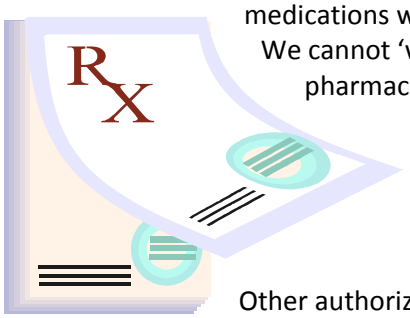
in prior to incineration. IDS does NOT routinely accept back cytotoxic agents or used infusion bags - if the sponsor requests these, special precautions need to be followed, sometimes at additional expense.

IMPORTANT: Patient returns cannot be processed on the day of a monitoring visit. Returns brought to IDS "with a study monitor" or on the day of a monitoring visit, will be processed after the visit. If your monitor needs to see these at his/her visit, make sure they are returned to IDS at least 2-3 days prior.

Once returns have been "monitored" we can either store them, return them or destroy them. We have regular pickups from both UPS and FedEx and the monitor should leave a copy of the return paperwork in IDS. For destruction, IDS contracts with an incinerator company.

Prescribing

The IDS is just like any other pharmacy, for the population we serve – clinical trial participants – and the medications we work with. However, we're still bound by the SAME rules and regulations. We cannot 'waive' these rules because they are inconvenient, any more than your CVS pharmacist can give you a pain medication 'just for stopping by'.



Per State of Pennsylvania Code (049 Pa Code § 27.1) a licensed prescriber is:
"A physician, dentist, veterinarian or other individual authorized and licensed by law to prescribe drugs"

Other authorized individuals can include a CRNP (nurse practitioner) or PA (physician assistant) when practicing under a collaborative practice agreement with a physician. There are NO provisions currently in state regulations, for other healthcare providers – including RNs, LPNs, RDs, RTs or un-licensed personnel – to sign a legal prescription.

Outpatient Trials

The IDS is in the EPIC database as a retail pharmacy option ("INVESTIGATIONAL DRUG SERVICE PHARMACY")

For commercially-available medications used in research (eg. provided free or paid for by the sponsor/grant), they can be ordered just like any other order, just make sure that you **indicate the STUDY** (and the subject's study ID# if applicable) in the comments, then transmit the order by **eFAX** (not ePrescribe).

For more complex orders, medications with a placebo control or which are not commercially available, we can work with an EPIC programmer to set up a study-specific order template.

When a subject is going to receive the same medication for a period of time, a PROPERLY WRITTEN prescription with enough refills on it, may cover the duration of the study course (maximum one year). That initial prescription can be written for enough medication to cover the course, or can have multiple REFILLS. Once the signed prescription is in place, other study personnel can then REQUEST REFILLS when a patient is returning to clinic. In this case that you're requesting refills, not sending a new prescription. A NEW PRESCRIPTION is needed if a NEW medication is added, a NEW dose is ordered or if the original prescription is expired (sooner of 12 months or when the refills are used up).

Don't forget to send prescriptions in advance – the day before for most studies, though some medications that are more complicated to prepare may require more than a day's notice. The IDS can't accommodate 'walk up' orders like a regular retail pharmacy.

Outpatient Trials where EPIC BEACON is in Use

This version of EPIC is currently in use in the Perelman Center for Advanced Medicine ("PCAM"). In some ways this system works similar to the regular EPIC system. However, in the BEACON system, the prescription goes to an electronic "work queue". It does NOT transmit/fax to the IDS like a regular retail prescription.

When using BEACON, let IDS know your patient schedule in advance. We'll search for the patient in BEACON that morning to find and print the orders. For medications that are expensive or short stability, we'll still wait for a phone call before we prepare the dose, but we pull all the supplies as soon as we have the orders.

