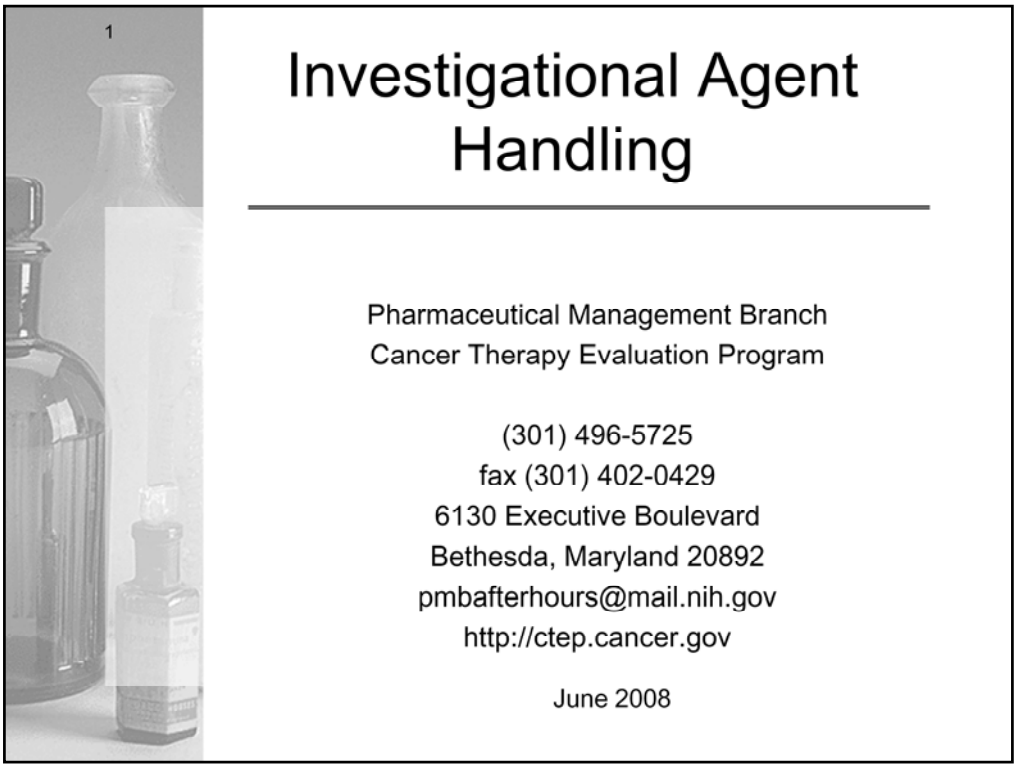
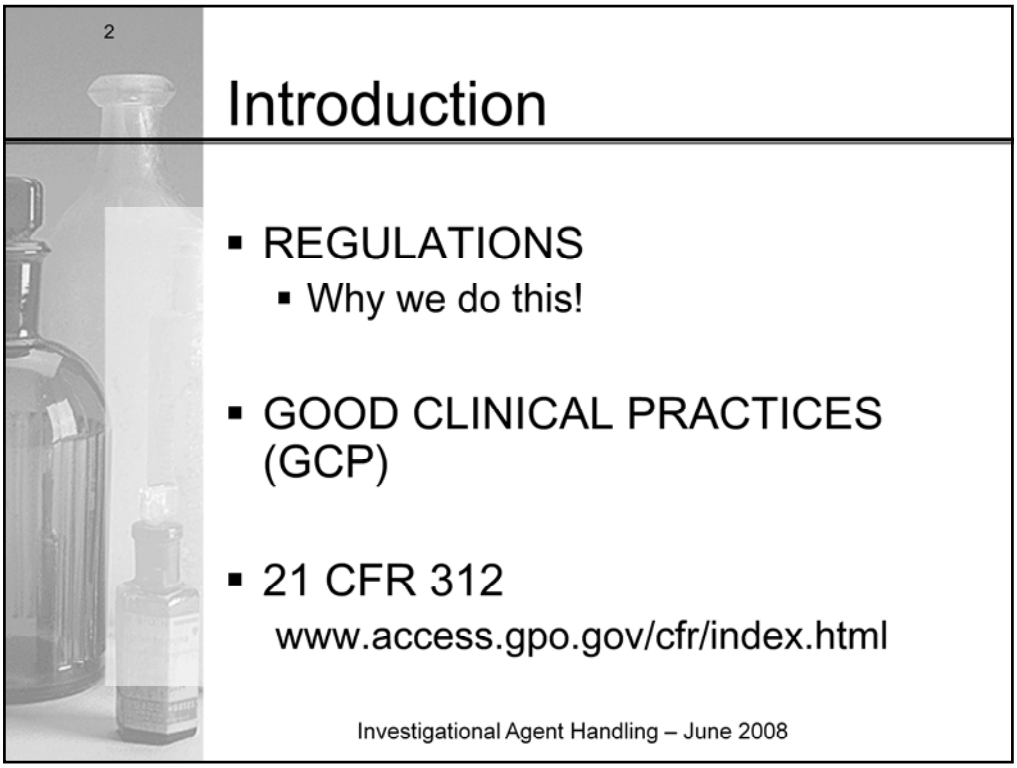


This is a presentation on Investigational Agent Handling provided by the Pharmaceutical Management Branch, hereafter called just “PMB.” The presentation includes an overview of procurement, storage, accountability, transportation, transfers, returns, QA/QC, and double-blind studies.

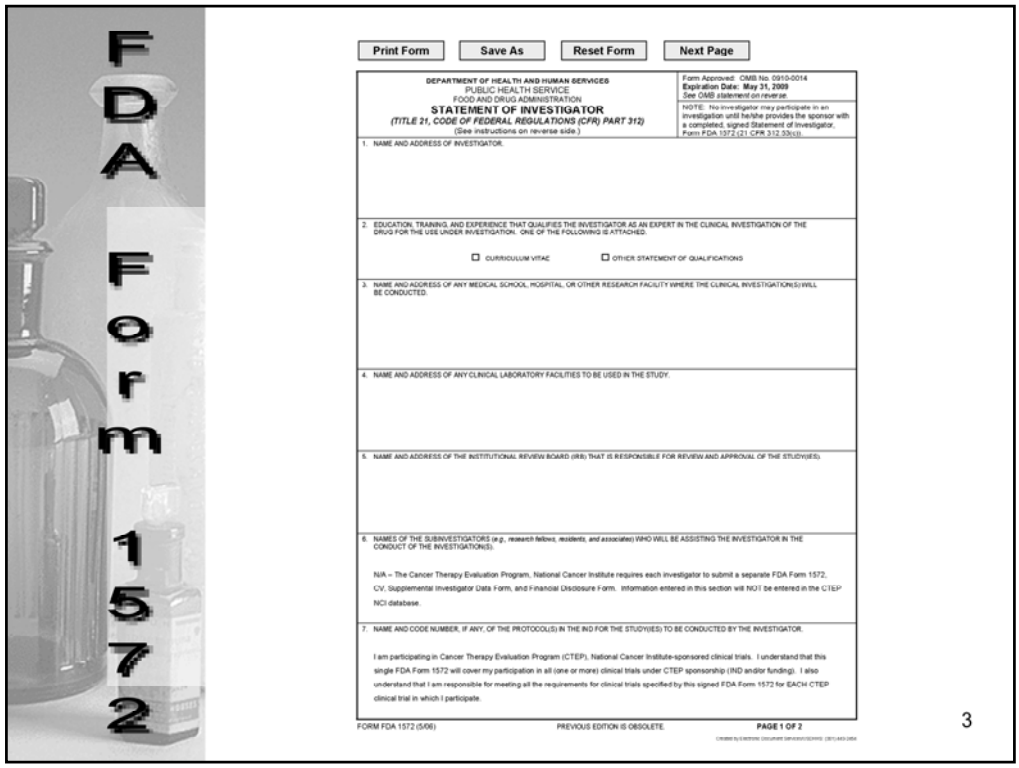
On the bottom of this slide you’ll see contact information for the Pharmaceutical Management Branch. Call this number, or better yet – send an E-mail! - if you have questions about anything in this presentation. You can use the PMBafterhours E-mail address at any time, not just when we are closed. The web site listed is for CTEP (Cancer Therapy Evaluation Program). This site includes information about conducting clinical trials and has a place to download forms. Please note that our web site is inaccessible if you use the habitual “www” before our address—just use ctep.cancer.gov!

Because we ship drugs, biologics, vaccines and heat shock proteins, we will refer to all of them collectively as “agents.”



The Food and Drug Administration's regulations require investigators to establish a record of the receipt, use, and disposition for investigational agents. The NCI, as a sponsor of clinical trials, must assure the FDA that investigators in its clinical trials program maintain investigational agent accountability systems.

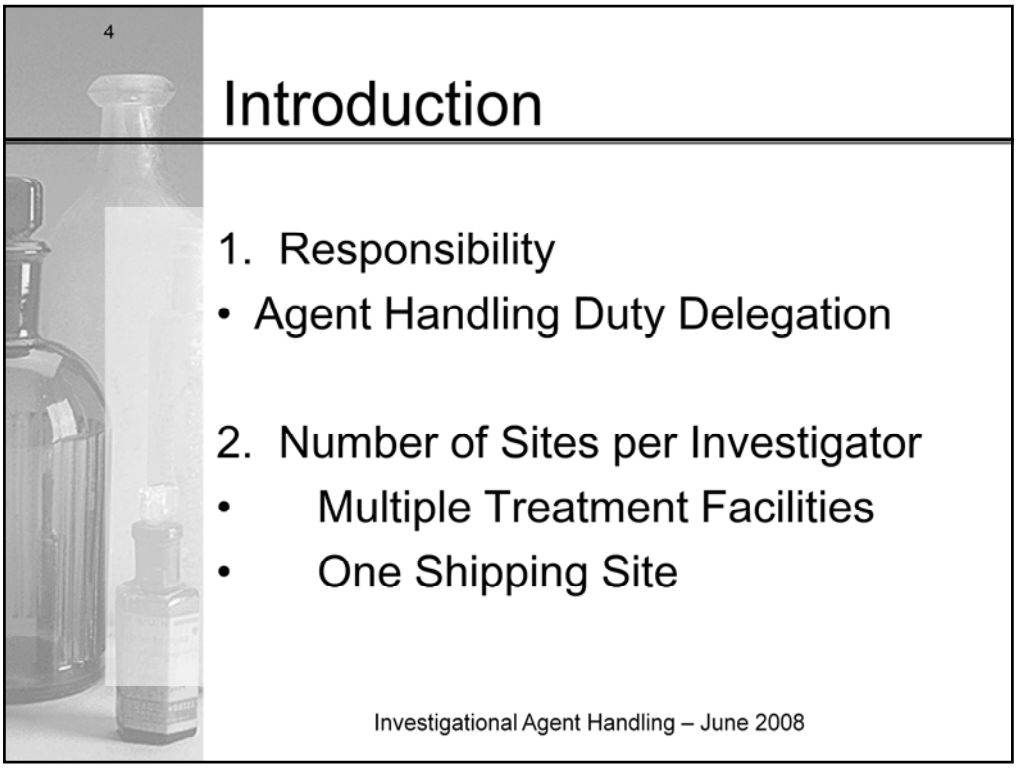
The Manual of Good Clinical Practice (GCP) and the Code of Federal Regulations (CFR) provide the rules, regulations, and guidelines that direct investigational agent handling. The GCP is available for sale from various commercial vendors. Find the CFR at the web site shown. The section for investigational agent accountability is title 21, part 312.



The investigator is directly responsible for investigational agents provided by NCI. This is the FDA Form 1572. Physicians who receive and administer NCI-supplied investigational agents must register with the NCI. To register, physicians must provide a completed FDA 1572 with original signature (meaning signed in ink), a supplemental Investigator Data Form, a Financial Disclosure Form (also with an original “wet” signature), and a current CV. The forms should be filled out precisely the way the instructions “suggest.” You can print these forms from the CTEP web site, or call PMB and ask us to fax them.

To change the address on the investigator’s registration materials permanently, investigators must submit a new 1572 to PMB. If the shipping address needs to be changed, the investigator may submit either a new supplemental data form, or make the request in writing using his or her letterhead.

Investigators must indicate ordering and shipping designees by name if they intend to use them. We’ll talk about this more later.



Again, when NCI provides investigational agents to a registered investigator, they become the direct responsibility of that investigator. Regulations allow investigators to delegate this authority to other health care providers. However, the physician/investigator is still ultimately responsible and should maintain internal controls to ensure guideline compliance.

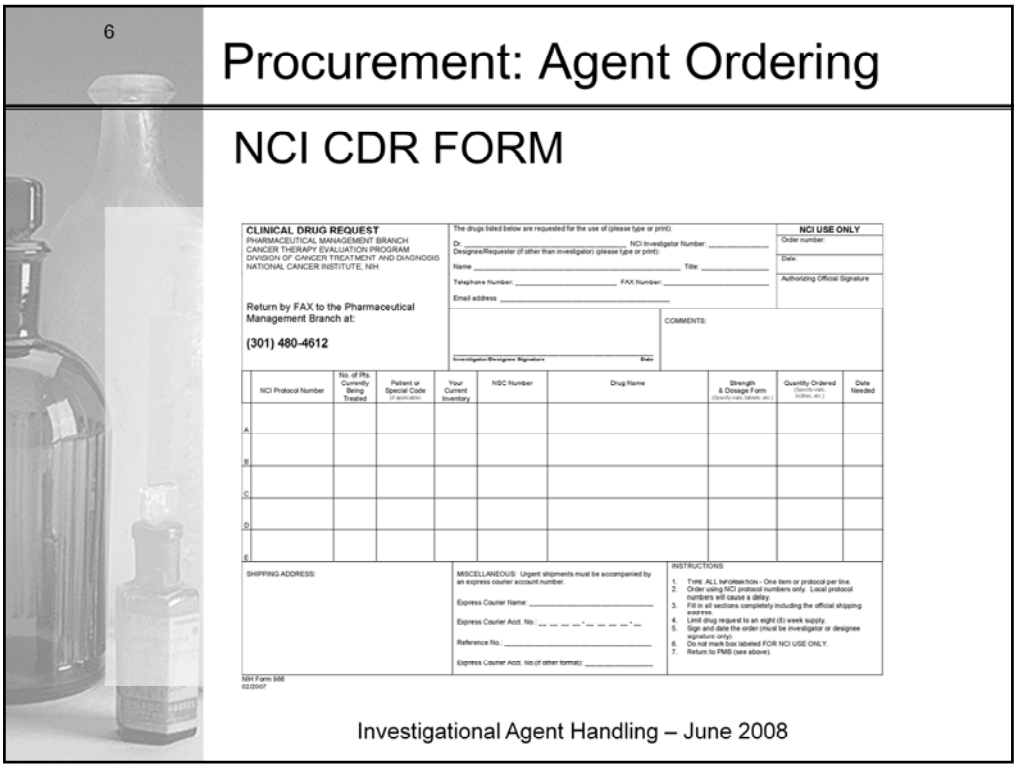
Some investigators treat patients with investigational agents at more than one institution. Although an investigator may treat at more than one institution, the investigator must designate a single location as custodian to receive and manage the investigational agents (that would be the **shipping address**!). This centralized location may provide coordinated pharmaceutical support to other local institutions and investigators.

You and your staff must establish and maintain a satellite record for each agent transported to each affiliate institution. Transport of NCI-supplied agents from your central location to your satellites should be done by your institution's staff or courier service. The ordering/shipping designee may order agents from PMB, but you must arrange for transport to affiliate locations.

1. You can order agent from the PMB at NCI by submitting the Clinical Drug Request form (CDR; NIH 986) by fax. PMB processes requests received at the NCI before 2 PM, Eastern time the same day.

2. When you receive an NCI-distributed agent, check these items: Is it the proper agent, dosage form and quantity delivered under the appropriate storage conditions without any damage – for the appropriate investigator and the correct protocol?

3. Once you receive the agent, establish agent accountability records immediately, and ensure that shipping receipts are appropriately stored for future reference.



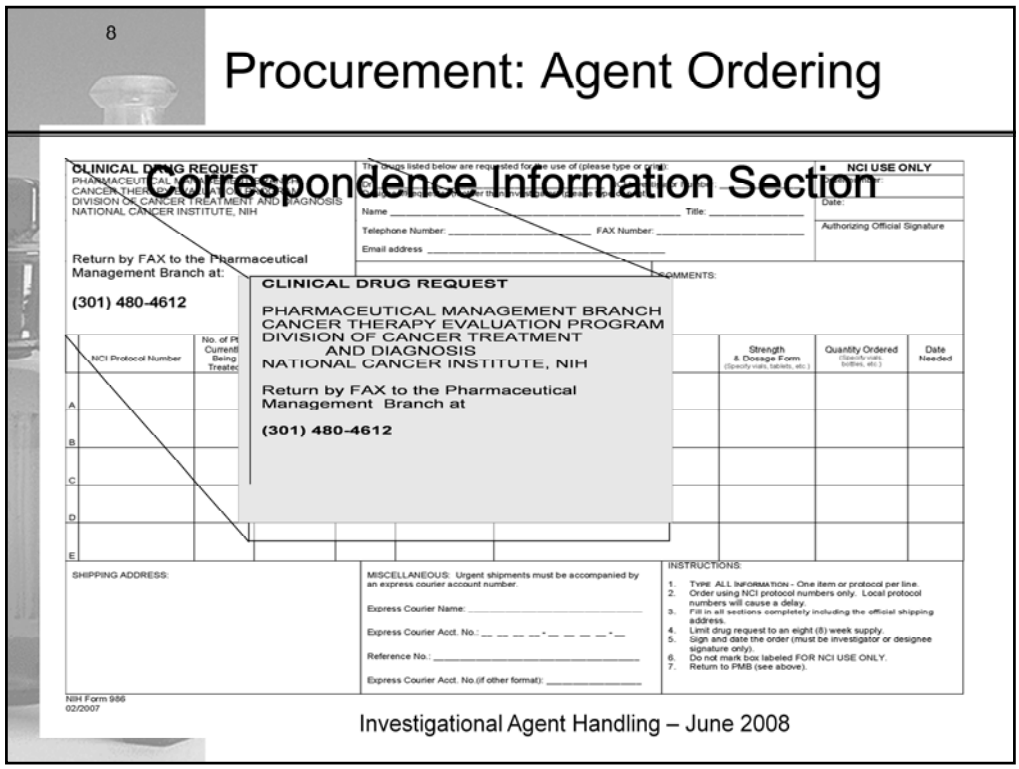
Use the NCI Clinical Drug Request form to order investigational agents distributed by the PMB. You can download this form from the CTEP website at http://ctep.cancer.gov or call us, and we can fax it to you.