Outpatient Trials –Outside Clinics with no EPIC Access

In these situations, you can either use a traditional prescription (fax it to IDS or drop it off in advance), or we can help create a pre-printed order fax sheet (with medications and regimen already filled in). For studies with a predictable regimen, the prescription can often be written for enough medication to cover the course, or for enough refills to cover the course (maximum of 12 months per law); after that the coordinator can request refills by fax (preferable) or e-mail, as long as the requests are sent before the visit. For regimens involving just 1-2 visits, or where the dose/regimen/meds may change from visit to visit, it might be necessary to use a new prescription each time. These considerations can be discussed prior to study launch so that things run smoothly later-on.

Narcotics (Schedule II)

In all 50 states, prescriptions for Schedule II medications are limited to a 30 day supply AND require an ORIGINAL signature by a prescriber with a DEA prescriber registration. What IDS typically does in these situations, is this: We can prepare the prescription based on a fax, however the person who picks up the medication MUST bring the original prescription. The medication may not leave IDS without an original prescription. An EPIC prescription is acceptable, but it should be printed in the clinic and physically signed by the prescriber first.

Inpatient Trials

For hospital inpatients, medication orders must be entered in SCM (Sunrise Clinical Manager). However, these do not "automatically" come to the IDS. Therefore, IDS might create an 'enrollment notice' – which the coordinator can complete and fax to IDS, telling us who the patient is, where they are, when they're expected to start treatment and if necessary, the information IDS might need to be able to randomize or calculate the dose.

When orders are properly entered in this system, separate notices sent to IDS are not considered a 'prescription'. IDS staff will look up the actual written order in SCM and print a copy of it. That printed copy of the electronic order, is treated as a copy of the prescription.

Pickups and Deliveries

There are a few options for pickup or delivery of medications or supplies. While patients CAN come to the IDS to pick up their medications, this is not common. Most medications are delivered to clinic, or picked up at IDS.

When is My Prescription Ready? We use an electronic system to track pickups and deliveries. Every pickup is 'logged' with the person who picked it up, while every 'delivery' is logged with the time/date, location and which IDS staff member delivered it. Another feature of this system is a READY ALERT. it's an opt-in feature, if you want to receive alerts (email) of medication ready for pickup, let us know at our pickup window. Once we have a study set up in the database, we can add a contact to the system. Your Penn or UPHS directory email is the default contact, but we can add a different one on request. ***Once added you'll receive an alert when a prescription is 'ready'.***

Pickups: There is a pickup window at our main entrance (Maloney Building, Ground Floor – look for the door next to the passenger elevators and we're right down the hall). Make sure that you bring an ID with you – our electronic tracking system logs the person who picked up each prescription. The system is linked to the Penn Directory and the UPHS Directory, so the user name, phone and email are linked – this way if there's a problem or question later, we have a way to track down the person who left with those meds.

Deliveries (local): There is no charge for deliveries to HUP inpatient units or to the HUP CTRC, however we do have a nominal charge for deliveries beyond that, intended to cover the time we have staff out of the IDS.

Deliveries (off-campus): We use an express courier which can deliver throughout the metro area 'same day'. Most pickups are within 30-60 minutes (may be longer during peak times) and delivery time depends on distance. We receive an electronic confirmation of delivery. Cost varies by distance and time.

Shipping: We use UPS for shipments that do not need to reach their destination 'same day', including shipments directly to study participants.

For any delivery where a charge applies (including pass-through charges for UPS shipping), these are tallied on a monthly basis and come through on the next month's charges. The statement will indicate the number of deliveries, or the total amount we are passing on that we were charged by UPS.

Budgeting and Billing Process

The IDS is a service center for the School of Medicine. We operate under the guidelines of OMB-A21 (http://www.whitehouse.gov/omb/circulars/a021/a21_2004.html) and University policy 2115 (http://www.finance.upenn.edu/vpfinance/fpm/2100/2115.asp). We are supported through user fees and are required to adjust these fees periodically to ensure we operate right at 'break even'. We are also required to apply our fees equitably based on our actual costs (materials and labor).

In Planning

The IDS will prepare a cost estimate based on the information you provide. The more detailed the information, the more accurate the estimate. This is only an estimate, however. In situations where the protocol is not clear as to how easy or complicated something is to prepare, or where the sponsor may present with additional requirements later that weren't mentioned in the protocol, costs may vary from the original estimate. Drug and supply purchases are always variable, we have no control over what the manufacturer charges for these.

On our website **www.itmat.upenn.edu/ctsa/ids**, go to the 'forms' tab and you'll see a 'Protocol Cover Sheet' to use with complete protocols, or a 'Preliminary Cost Estimate' sheet to use when your protocol is still being written.

Study Start

The cost estimate worksheet should be returned to IDS (a copy/fax/scan is fine) by the time the study starts. Medications or supplies that will be purchased, are pass-through costs. However, we cannot purchase anything without a valid account number.

- For external customers (eg. without a University account), the account number field can be left blank, but the other fields should be completed to the extent possible.

University (Internal) Accounts

The IDS debits expenses monthly. Our batch file is created on the last day of the month and uploaded the first week of the next month. An itemized statement is then sent in PDF format to the business administrator and to the investigator.

External Accounts

- Affiliated institutions (CHOP, Wistar, UPHS) - an invoice will be sent out, either by mail or PDF, with instructions for payment. Checks should be returned to our business administrator and made out to "Trustees of the University of Pennsylvania".
- Outside institutions – invoicing works the same way, except that the IDS may be required to incorporate F&A ("overhead") into our fees. F&A is usually transferred to the University after funds clear.

Other Services We Provide

A primary function of the IDS to facilitate investigator-initiated research by providing services that would otherwise not be available to investigators, or would be available elsewhere only at a much higher cost.

Medication Compounding, Formulation

The IDS prepares blinded medications or customized products for hundreds of trials every year. We can prepare products for oral, topical, ophthalmic, rectal or other routes. Each product is different and some products are much easier to 'blind' than others. When a study may involve customized products or blinding, we encourage discussing the project with a pharmacist early in protocol development, to determine what is feasible and to estimate costs.

Capsules

We can prepare capsules in a wide range of sizes and colors. For blinding of commercial medications, capsules can mask the color or taste of a product – and in cases where a whole tablet or capsule can fit into a new capsule shell, the dose itself is intact and unaltered – ensuring the full dose is administered each time. Our equipment is cGMP grade, using 316 surgical stainless steel. All products are prepared in a positive-pressure room with trained personnel wearing protective garb.

Tablets

Tablets are difficult to copy, largely because unlike capsules, tablets are very customized – the manufacturer typically creates a 'die punch' specific to that product – with a custom shape and imprint (every prescription medication in the US has its own unique imprint for identification). Tablet colors and coatings also vary widely. IDS can work with outside companies that can manufacture placebo tablets – however these may be very expensive and minimum runs are high (often 250,000 tablets or more). For vitamins or herbal products, there may be more options since some of these use generic shapes with no markings. Sometimes IDS can locate a different product, such as a vitamin or herb which might not affect the outcome of the study, then use that as a placebo. Otherwise, the best source for a placebo 'tablet' is the manufacturer itself – and this is a process that the investigator needs to pursue, as the manufacturer may have its own 'review' process.

Repackaging

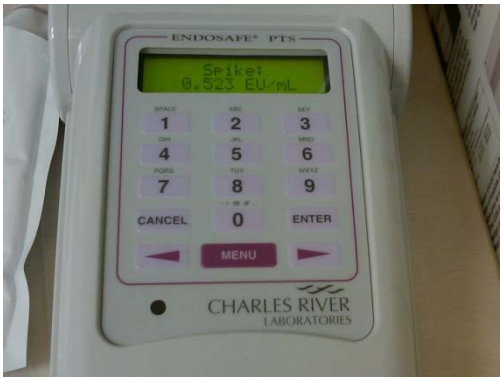
IDS can prepare medications in bottles with tamper-evident seals, as well as blister cards in various sizes. At this time we do not have equipment to prepare entirely custom blister cards, but we do often 'modify' the products that are available commercially – we can trim them, add custom labeling or sometimes have them custom printed (if the study requires at least 20,000). IDS can also put together treatment 'kits'.