Once your local IRB has approved a protocol, you may order investigational agent for that study. The protocol will contain useful information that you'll need for ordering agent. So, the person handling agent procurement must have access to the clinical protocol before ordering.

The following slides highlight each section of the Clinical Drug Request, and the information necessary to properly complete the form.

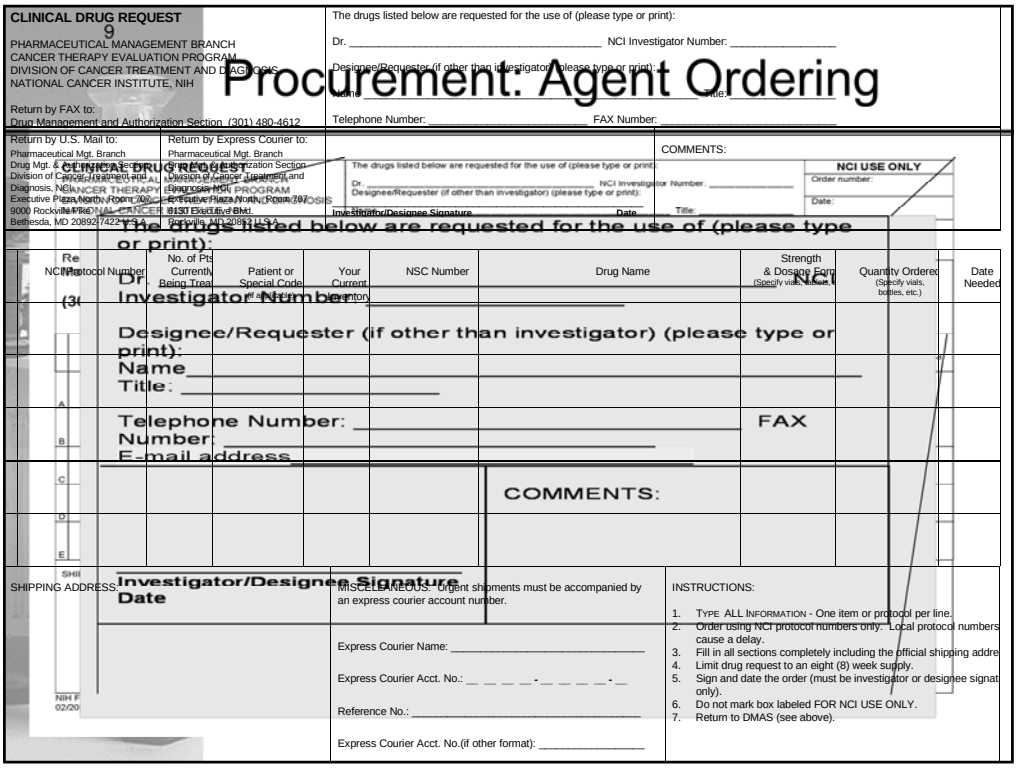
Once you complete the form in its entirety, submit it to the NCI by fax.

The form is divided into four major sections….Correspondence Information, Investigator Information, Drug Information, and the Shipping Address.



This section contains the PMB contact information. This includes the fax number.

Procurement: Agent Ordering



CLINICAL DRUG REQUEST

PHARMACEUTICAL MANAGEMENT BRANCH
CANCER THERAPY EVALUATION PROGRAM
DIVISION OF CANCER TREATMENT AND DIAGNOSIS
NATIONAL CANCER INSTITUTE, NIH

Return by FAX to:
Drug Management and Authorization Section (301) 480-4612

Return by U.S. Mail to:
Pharmaceutical Mgt. Branch
Drug Mgt. & Authorization Section
Division of Cancer Treatment and Diagnosis, NCI
Executive Plaza North, Room 7070
9000 Rockville Pike
Bethesda, MD 20892-7422 USA

Return by Express Courier to:
Pharmaceutical Mgt. Branch
Drug Mgt. & Authorization Section
Division of Cancer Treatment and Diagnosis, NCI
6130 Executive Blvd.
Rockville, MD 20852 USA

The drugs listed below are requested for the use of (please type or print):

Dr. _____ NCI Investigator Number: _____

Designee/Requester (if other than investigator) (please type or print):

Name _____ Title: _____

Telephone Number: _____ FAX Number: _____

Investigator/Designee Signature _____ Date _____

COMMENTS:

NCI USE ONLY
Order number:
Date:

NCI Protocol Number	No. of Pts Currently Being Treated	Patient or Special Code (if applicable)	Your Current Inventory	NSC Number	Drug Name	Strength & Dosage Form (Specify vials, tubes, etc.)	Quantity Ordered (Specify vials, bottles, etc.)	Date Needed
A								
B								
C								
D								
E								

SHIPPING ADDRESS:

MISCELLANEOUS: Urgent shipments must be accompanied by an express courier account number.

Express Courier Name: _____

Express Courier Acct. No.: __ __ __ __ - __ __ __ __ - __

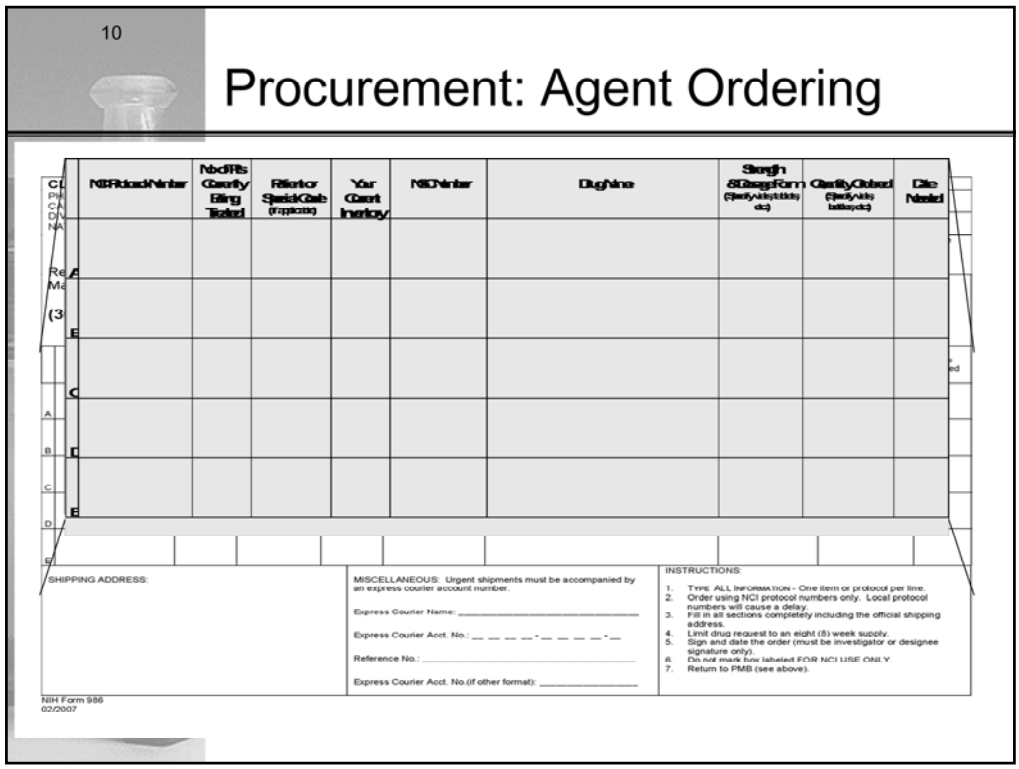
Reference No.: _____

Express Courier Acct. No.(if other format): _____

INSTRUCTIONS:

1. TYPE ALL INFORMATION - One item or protocol per line.
2. Order using NCI protocol numbers only. Local protocol numbers cause a delay.
3. Fill in all sections completely including the official shipping addre
4. Limit drug request to an eight (8) week supply.
5. Sign and date the order (must be investigator or designee signat only).
6. Do not mark box labeled FOR NCI USE ONLY.
7. Return to DMAS (see above).

Complete the investigator information section by following the prompts (the hints under each blank line) for each line of information requested. The physician's name and investigator number is on the first line. The investigator number is important; it ensures that PMB selects the correct physician responsible for the agent. The next two lines are used to insert the information about the person completing the form (designee). Designee information on this form is very important. Often, PMB can resolve problems with the order with a phone call or a fax to the designee. These days, it's also a good idea to include your e-mail address. The designee or responsible physician must sign the form before submission to PMB. The comment section can be used to relay information that we can use to fill your order.



The Pharmaceutical Information Section is where you add agent specific details, requesting up to five line items on each form. For each line item, complete all sections:

•NCI Protocol Number is a number assigned by the NCI, usually appearing on the protocol's cover page. Avoid using institutional or departmental numbers in this section.

•Number of Patients Currently Being Treated reflects the active patients at your institution for the specific protocol.

•Patient or Special Code (If applicable) usually applies to double blind studies, but may apply to any protocol if the investigational agent is distributed on a patient specific basis.

•Your Current Inventory is the amount of agent you have available at your main and satellite pharmacies for this specific protocol.

•NSC Number refers to the former cancer chemotherapy National Service Center. A unique number is assigned to every chemical entity. Find the NSC on the protocol's title page and in the pharmaceutical section.

•Agent Name – You can use the agent's trivial, generic, or brand name here.

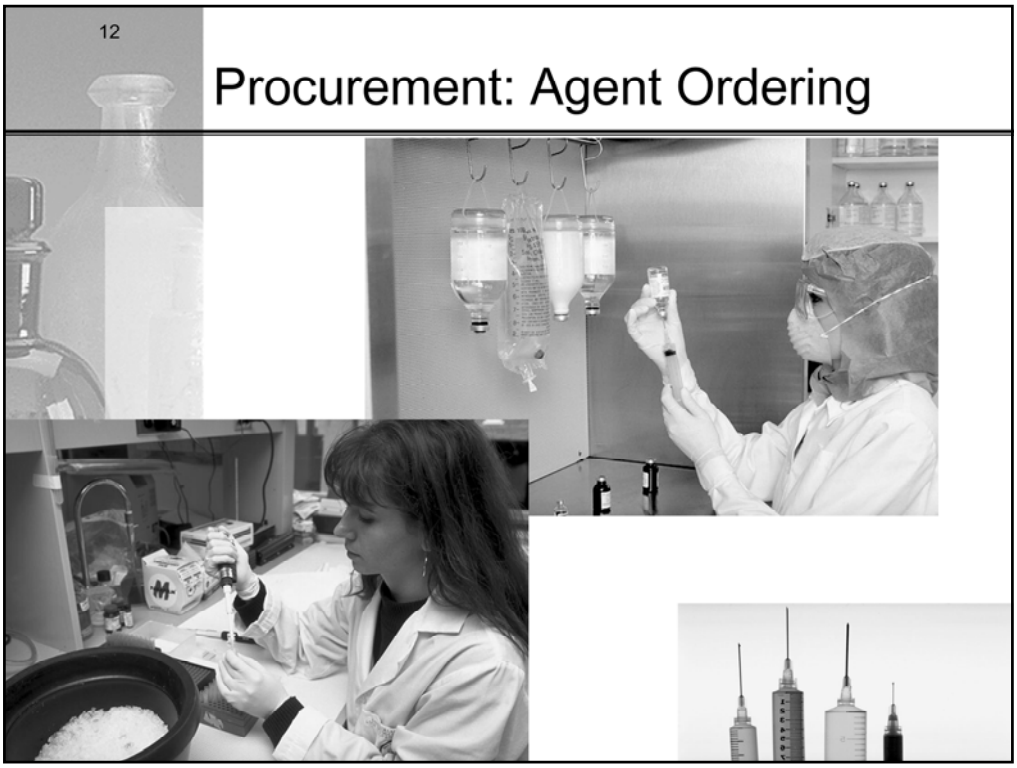
•Strength & Dosage Form – Record the strength of agent and also specify dosage form such as vial, tablet, or ampule.

•Quantity Ordered is what you need for all patients registered on the protocol, but never more than an 8 weeks supply. Unless you are ordering for a blinded trial, use one line to order for all patients on the study. Do not place individual orders for open label trials.

•Date Needed - The date you would like to have agent at your institution. It's a good idea to order the agent for a day prior to when you need it. And remember: agents that require refrigerated or frozen shipping cannot be shipped unless someone will be there to receive them. They are generally not shipped on Fridays. Do not use vague terms like ASAP. Your ASAP and ours may not be the same. Always provide a specific date—we'll call you if it's a problem.

The shipping information for the Clinical Drug Request is located on the bottom left corner of the form. This address should be the same address as designated in the investigator's registration documents. If the address provided in this section is different, then the order will be delayed until the address is verified. Count on it! Equate a different address with an order delay.

If urgent shipment is required, you must supply express courier information – that is, you foot the bill.



Once the shipment is received at the investigator's institution, the physician or designee should ensure that the shipment is correct, intact, at the proper temperature, and the proper documentation is included.

•Check shipment for breakage.

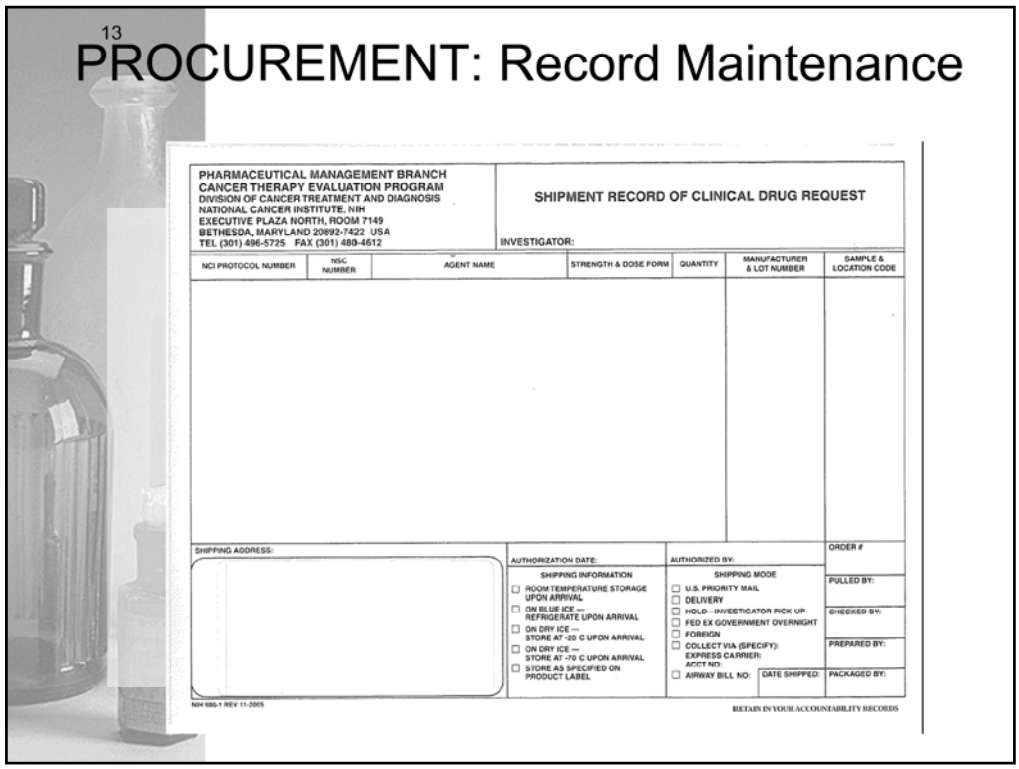
•Ensure correct agent, strength and dosage form is received according to what was requested.

•Review the shipping record to ensure the lot received, quantity, strength, and dosage form are accurate.

•Maintain accountability, storage, and shipping records for future audits.

13

PROCUREMENT: Record Maintenance



PHARMACEUTICAL MANAGEMENT BRANCH
CANCER THERAPY EVALUATION PROGRAM
DIVISION OF CANCER TREATMENT AND DIAGNOSIS
NATIONAL CANCER INSTITUTE, NIH
EXECUTIVE PLAZA NORTH, ROOM 7149
BETHESDA, MARYLAND 20892-7422 USA
TEL (301) 496-5725 FAX (301) 480-4612

SHIPMENT RECORD OF CLINICAL DRUG REQUEST

INVESTIGATOR:

NCI PROTOCOL NUMBER	NSC NUMBER	AGENT NAME	STRENGTH & DOSE FORM	QUANTITY	MANUFACTURER & LOT NUMBER	SAMPLE & LOCATION CODE

SHIPPING ADDRESS:

AUTHORIZATION DATE:

SHIPPING INFORMATION

- ☐ ROOM TEMPERATURE STORAGE UPON ARRIVAL
- ☐ ON BLUE ICE — REFRIGERATE UPON ARRIVAL
- ☐ ON DRY ICE — STORE AT -20 C UPON ARRIVAL
- ☐ ON DRY ICE — STORE AT -70 C UPON ARRIVAL
- ☐ STORE AS SPECIFIED ON PRODUCT LABEL

AUTHORIZED BY:

SHIPPING MODE

- ☐ U.S. PRIORITY MAIL
- ☐ DELIVERY
- ☐ HOLD—INVESTIGATOR PICK UP
- ☐ FED EX GOVERNMENT OVERNIGHT
- ☐ FOREIGN
- ☐ COLLECT VIA (SPECIFY): EXPRESS CARRIER: ACCT NO:
- ☐ AIRWAY BILL NO: DATE SHIPPED:

ORDER #

PULLED BY:

CHECKED BY:

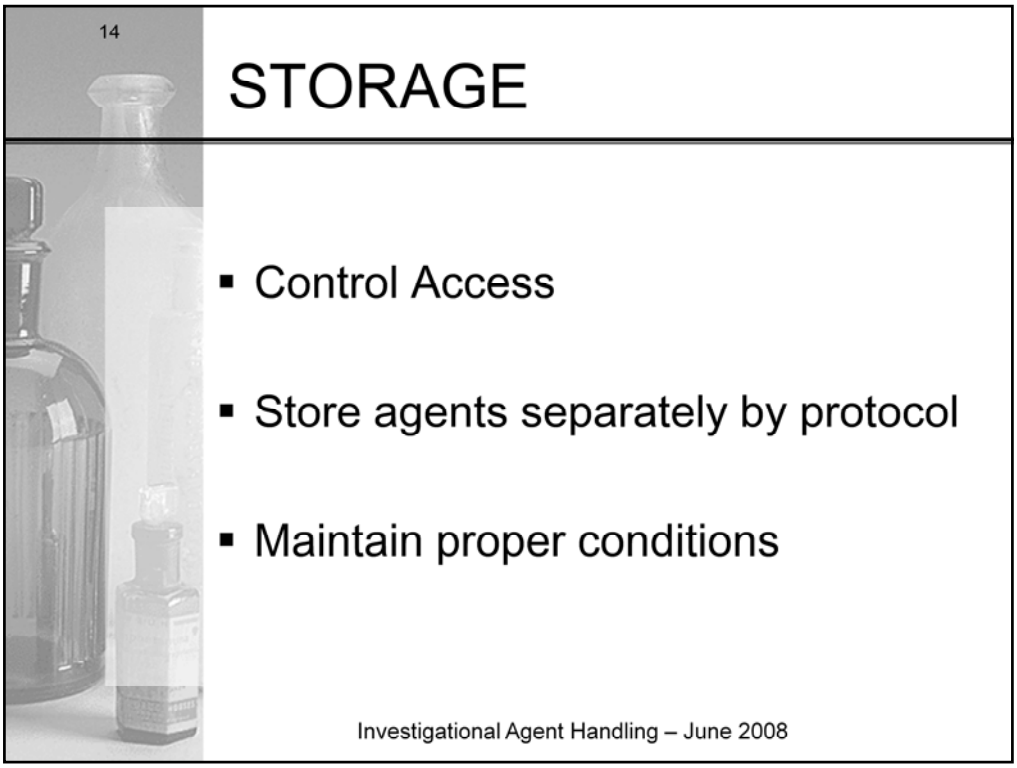
PREPARED BY:

PACKAGED BY:

NIH 586-1 REV 11-2005

RETAIN IN YOUR ACCOUNTABILITY RECORDS

All shipping receipts must be maintained by the physician or designee. These receipts may be used for auditing purposes and hence should be readily retrievable.



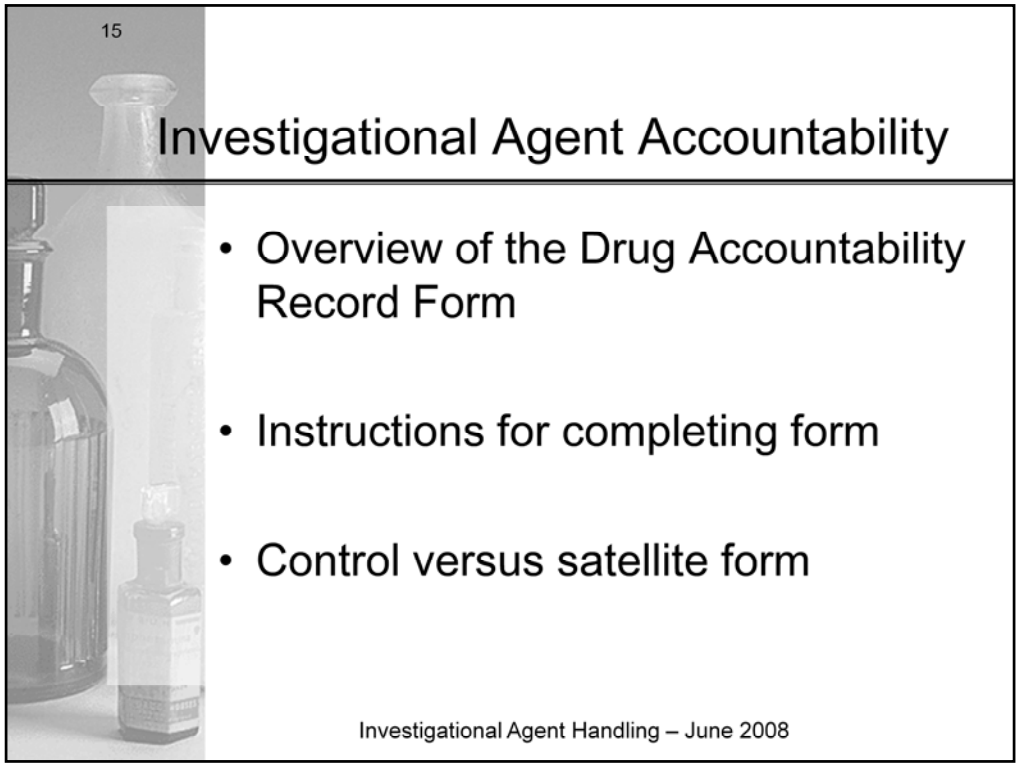
Secure investigational agents where only authorized personnel have access. In addition, use investigational agents supplied by the NCI only for those protocols for which agent has been ordered.

Store each investigational agent separately by protocol. Keep multiple supplies of an agent that is used for more than one protocol physically separate and labeled by protocol.

Store agents under proper conditions with validation documentation (like a daily temperature log). The four types of storage are:

- room temperature (15-30° C)
- Refrigerated (2-8° C)
- Freezer (-10 to -20° C)
- Deep Freeze (≤70° C).

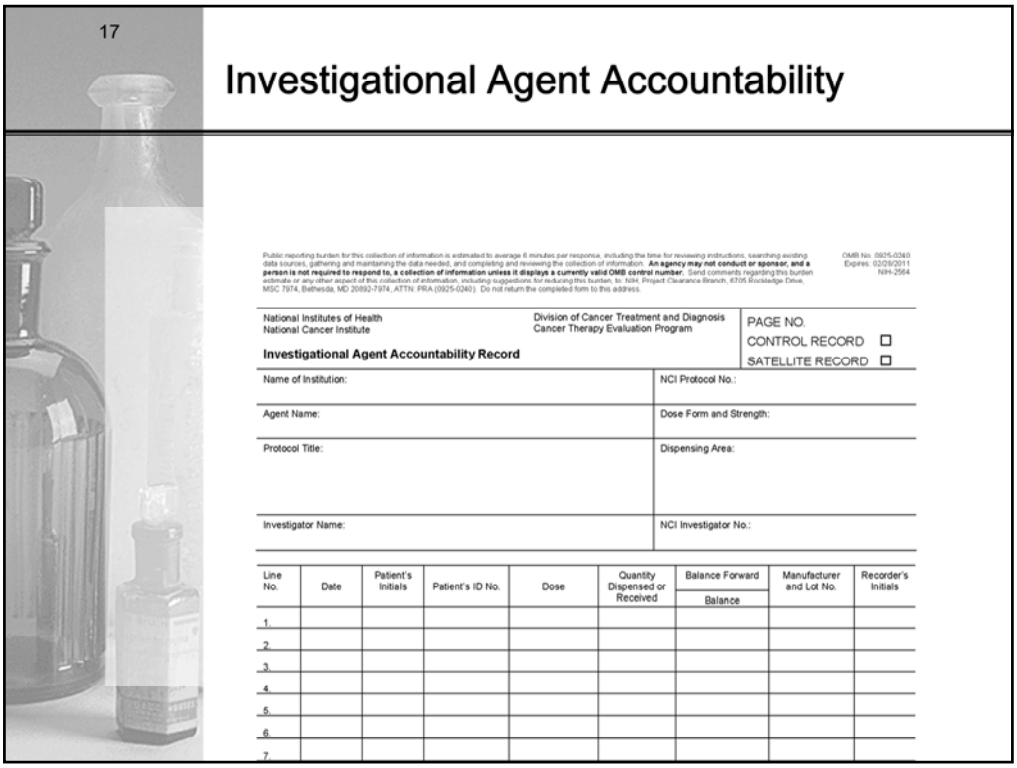
Neither regular freezers nor deep freezers should be the frost free type.



In this section, we'll introduce you to the National Cancer Institute's Investigational Drug Accountability Record form NIH-2564 (DARF). We'll explain the form sections, and provide detailed instructions on how to complete each section.

And yes, the DARF uses the "drug" word. Someday, we will get around to changing its name to the……..

AARF!

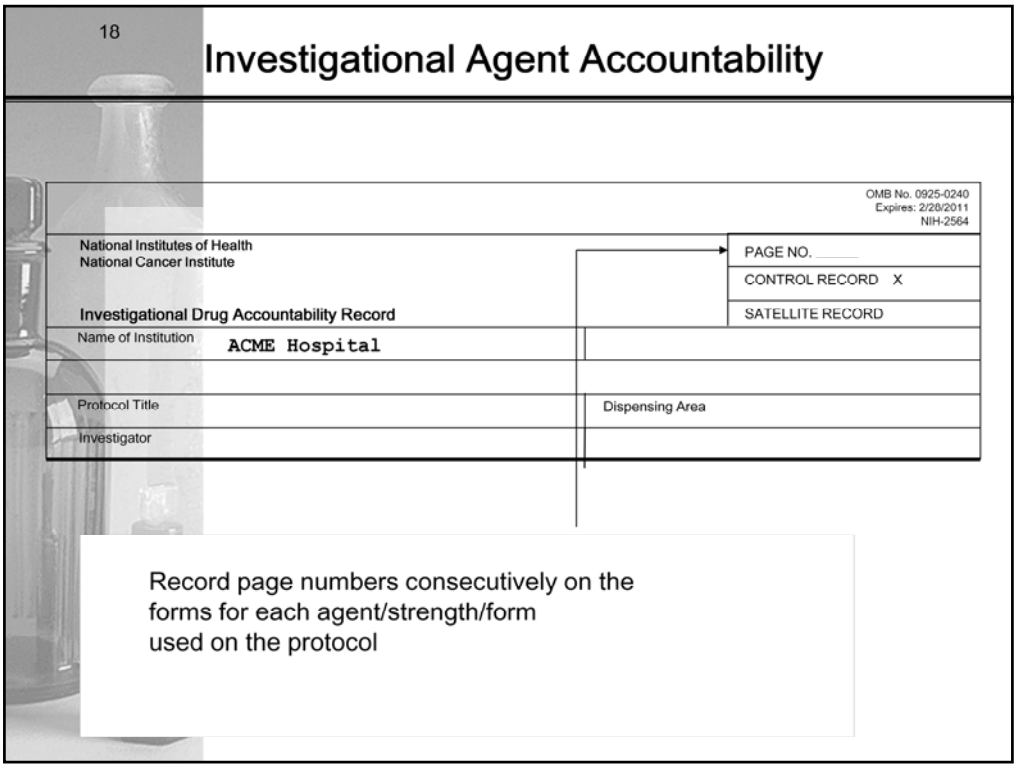


Use the DARF for any transaction involving NCI-supplied agents. The form tracks dispensing to study participants, and other types of transactions such as receipts, returns, broken vials, etc.

For purposes of this presentation, the form will be broken down into two main sections:

•The upper portion of the form requires information related to the specific protocol and treatment sites.

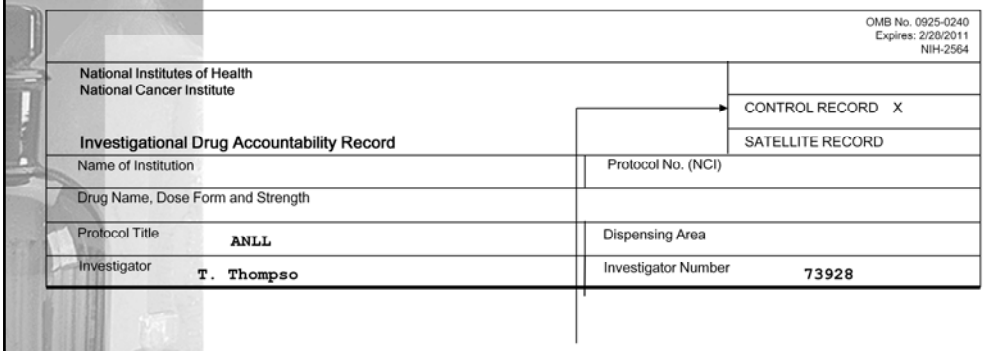
•The lower portion of the form is designed to record investigational agent transactions.



The upper portion of the DARF requires information related to the specific protocol and the treatment facility. Use a separate form for each agent. Also maintain a separate DARF for each different strength or dosage form of the particular agent being used. Be sure to record the NCI protocol number in addition to any local protocol number.

This form can be downloaded from the CTEP web site.

Investigational Agent Accountability



OMB No. 0925-0240
Expires: 2/28/2011
NIH-2564

National Institutes of Health
National Cancer Institute

CONTROL RECORD X

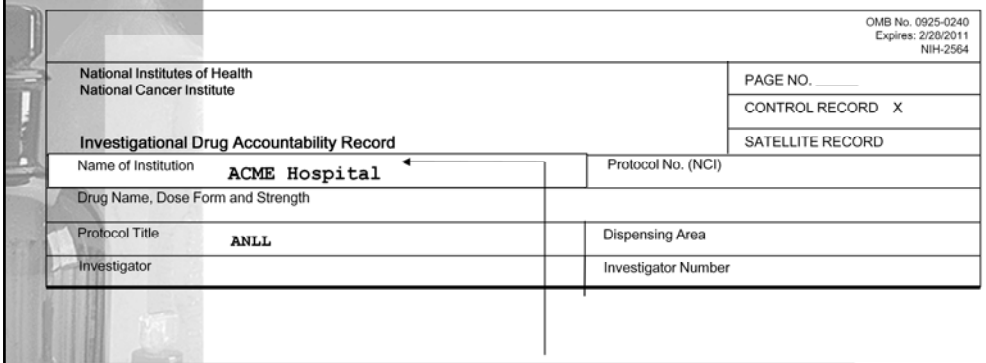
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution	Protocol No. (NCI)
Drug Name, Dose Form and Strength	
Protocol Title ANLL	Dispensing Area
Investigator T. Thompso	Investigator Number 73928

A check in the control record box indicates that the form is being used in the area where the initial shipment of the agent is stored. If the investigational agent is dispensed only from this area, the control record will be the only form used.

Investigational Agent Accountability



OMB No. 0925-0240
Expires: 2/28/2011
NIH-2564

National Institutes of Health
National Cancer Institute

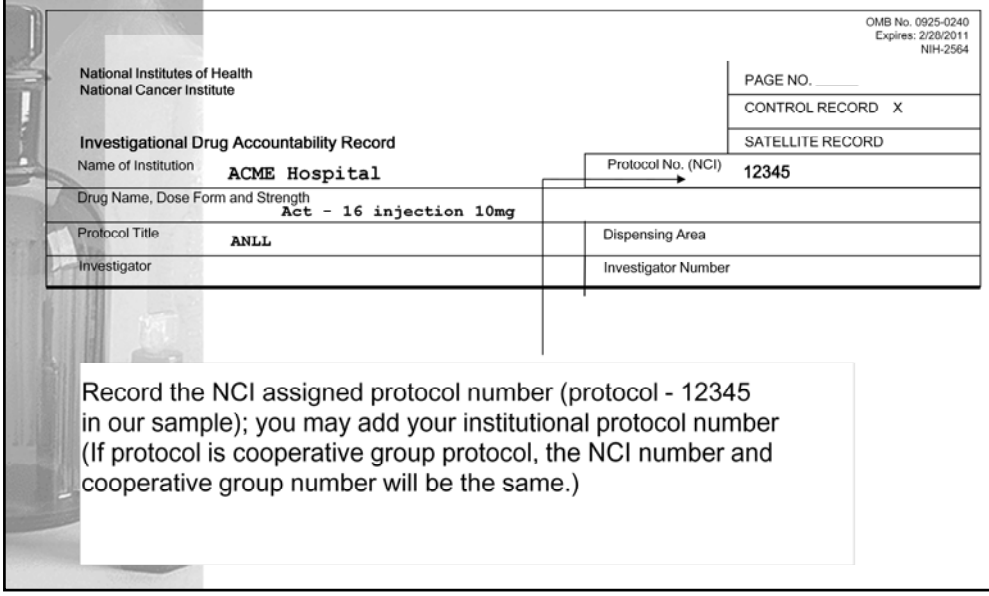
PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution **ACME Hospital**	Protocol No. (NCI)
Drug Name, Dose Form and Strength	
Protocol Title **ANLL**	Dispensing Area
Investigator	Investigator Number

Record the institution name or other identifier, e.g., private physicians office, med oncology pharmacy, etc., to which NCI ships the agent. The identifier in sample form is ACME Hospital.

Investigational Agent Accountability



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NIH-2564

National Institutes of Health
National Cancer Institute

PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution: ACME Hospital	Protocol No. (NCI): 12345
Drug Name, Dose Form and Strength: Act - 16 injection 10mg	
Protocol Title: ANLL	Dispensing Area
Investigator	Investigator Number

Record the NCI assigned protocol number (protocol - 12345 in our sample); you may add your institutional protocol number (If protocol is cooperative group protocol, the NCI number and cooperative group number will be the same.)