Sterile Products

IDS maintains two aseptic glovebox isolators – one negative pressure (for toxic compounds) and one positive pressure. Both maintain an ISO-5 (Class-100) or better environment inside. For trials which require specialized preparations or creation of placebos or blinding for sterile products, we encourage discussing the trial needs with a pharmacist before finalizing the protocol.

Testing Services

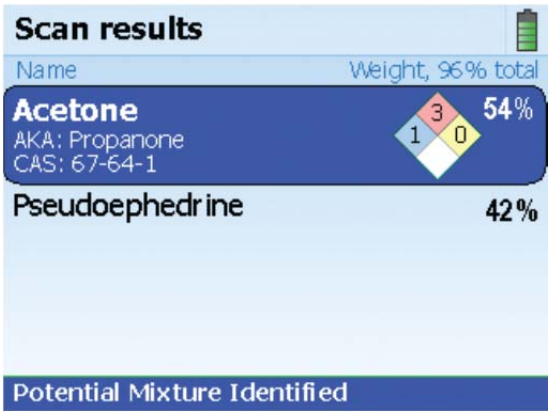
IDS can perform the following tests on products we prepare:



Endotoxin/Pyrogen: We use the Endosafe-PTS™ system, with disposable testing cartridges. The system is an FDA-licensed alternative test for compliance with USP<85> to test for the presence/absence (and quantity) of endotoxin in a sample. We run two actual samples plus two positive controls simultaneously.

Sterility: We have two methods of testing sterility. One method is 'Rapid Microbial'. While this is not the official method outlined in USP<71>, it is commonly used in the pharmaceutical industry. The test involves a laser light that scans a sample tagged with a special dye, then counts the actual number of items it finds. It's able to test for the presence of bacteria, yeast and fungi. The other method we use is a 14-day incubation in agar. This is the official method described in USP<71> when two separate growth media are used. IDS will use 2 separate media on request. The media are incubated and visually checked at several time points to determine whether there is any growth (indicated by cloudiness/opacity in the growth medium).

Particulates: The IDS can perform the test for particulates in solution as described in USP<788>. This test requires pooling of a sample (often from several vials) and inspecting visually against 2 different backgrounds and 2 different sources of light, under magnification, for the presence of particles that may not be visible under regular light.



Chemical Identity: The IDS has a raman spectrophotometer, which can be used to confirm the identity of raw materials that we use for compounding (by spectral signature) upon receipt. The equipment is also able to confirm or refute the identity of various medications and chemical compounds and to determine whether a dose contains active medication or placebo, though for combination products a method must first be developed for each. It can scan directly through some packages, avoiding direct contact with the medication.

Other Services

The IDS can assist with protocol language to describe services IDS is going to perform, writing up parts of the Chemistry, Manufacturing and Control (CMC) section of your IND submission, or training study personnel. However, these services are performed "as time allows" and time is billed at an hourly rate.

Study Closure and Records Archival

At the end of the trial, or once all medications/supplies have been shipped out or destroyed (if the sponsor indicates that a later closeout visit isn't needed), we will pack up the records and prepare them to ship to archives.

We use the **University Records Center** for archival. Their website is **http://www.archives.upenn.edu/urc/urc.html.** They have a 'main' storage facility at 4015 Walnut St and other storage facilities within a short drive. The records are secure and the box contents are tracked in our electronic inventory system – so that we can find the 'study' quickly and determine which box the records are in, as well as when they were archived.

Typically we maintain files here in IDS for an average of 3 months before archiving.

Why can't records just be handed over to the investigator and filed with everything else? We can either provide a copy of the records for archival with the study master files, OR if the sponsor requests the originals, we need to have a copy here that we archive ourselves. We need our own copy of everything available for retrieval – if the study is ever audited in the future, questions about inventory/accountability, preparation/dispensing, etc will involve the IDS. We can much better address these questions if we have access to the records ourselves.

Additionally – one benefit of our electronic inventory system, is that the dispensing records are retrievable 'same day' without having to pull the paper records. If the sponsor requests hand-written records, then those would have to be retrieved from archives first. Another reason to encourage that study sponsors migrate to electronic records!

Investigational Drug Service

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