Investigational Agent Accountability

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Expires: 2/28/2011
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National Institutes of Health
National Cancer Institute

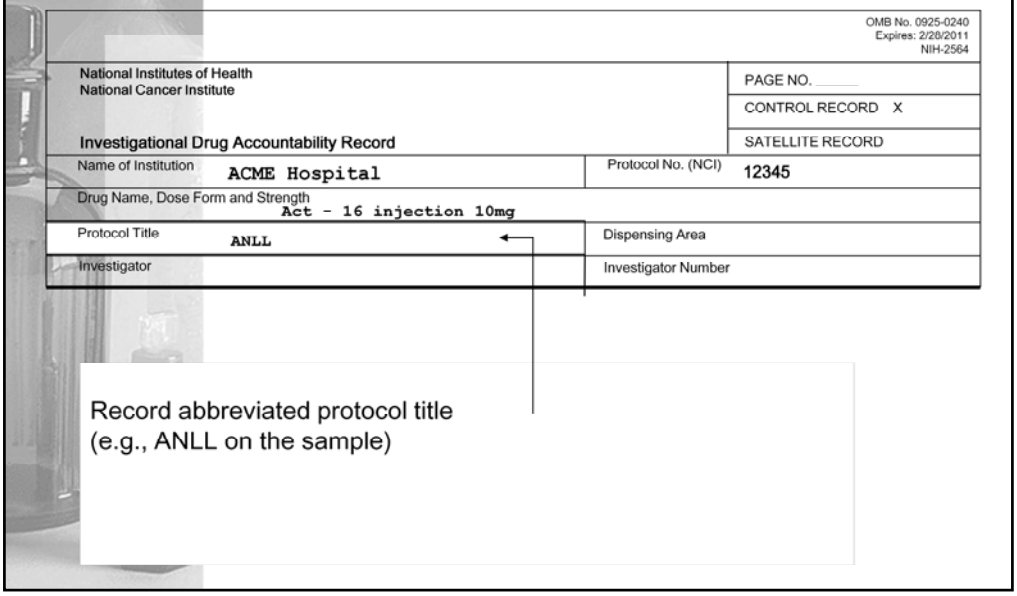
PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution: ACME Hospital	Protocol No. (NCI): 12345
Drug Name, Dose Form and Strength: Act - 16 injection 10mg	
Protocol Title	Dispensing Area
Investigator	Investigator Number

Record the agent name, dosage form (tablet, injection, etc.), and strength. Use a different form for each dosage form and strength. The sample form is used for Act-16, 10 mg injection.
If another agent or another dose form is used on protocol 12345, a separate Investigational Drug Accountability record form must be maintained for each.

Investigational Agent Accountability



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National Institutes of Health
National Cancer Institute

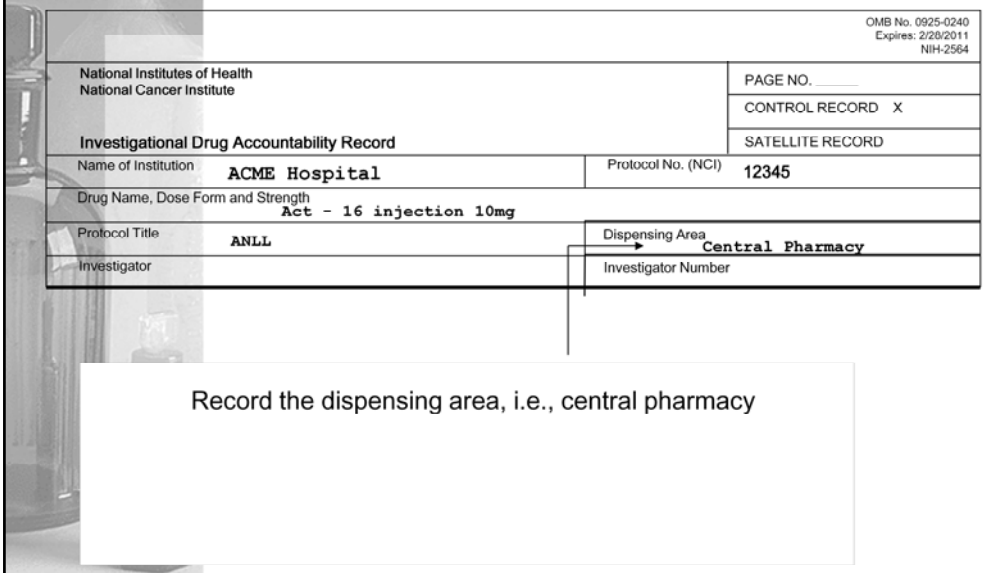
PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution: ACME Hospital	Protocol No. (NCI): 12345
Drug Name, Dose Form and Strength: Act - 16 injection 10mg	
Protocol Title: ANLL	Dispensing Area
Investigator	Investigator Number

Record abbreviated protocol title
(e.g., ANLL on the sample)

Investigational Agent Accountability



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National Institutes of Health
National Cancer Institute

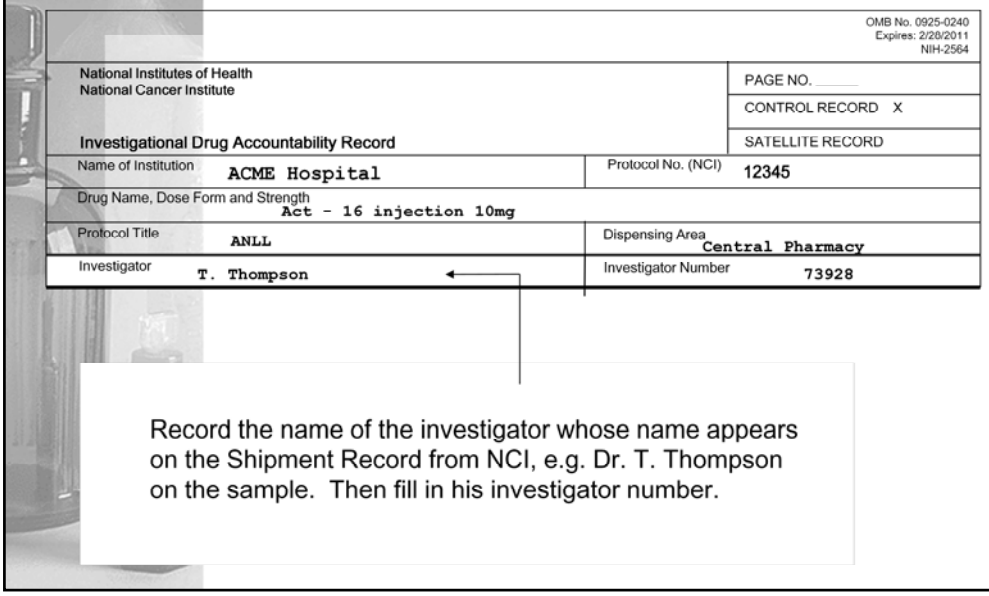
PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution: ACME Hospital	Protocol No. (NCI): 12345
Drug Name, Dose Form and Strength: Act - 16 injection 10mg	
Protocol Title: ANLL	Dispensing Area: Central Pharmacy
Investigator	Investigator Number

Record the dispensing area, i.e., central pharmacy

Investigational Agent Accountability



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NIH-2564

National Institutes of Health
National Cancer Institute

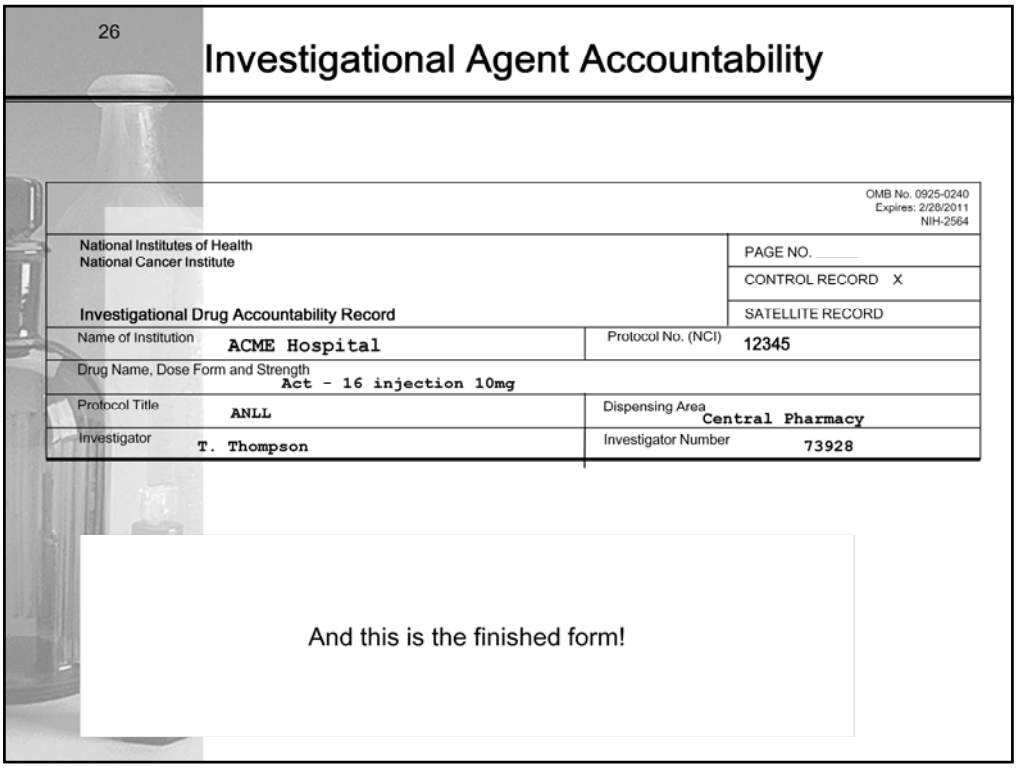
PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution	ACME Hospital	Protocol No. (NCI)	12345
Drug Name, Dose Form and Strength	Act - 16 injection 10mg		
Protocol Title	ANLL	Dispensing Area	Central Pharmacy
Investigator	T. Thompson	Investigator Number	73928

Record the name of the investigator whose name appears on the Shipment Record from NCI, e.g. Dr. T. Thompson on the sample. Then fill in his investigator number.

Investigational Agent Accountability



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National Institutes of Health
National Cancer Institute

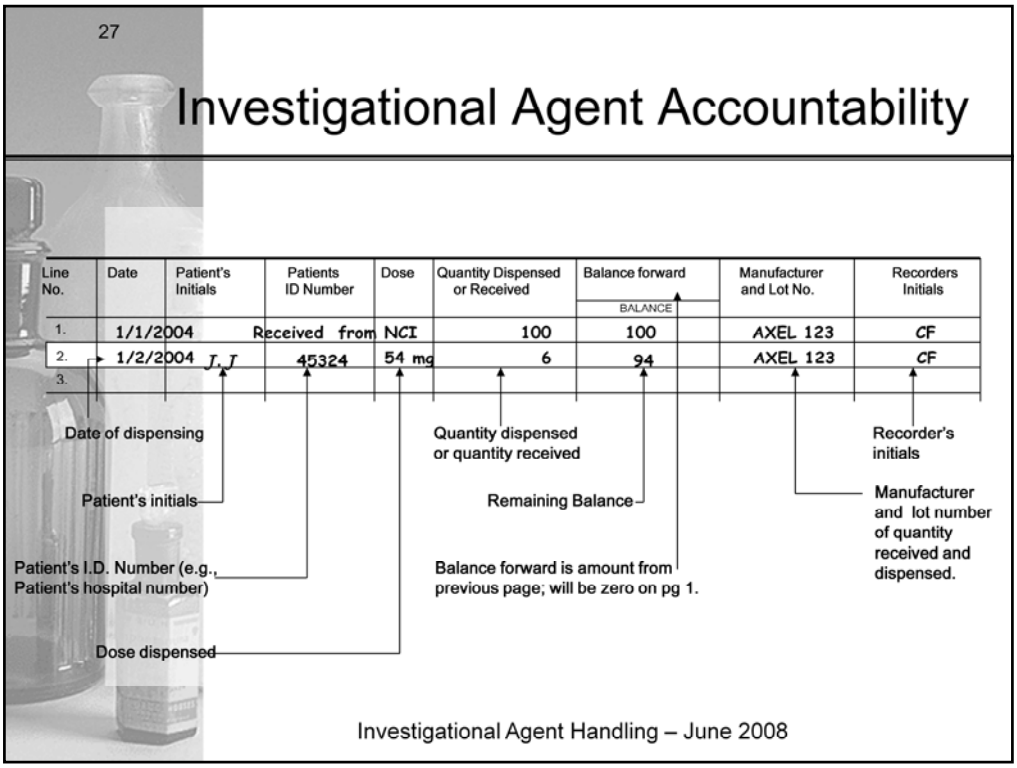
PAGE NO. _____
CONTROL RECORD X
SATELLITE RECORD

Investigational Drug Accountability Record

Name of Institution	ACME Hospital	Protocol No. (NCI)	12345
Drug Name, Dose Form and Strength	Act - 16 injection 10mg		
Protocol Title	ANLL	Dispensing Area	Central Pharmacy
Investigator	T. Thompson	Investigator Number	73928

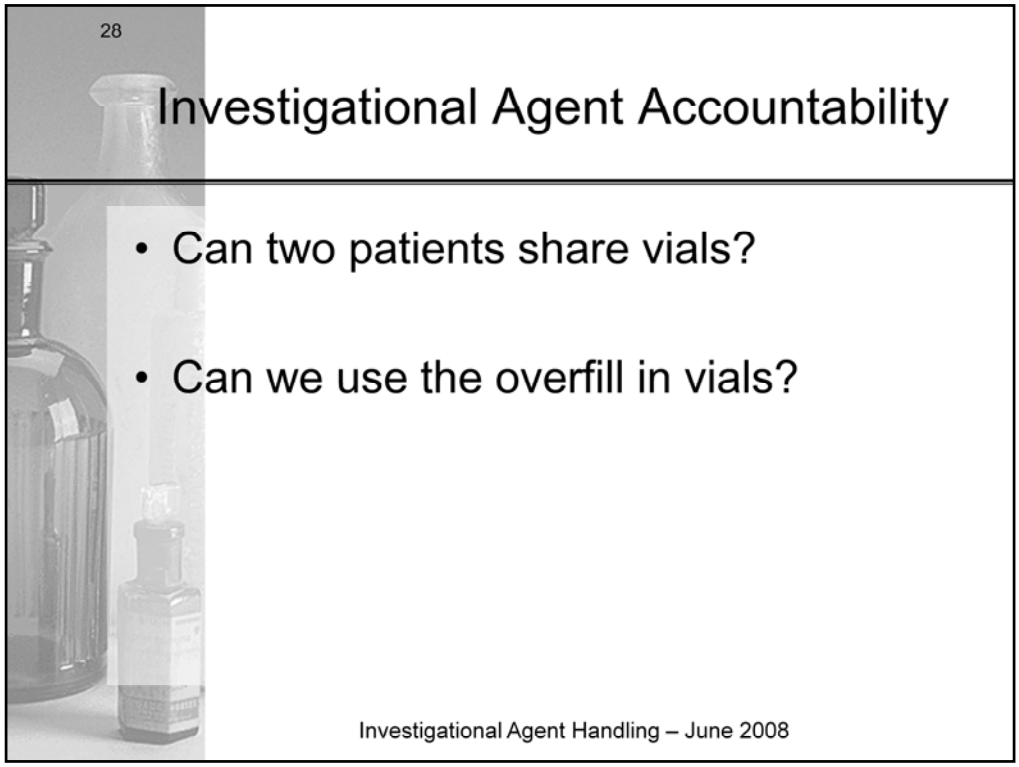
And this is the finished form!

This form can be downloaded from the CTEP web site.



The lower portion of the DARF is designed to record agent transactions. The form can be used for recording dispensing to individual patients, as well as for other transactions such as agent receipts, agent transported to satellite pharmacies, etc.

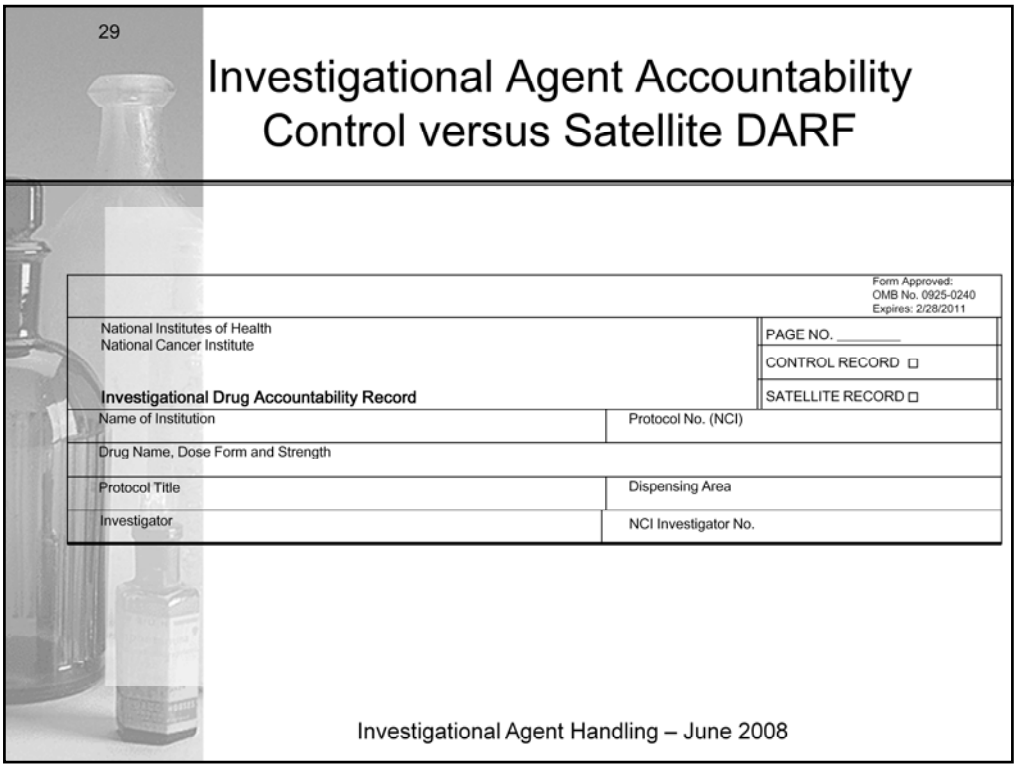
Here's a handy hint: when recording the date, please include the **year**! Studies can go on FOREVER!



Often, clinicians ask if two patients receiving the same agent on the same open label NCI study at the same institution can share vials. Our answer: Yes, if the patients are being treated on the same day, this is acceptable. Document this on the DARF by noting patient initials/ number used 1 vial and patient initials/ number used 0 vials. Tie the lines together with a "}" (speaker ay" Parenthesis or bracket).

And, some clinicians have asked about overfill. So suppose your patient's dose of godzillaplatin is 104 mg, and the NCI-supplied vials contain 100 mg in 5 mL, but they have ample overfill. If you can draw 5.2 mL from the vial, can you use it instead of opening another vial?

You bet! Have at it, especially if the vial was filled by the manufacturer. If the product is lyophylized, however, please make sure that you reconstituted it exactly as directed, and the overfill isn't the result of an error. (Please note that you might want to suggest to your physicians that the difference between 104 mg and 100 mg is very small, and they can round to 100 mg without a problem in most cases.)

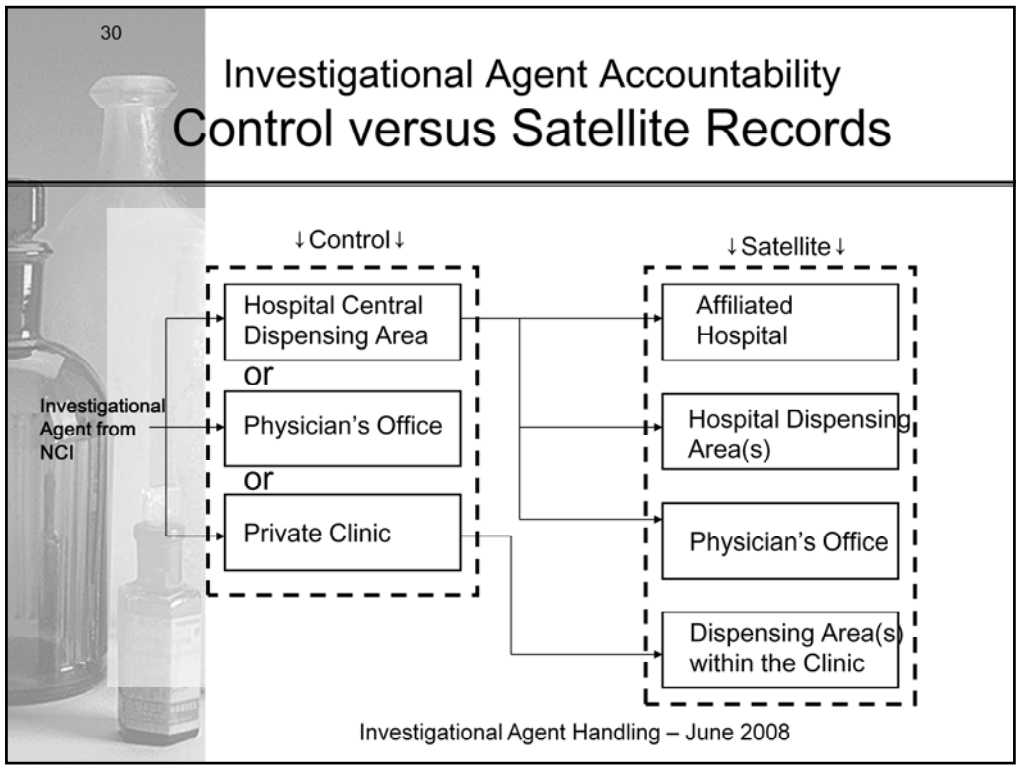


This is an auto-fill form. Please keeping hitting “enter” until the entire form is filled in.

The control record indicates that the form is being used in the area where the initial shipment of agent was received. The site receiving the initial shipment of investigational agent should check the “control record” box. If the investigational agent is dispensed only from this area, the control record will be the only form used.

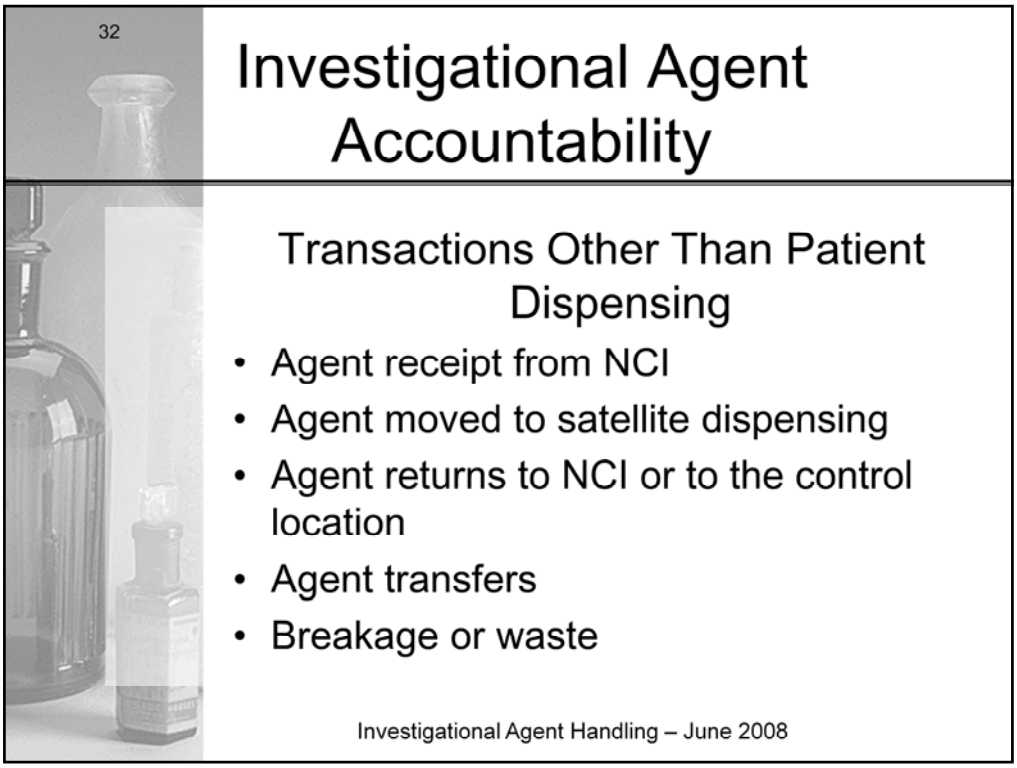
Use a satellite record when agents are moved to other areas away from the control area or primary storage area. This could be satellite pharmacies within or outside the primary institution, or the physician’s office.

The satellite form will normally contain the same information as the control record, with the exception of the dispensing area and a check in the satellite record box.



This flow diagram illustrates the relationship between control and satellite records; all of the areas on the left would use a control record. Those on the right would use a satellite record.

PMB defines a “Satellite Location” as a remote location away from the control area or primary storage area. Transportation of the investigational agent between the control location and satellite location must remain in the immediate control of the institution. If delivery of an agent requires the use of a secondary carrier (e.g. US postal service, Fed-EX, UPS), the remote location is not a satellite and delivery is prohibited.



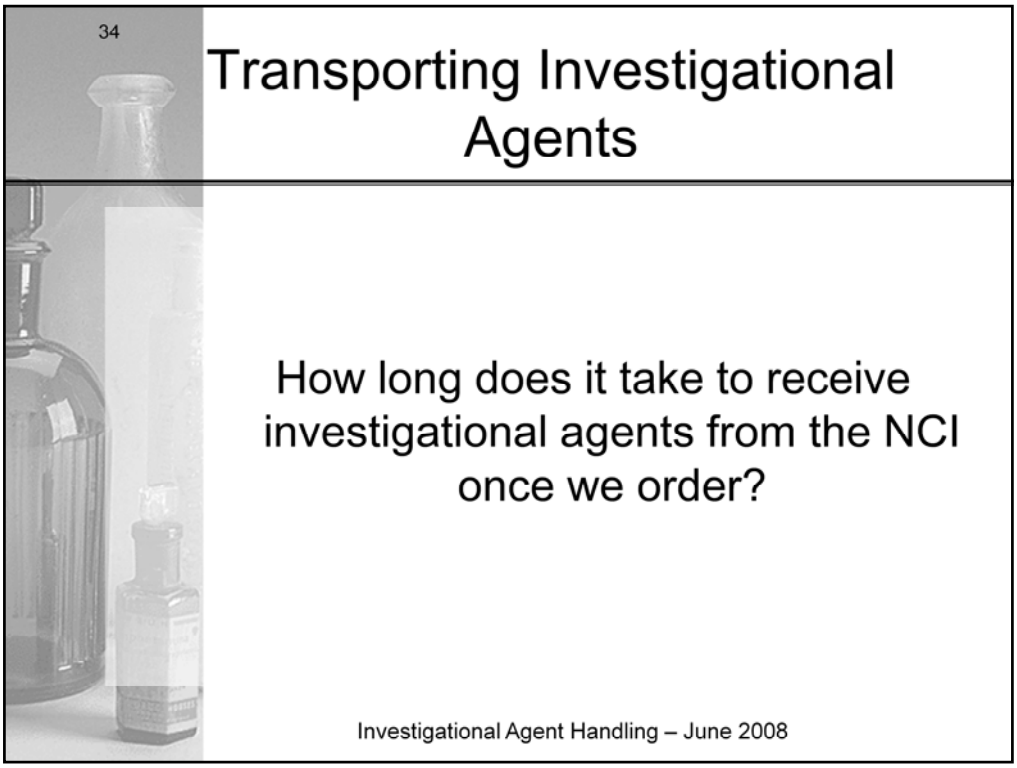
Document any activity that involves a transaction with NCI-supplied agents on the DARF. This slide lists the most common DARF entries.

Document other discrepancies, agent waste and damaged shipments on the DARF. Use ink. Don't use crayon, pencil, or correction fluid! If you make an error, make a single line through and initial the error. Do not obscure the entry with blots or black magic marker or scribble.

The NCI maintains PMB-distributed agents at the NCI Clinical Repository, a state-of-the-art facility. This facility is staffed with experts who are experienced in all aspects of procurement, storage and distribution of investigational agents from the NCI to sites conducting clinical research.

Please note that the NCI Clinical Repository is a facility that is separate and distinct from the area where PMB's excellent staff fields your calls and works diligently. PMB staff cannot rise from their desks and walk to the shelf to examine an agent.

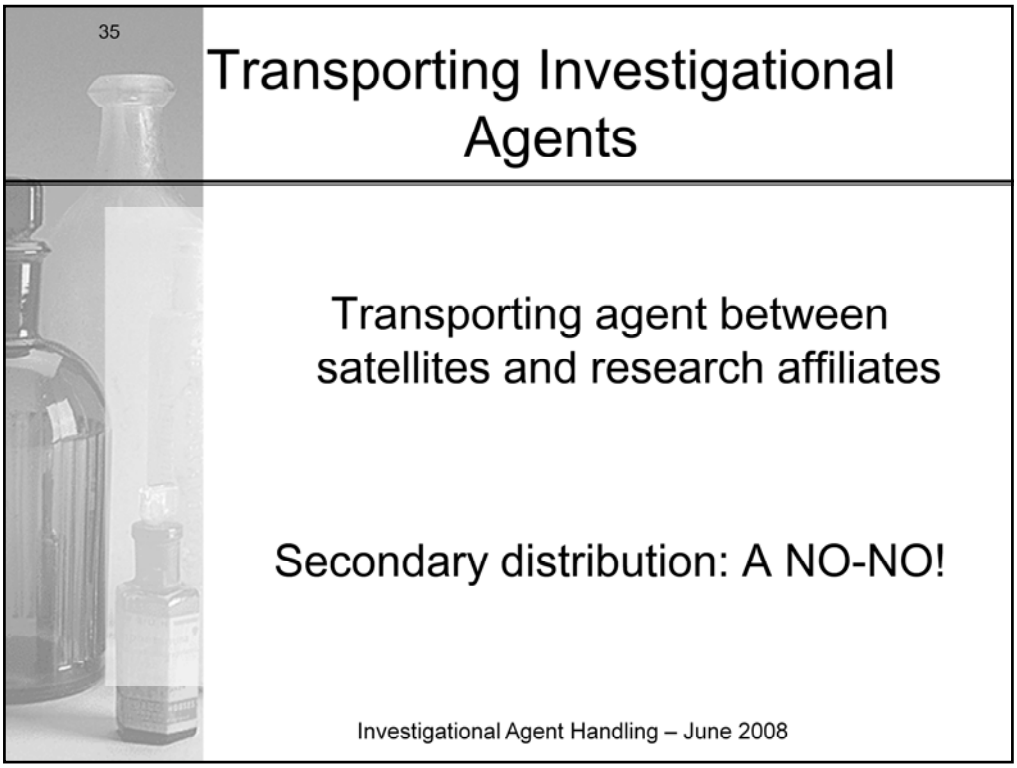
The NCI Clinical Repository has established a set of validated shipping procedures to ensure that all agents maintain pharmaceutical integrity. They maintain very specific packaging criteria, temperature controls, and time-line criteria when pharmaceutical agents are shipped to a clinical site.



PMB processes orders received by 2 PM Eastern time the same day, unless they require refrigeration or iced shipping (we do not ordinarily ship these on Friday). PMB realizes that occasionally this deadline may pass before an order is placed for next day delivery. If this situation arises, please call PMB immediately and directly; we will make every effort to accommodate your request.

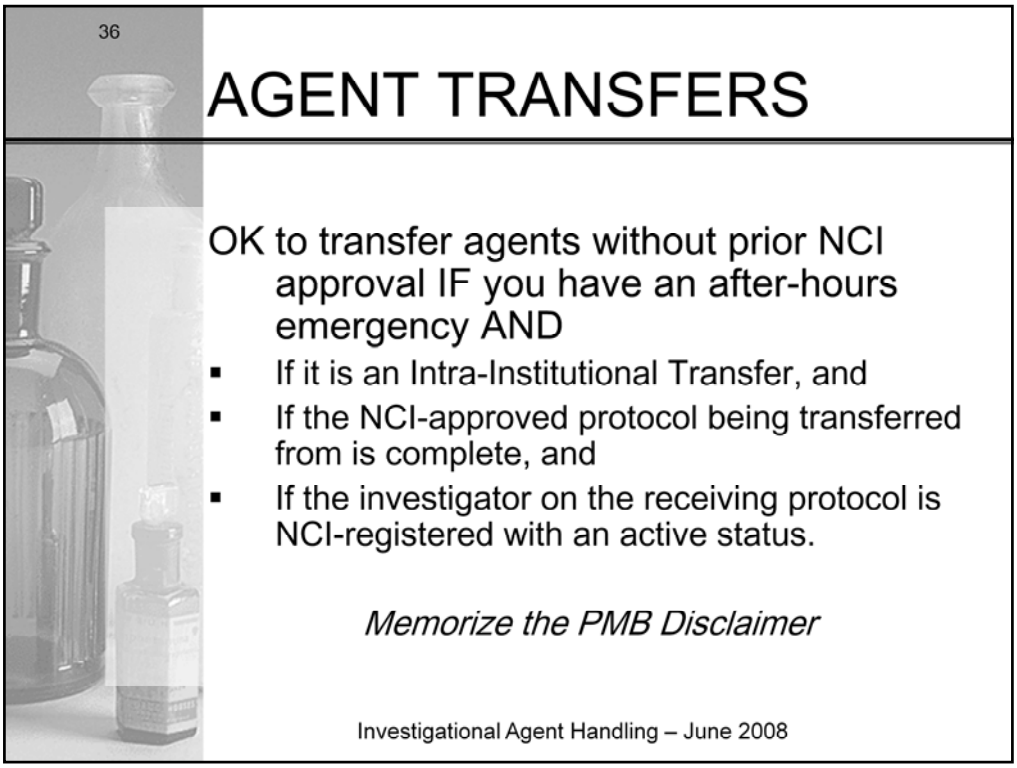
If you have an order that requires next day delivery, then you must communicate that information to PMB on the Clinical Drug Request form. Include an express courier account number on the bottom of the form.

If the order is not of an urgent nature, then agents that are not temperature sensitive will be sent by regular US postal service. When agents are shipped by regular mail, please expect 5 working days for receipt of shipment.



You may transport investigational agents that you receive at the control location to satellite locations or other research affiliates. Transportation of investigational agents must be in the direct control of the receiving institution, and a third party shipper may not be used. NCI established this to protect the agent's validated shipping conditions when agents are used for clinical research.

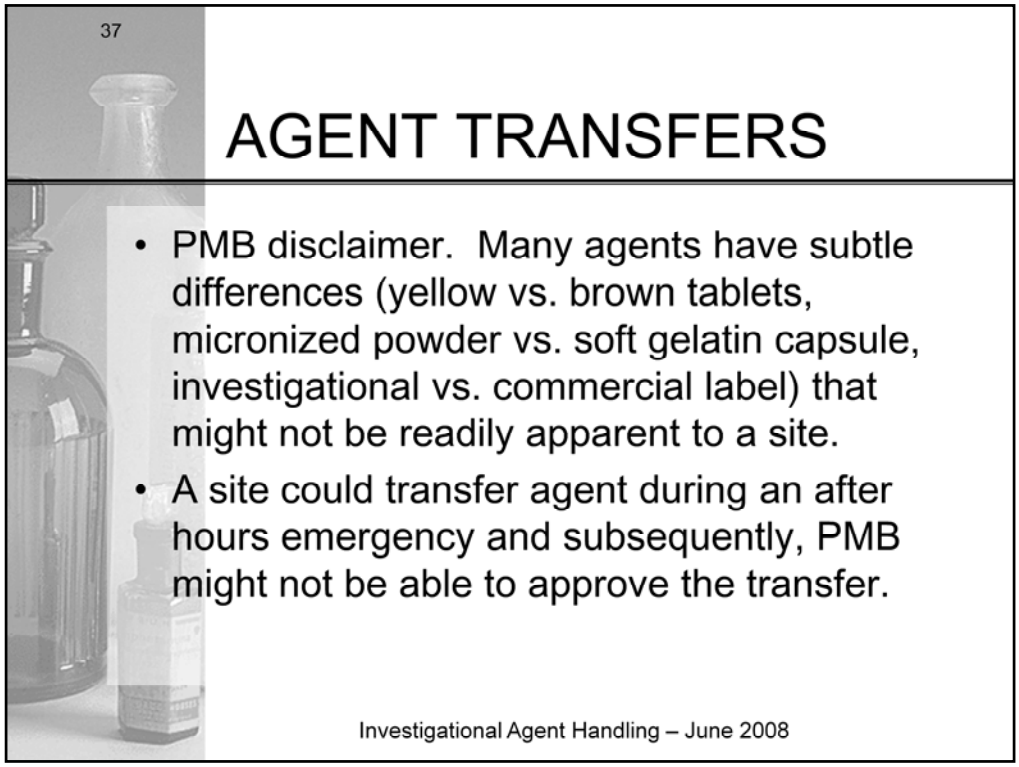
Any transportation of investigational agents outside the direct control of the institution receiving the agent is considered secondary distribution. Secondary distribution is a violation of NCI policy and procedures.



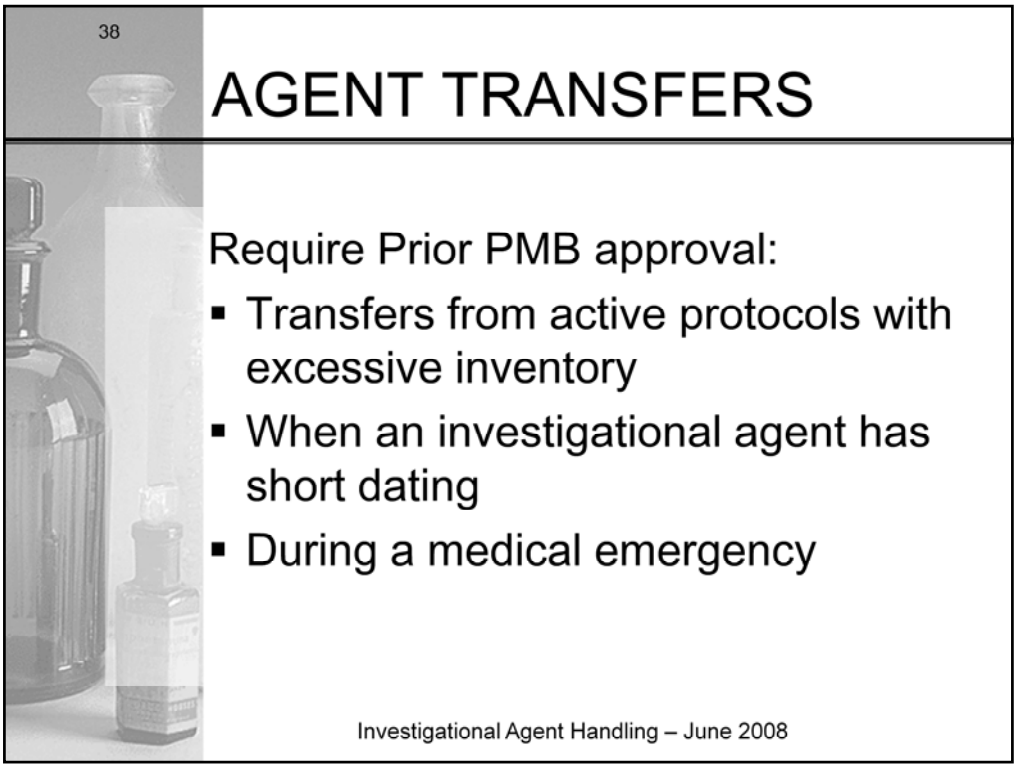
You may transfer investigational agents between protocols in defined situations. Depending on the reason for transferring the agent, the investigator or designee may or may not be required to get PMB's prior approval. Generally speaking, agent transfers from a completed protocol may be transferred without prior approval if:

1. The transfer is taking place within the same institution.
2. The protocol being transferred from is completed.
3. The receiving protocol—or the protocol being transferred to—is an NCI-sponsored protocol using the same agent and formulation.
4. Investigators transferring and receiving the agent are registered and have an "active" investigator status with the NCI. (You'll need to contact PMB to verify this.)

Although agent transfers in the above situation can be completed without prior PMB approval, an agent transfer form must be submitted to PMB with 72 hours of the actual transfer, and PMB approval of the transfer is not guaranteed.



Now here is a disclaimer. PMB is seeing more and more subtle differences (yellow vs. brown tablets, micronized powder vs. soft gelatin capsule, investigational vs. commercial label) that might not be readily apparent to you (the site). So even the preferences stated above, a site could still get caught in an after hours emergency and we would not be able to subsequently approve the transfer. PMB strongly recommends obtaining approval before making any transfer.

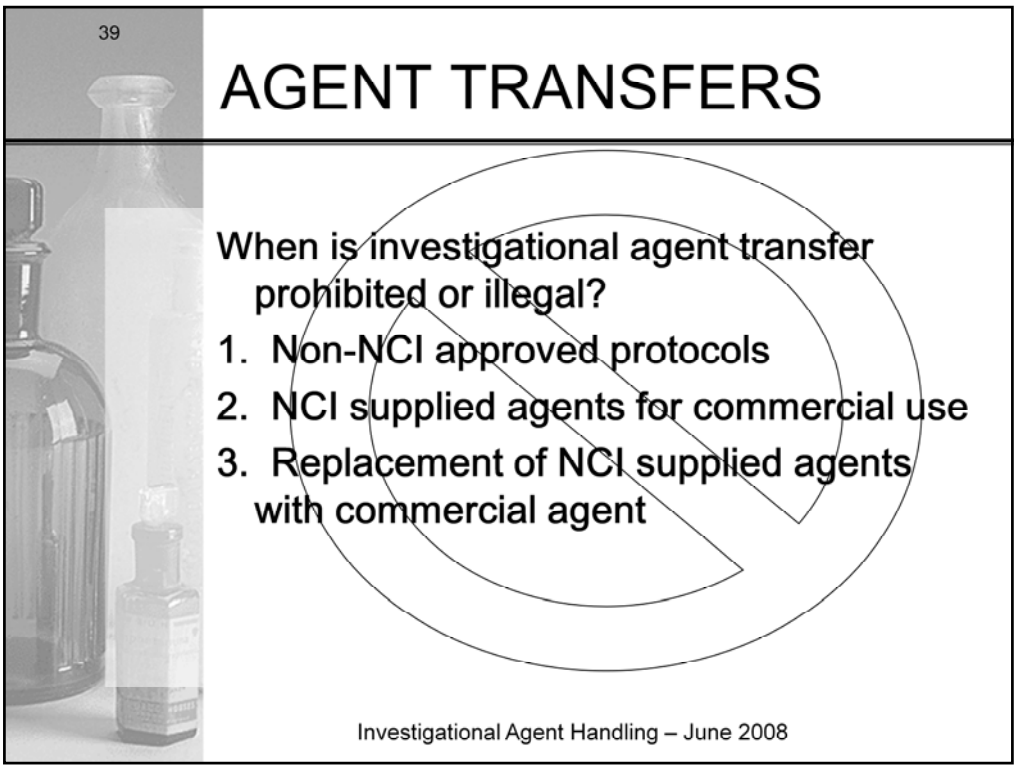


Unlike transfer from a completed protocol, transfer of NCI-supplied investigational agent from an active protocol always requires prior PMB approval. Please restrict transfer of investigational agents from an active protocol to the following situations:

1. When a protocol has excess inventory that cannot be used expediently, you can request a transfer to a protocol that will use the agent faster and save a shipment from the NCI Clinical Repository.

2. When an investigational agent has short dating and will not be used up before its expiration date, you can request a transfer to a protocol that will use the agent prior to expiration.

3. You can arrange medical emergency transfers with PMB during normal working hours. Please notify PMB the next working day if emergency transfers are required during weekends or holidays.

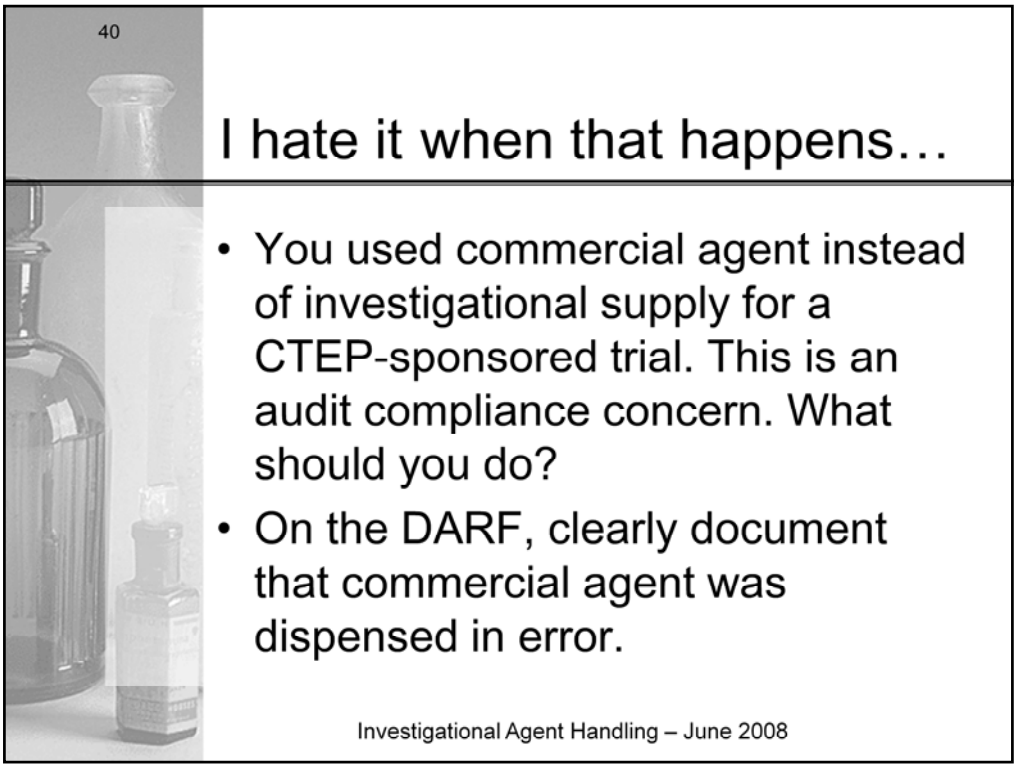


Please do not ever request transfer of PMB-supplied agents if:

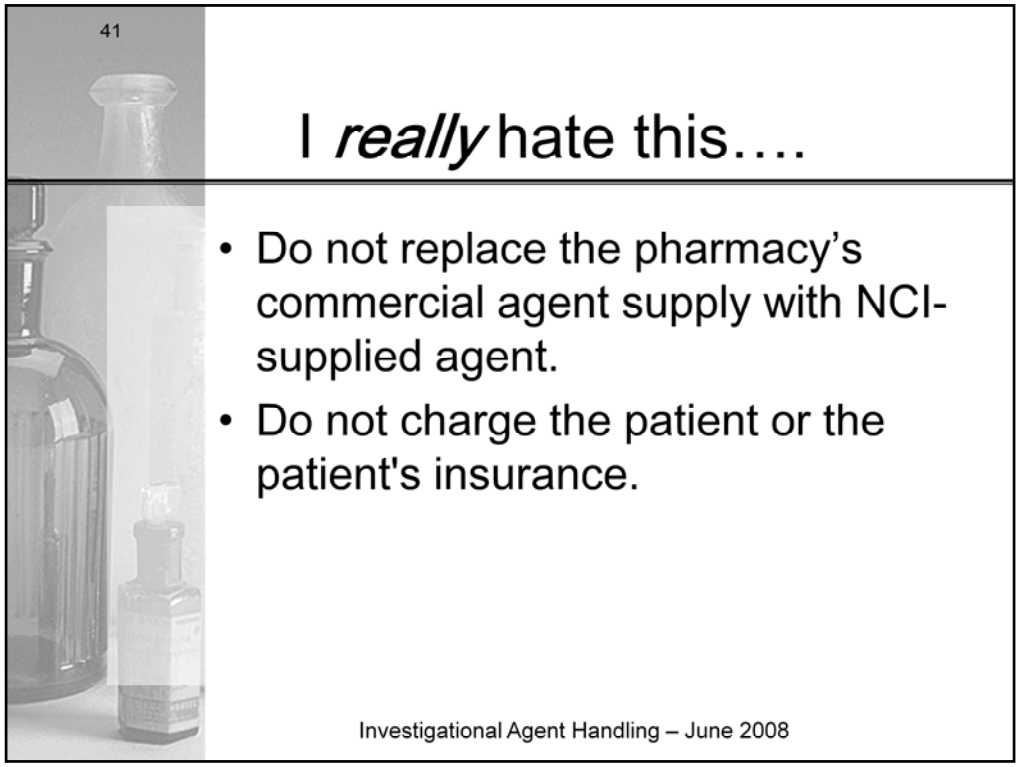
1. Either the transferring from or the transferring to protocol is not an NCI-approved protocol. Do not request transfer if the protocol is NCI-approved, but the agent is not NCI-supplied. DCTD, NCI, and FDA policies and regulations do not permit this.

2. Transfer of NCI supplied agents for commercial use is both prohibited and illegal.

3. Replacement of NCI supplied agents with commercial agents is also prohibited and illegal.

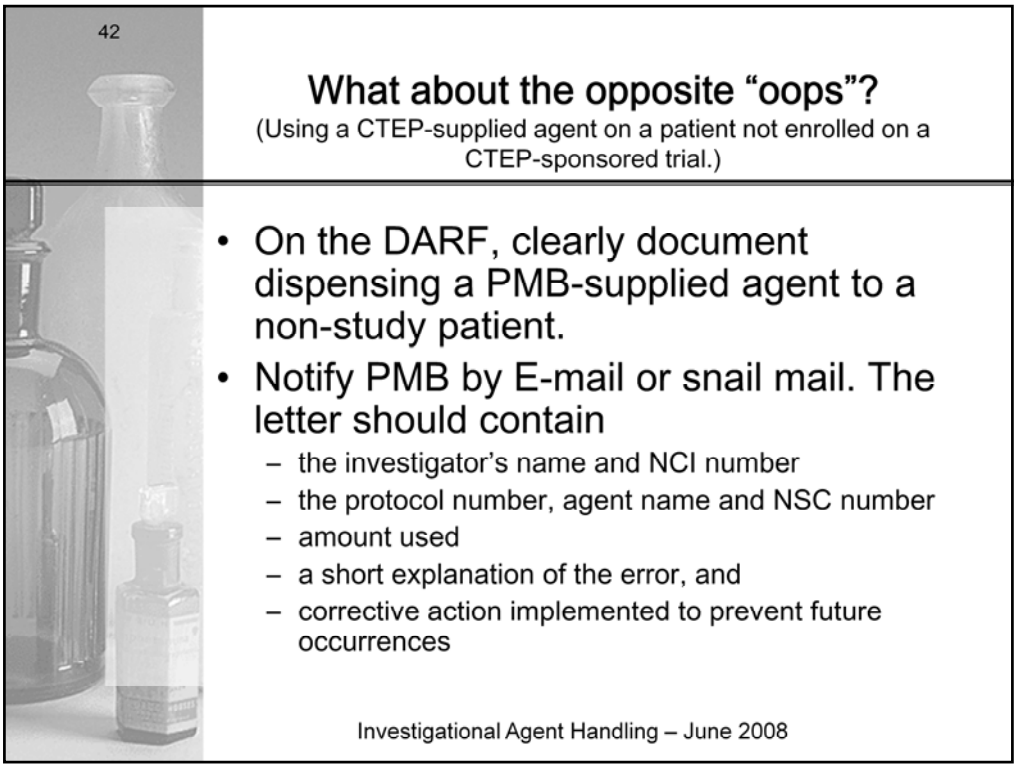


Using commercial agent instead of investigational agent is an audit compliance concern.



Do not replace the pharmacy's commercial supply of the agent with the NCI-supplied agent.

Do not charge the patient or the patient's insurance.



Note that the opposite “oops” is a more grievous error than the previous situation.

Should this happen, document well. On the DARF, clearly document dispensing a PMB-supplied agent to a non-study patient.

Notify PMB by E-mail or snail mail. The letter should contain

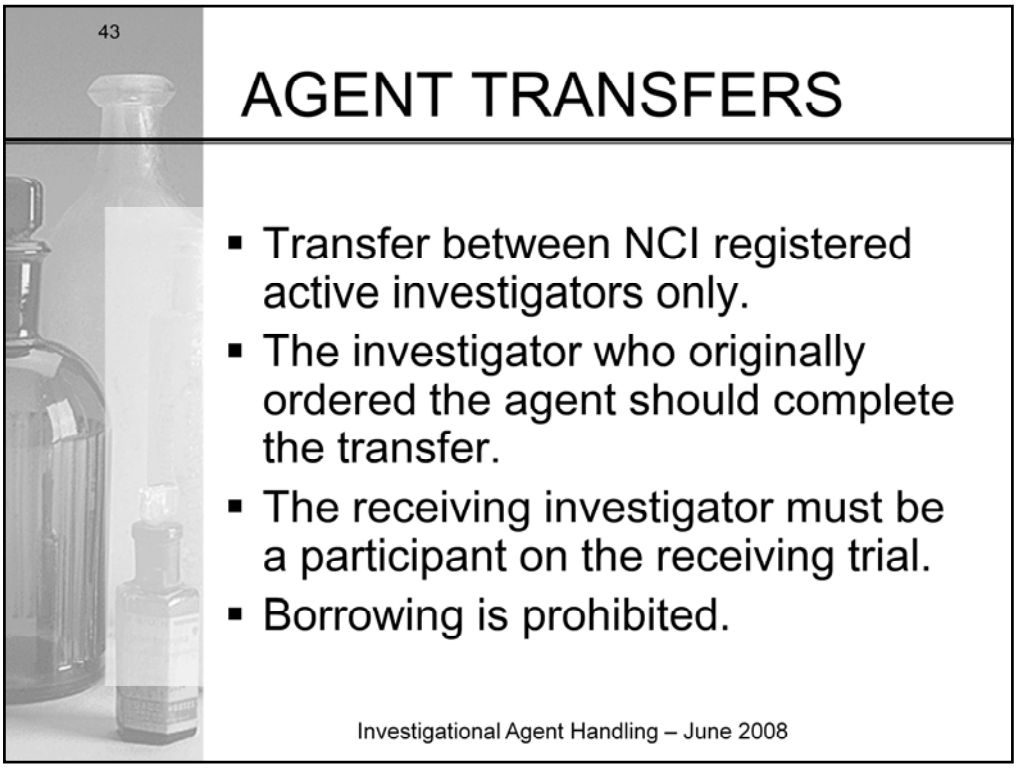
the investigators name and NCI number

the protocol number, agent name and NSC number

amount used

a short explanation of the error, and

corrective action implemented to prevent future occurrences



These four general rules for the transfer of investigational agents can, along with common sense, guide you when agent transfer comes up.

1. All transfers must be to investigators that are registered and active.

2. The transferring investigator must be the investigator who originally ordered the agent or the investigator to whom the agent was previously transferred. (double transfer)

3. The investigator who receives the investigational agent must be a participant on the trial to which the agent is being transferred and have an active investigator status.

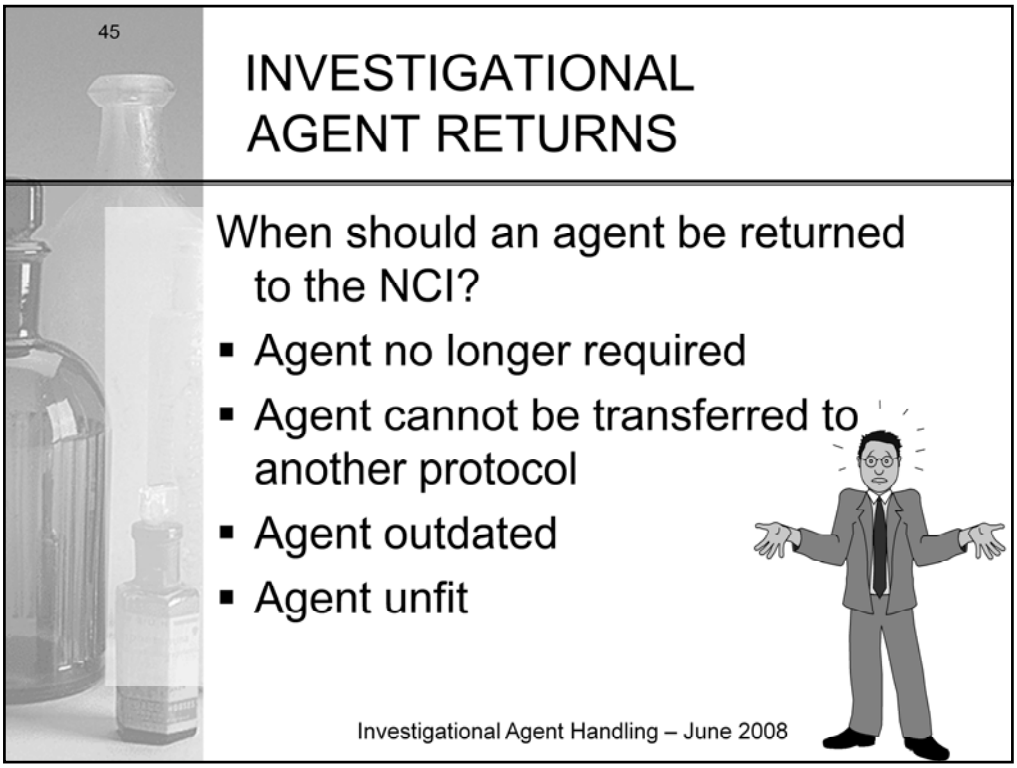
4. Borrowing investigational agents is prohibited. All transfers must be documented. Investigational agents should NOT be ordered for one protocol to replace what was used from another protocol.

Always complete the agent transfer form neatly and in its entirety:

1. Record the name and NCI investigator number of the investigator transferring the agent, include the address and the date of transfer.
2. Check the box that indicates the reason for the transfer request.
3. Record the name and NCI investigator number of the investigator receiving the agent. Use one form per set of investigators.
4. Use the lower portion of the form to record the protocol and agent information as follows:

- Protocol number for which the agent was received—use only the NCI protocol number.
- Protocol number to which the agent is being transferred—use only the NCI protocol number.
- The agent's NSC number
- Agent name
- Strength and formulation of the agent
- Quantity being transferred. Only whole bottles of oral agents may be transferred.
- Manufacturer
- Lot number

5. Sign the form, add a phone number and an e-mail address, and fax it to PMB at the number shown.

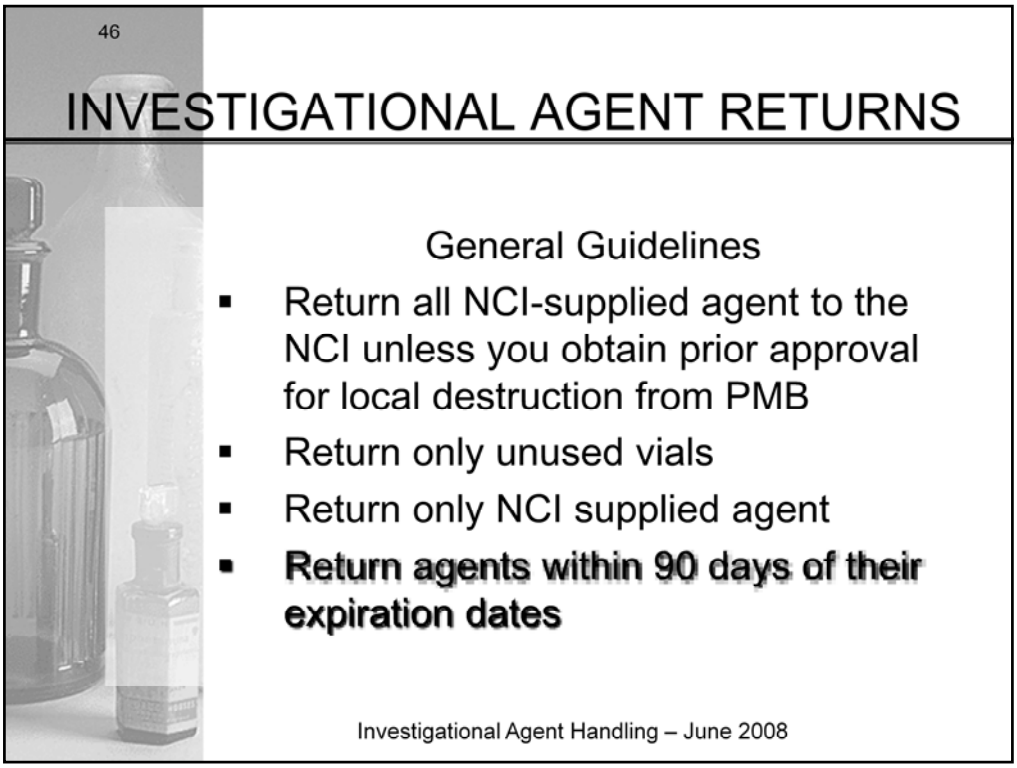


Make every effort to minimize the amount of agent ordered and returned unused. Everything you return to the NCI is going to be destroyed. Orders should be limited to an 8 week supply or less. Investigators or their designees should return unused NCI supplied investigational agent to the NCI Clinical Repository when:

1. The agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another protocol.

2. The agent is outdated. Return outdated agents with a firm expiration date, or when written notification is received from PMB.

3. The agent is unfit for use. Contact the PMB prior to returning investigational agents because of stability concerns. This could be loss of refrigeration or if the agent becomes unfrozen. Do NOT return broken vials. Destroy broken vials at your clinical site according to your local destruction policy, and state and federal law.



When in-date agents cannot be transferred to another NCI sponsored protocol, use these guidelines to return them to the NCI Clinical Repository.

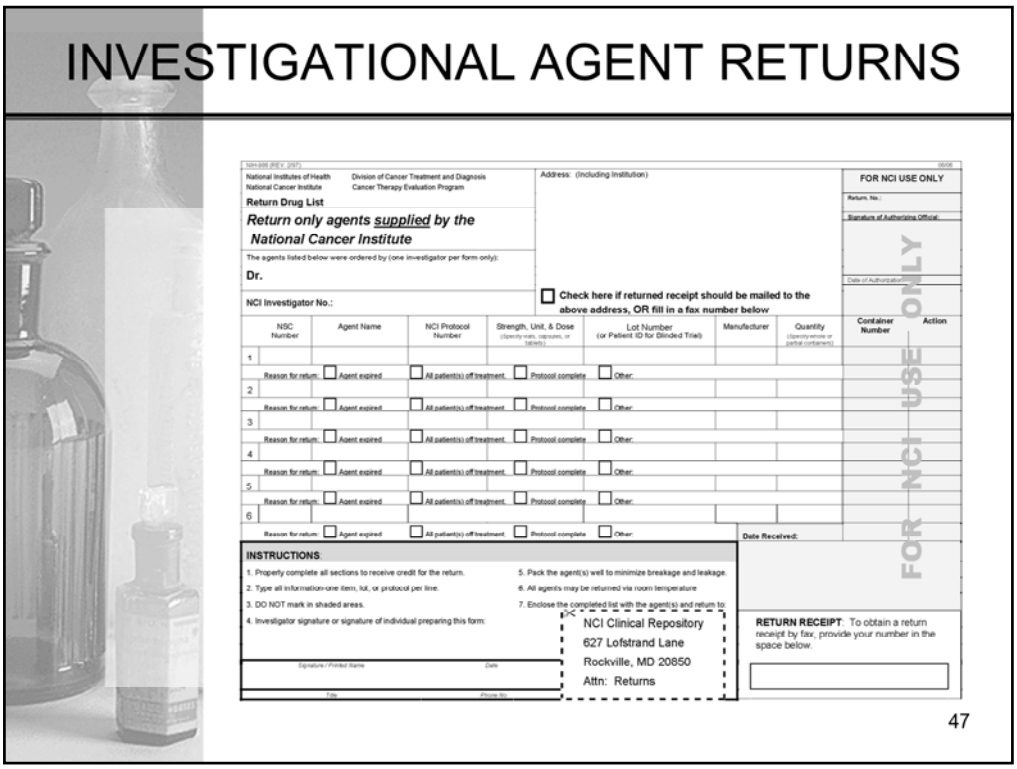
1. Regulations require that the NCI destroy all returned agents, so please be prudent about ordering just what you need.

2. Do not return opened or partially used vials or bottles. Do not return agent that has been dispensed to a patient and returned.

3. Return only NCI supplied agents to the NCI Clinical Repository. Do not send agents from other sources to the NCI Clinical Repository.

4. Return items within 90 days of their expiration.

5. If the agent is considered a dangerous good (DG) for shipping purposes (as noted by **DG** on the Shipping Record), call PMB if your site does not have an individual certified to do DG shipping to inquire about approval for local destruction.



Complete all sections of the Drug Return Form neatly and accurately. Please double check all quantities and lot numbers. Follow the instructions exactly as they are stated on the form.

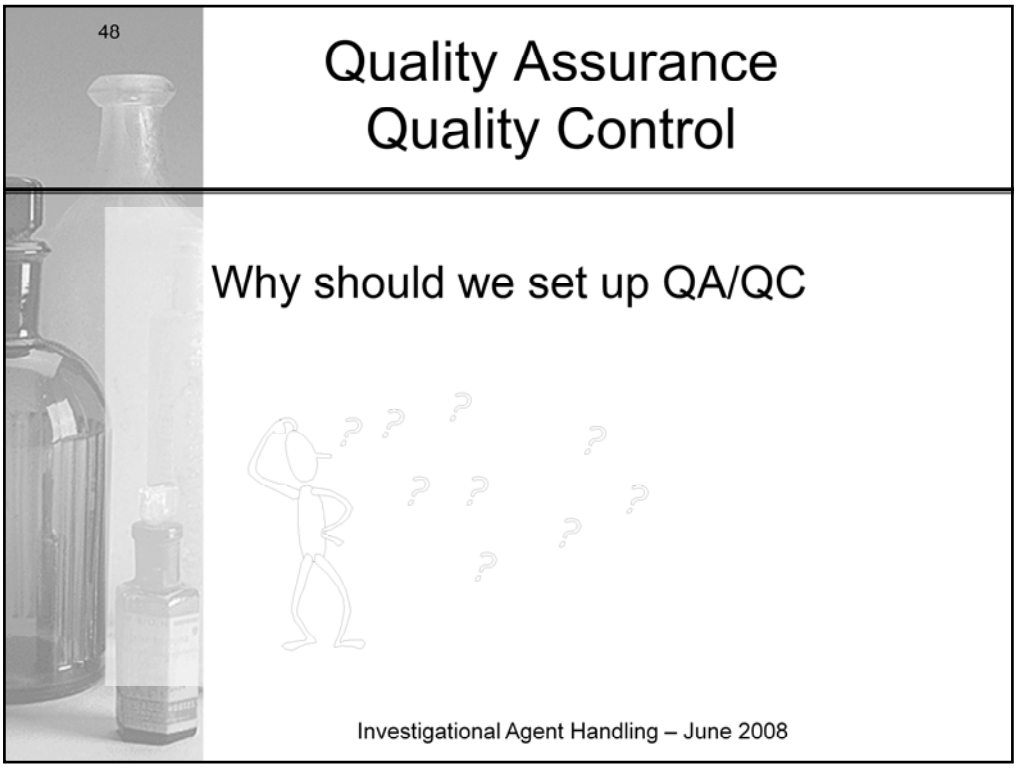
Enclose the Return Drug Form with the returned agents. Keep a copy for your records. Maintain this form, as with all other forms, for 2 years after the IND withdrawal letter designating an actual withdrawal effective date is received by your site. Your records should be readily retrievable.

Package agents securely to prevent breakage. We recommend double bagging to minimize the risk to couriers and the NCI Clinical Repository staff.

Ship all agents at room temperature. Express courier is not required.

The “ship-to” address is located on the form. All shipping costs are the investigator’s responsibility. Collect or COD shipments are not accepted.

Fill out the area on the bottom right of the form if you want a return receipt confirmation.



PMB highly recommends institutions handling investigational agents set up internal systems for QA/QC. Establishing, implementing and maintaining a QA/QC system has been successful in ensuring that NCI policies and procedures for the handling and documentation of investigational agents are being observed.

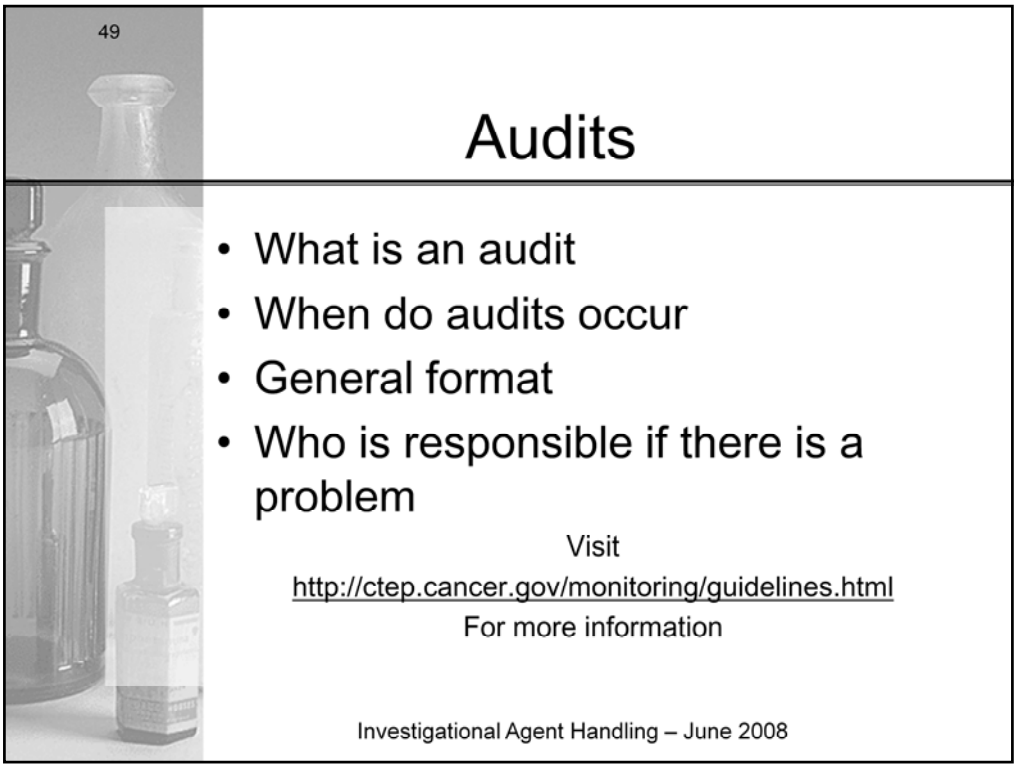
Consider implementing at least four components in your QA/QC program:

•Conduct a monthly inventory of investigational agents at control and satellite locations.

•Maintain a daily refrigerator and freezer temperature log.

•Conduct “mini-audits” of the investigational agent recordkeeping.

•Formally train support staff on the handling of investigational agents.

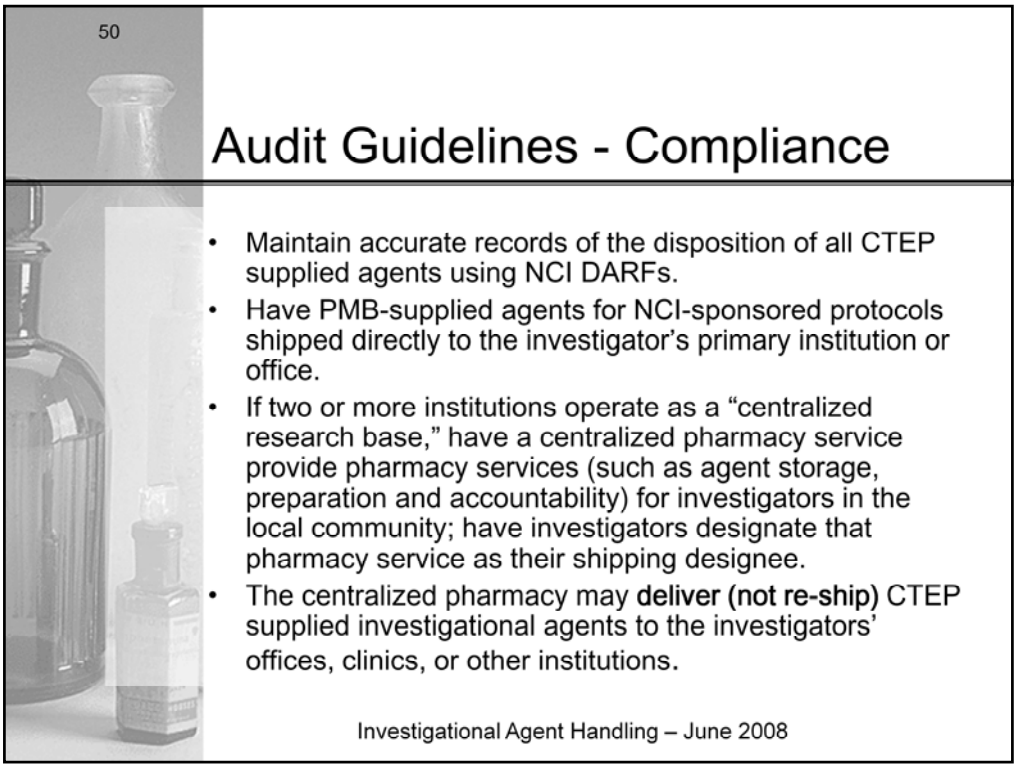


Audits of clinical research are done to ensure that research is being conducted in accordance with federal and state laws, and research affiliation policy and procedures. Oftentimes the audits consist of several components, and the handling of investigational agents is a part of the total audit. You may be asked to submit your records to the person conducting the audit. Alternatively, individuals may physically come to your facility and review your records. The next few slides demonstrate NCI's audit criteria for sites using investigational agents.

Audit timing varies depending on the institution sponsoring the clinical research. All NCI-funded cooperative groups conduct audits of their clinical sites every 3 years.

Most audits consist of the clinical site submitting copies of their receipt and accountability of investigational agents prior to a site visit. These records are reviewed, and then inventories are physically counted during the site visit.

Ultimately, the physician registered as an investigator for the NCI is responsible for investigational agents received under his/her name.



The next seven slides present guidelines that you can use to determine compliance or non-compliance to NCI requirements for investigational agent handling. These criteria may be used by auditors when they are reviewing your records. You can also find these criteria at our web site:

http://ctep.cancer.gov/monitoring/2006_ctmb_guidelines.pdf

Audit Guidelines - Compliance

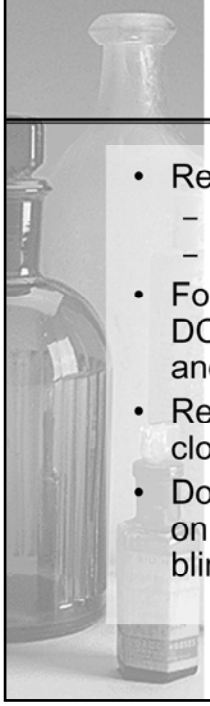
- Dispense, deliver, and account for an individual patient's treatment order or a prescription for a single dose at the treatment site. This eliminates the need for satellite accountability records.
- Maintain satellite accountability records if a physician's office, clinic, or other institution receives a multiple day or overnight storage supply of CTEP-supplied investigational agents.
- Use PMB-supplied agents only for patients entered onto an approved DCTD-sponsored protocol
- Account for each agent separately by protocol

Audit Guidelines - Compliance

- Maintain a separate DARF for an agent used for more than one protocol for each protocol
- Maintain a separate DARF for each agent on multi-agent protocols
- Maintain separate accountability forms for each different strength or dosage form of a particular agent
- If the protocol requires it (double-blinded studies), use a separate DARF for each patient
- Document appropriately on separate lines of the DARF when dispensing agents to multiple patients using multi-dose medication

Audit Guidelines - Compliance

- Maintain a DARF at each location where agents are stored and/or dispensed, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas.
- Retain agent order receipts (Shipment Record of Clinical Drug Request, NIH 986-1) in a readily retrievable fashion.
- Document other agent transactions on the DARF: agent returns, broken vials, etc.
- Have inter-institutional transfer of DCTD investigational agents approved or authorized by PMB
- Ensure that the DARF balance matches actual supply

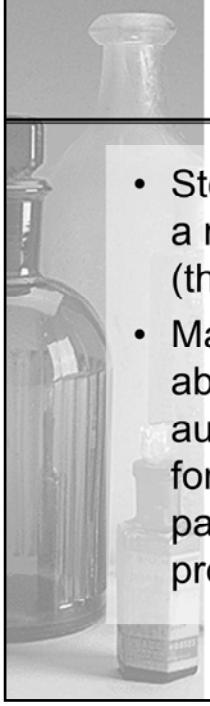


Audit Guidelines - Compliance

- Return to DCTD agents
  - (a) that are outdated; and
  - (b) that are damaged or unfit for use
- For studies that are completed or discontinued, return DCTD agents to the NCI or appropriately transfer to another NCI protocol
- Return PMB-supplied agents within 90 days of study closure
- Do not record patient returns of IND supplied agents on DARFs unless agents are supplied as double blinded

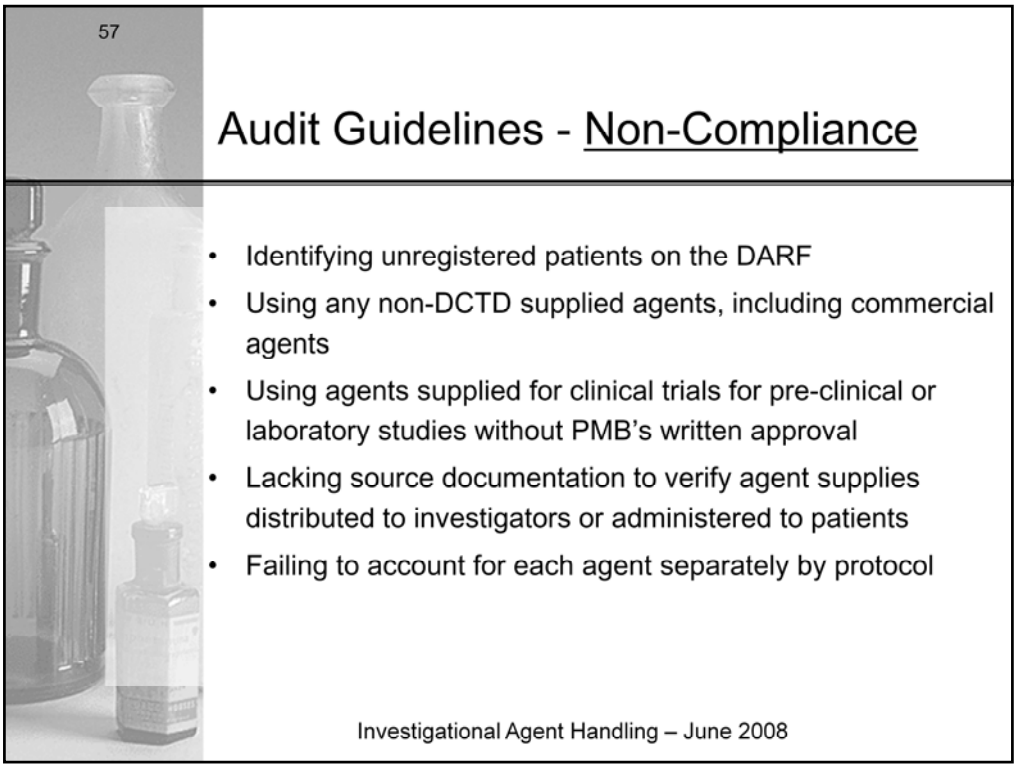
Audit Guidelines - Compliance

- Store each investigational agent separately by protocol
- Store agents used for more than one protocol separately for each protocol
- Store agents under proper conditions (refrigerator, freezer, etc.) with validation documentation



Audit Guidelines - Compliance

- Store agents in areas that can be locked with a minimum number of people having access (the key or combination).
- Make storage areas accessible only to an absolute minimum number of specifically authorized employees. When it is necessary for unauthorized persons to be present in or pass through, an authorized person must provide adequate observation of the area.



The next five slides are examples of Non-compliance to NCI policies for the handling of investigational agents.

Audit Guidelines - Non-Compliance

- Using one DARF for more than one protocol, for a multi-agent protocol, or for multiple strengths or dosage forms of an agent
- Using a single DARF for multiple patients for double blinded study; multiple dose vials recorded for one patient instead of multiple patients; or multiple doses recorded on a single line of the DARF, etc

Audit Guidelines - Non-Compliance

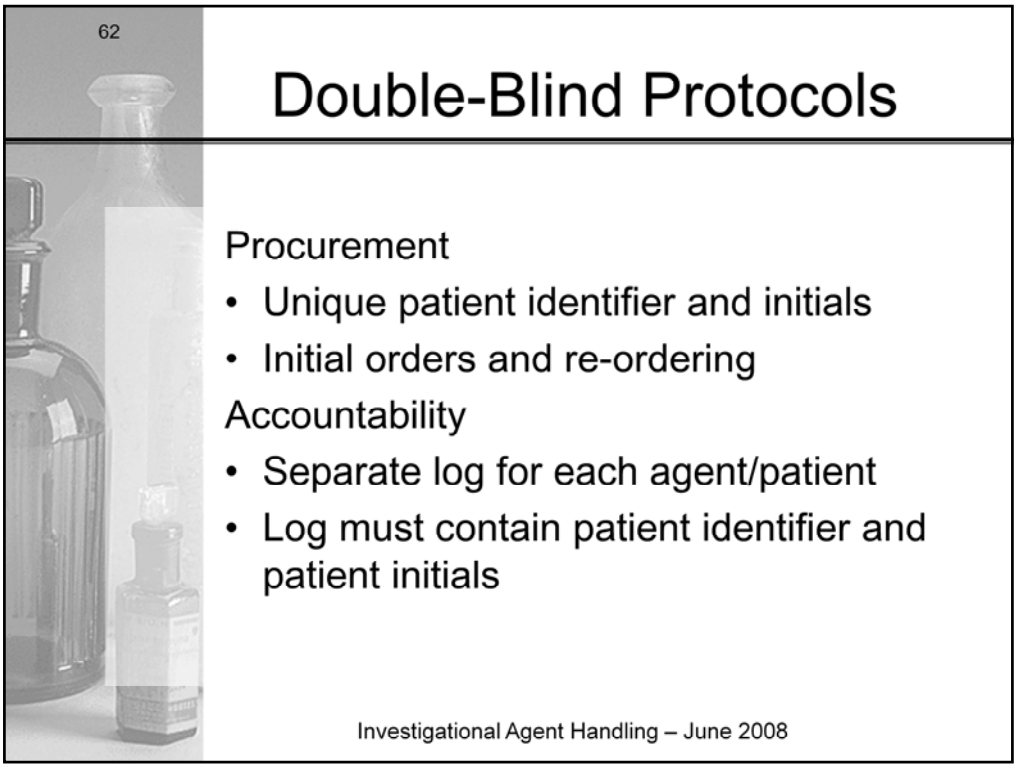
- Failing to maintain satellite and control records accurately
- Allowing discrepant satellite and control records
- Failing to retain agent order receipts (Shipment Record of Clinical Drug Request, NIH 986-1) in a readily retrievable fashion
- Missing documentation of other agent transactions

Audit Guidelines - Non-Compliance

- Borrowing agents
- Failing to use Transfer Investigational Drug Form (NIH-2564) when transferring agent
- Mismatched shelf counts and inventories
- Missing faxed documentation from PMB of approval for agent transfer
- Missing satellite NCI DARF
- Neglecting to return PMB-supplied agent to NCI or to transfer it to an appropriate NCI protocol

Audit Guidelines - Non-Compliance

- Recording patient returns of PMB-supplied agents on the DARF for non-double blinded studies
- Combining agents used for more than one protocol in storage
- Storing agent improperly
- Storing agent in an unsecure dispensing area
- Allowing unauthorized people unsupervised access to a secure area



All orders for double blind protocols are protocol and patient specific.

The PMB will send initial patient-specific order for most protocols to the clinical site automatically once you randomize the patient.

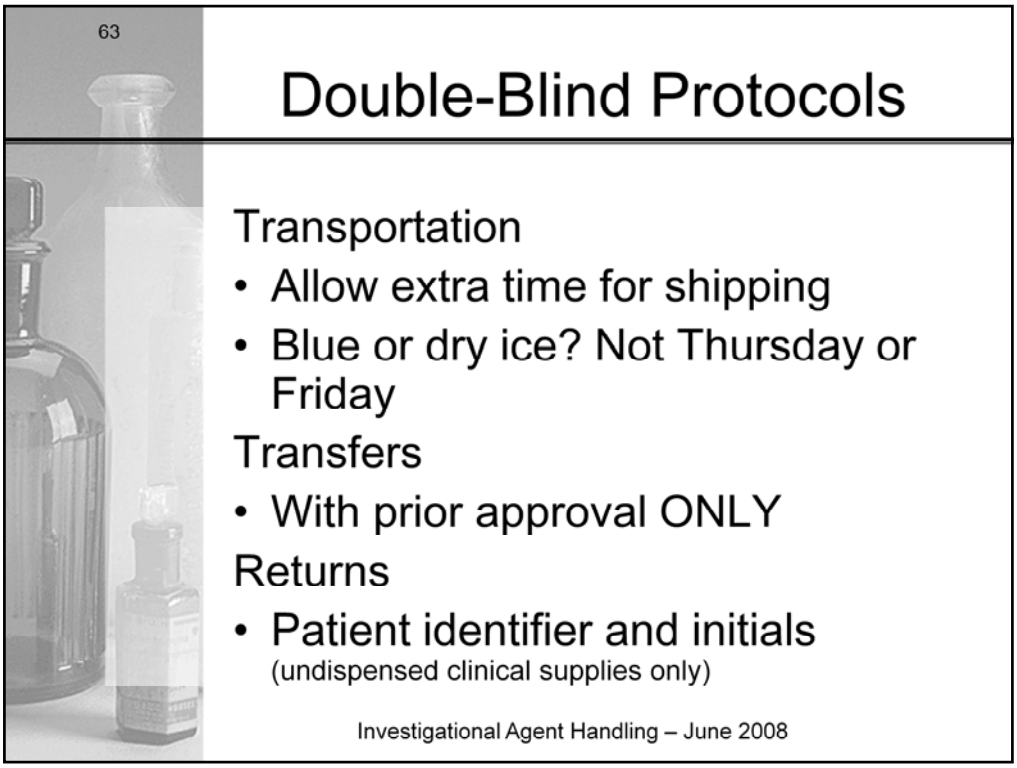
Check your protocol to determine if reorders will be sent automatically OR require you to submit a Clinical Drug Request.

On the CDR, you must indicate the protocol, patient ID, and patient initials. You must also submit reorders under the NCI investigator who registered the patient unless you send and PMB approves a request to transfer the patient to a new NCI investigator.

Maintain a separate DARF for each patient ID on a blinded protocol.

Record the patient ID and patient initials in the upper right corner. Also record receipts, dispensings, returns from patient, destructions, and returns to NCI on the patient-specific DARF.

Always check your protocol. Some protocols have specific accountability procedures.



Because of patient-specific labeling and the extra QC checks, all blinded orders require an extra day to ship. PMB enters all orders received by 1:00 PM Eastern Time on the same day, and ships them the next business day. Do not expect to receive overnight even if you provide an express courier account name and number. It simply cannot be done.

Please remember that shipments sent on blue or dry ice cannot be shipped over the weekend, so an order received Thursday for a refrigerated or frozen item will not be sent until Monday for Tuesday delivery.

Transfers on blinded protocols are allowed only in certain circumstances and require prior approval by PMB before the agent can used.

Return only undispensed agent to the NCI. Record returns from each patient and for each agent as a separate line item on the NCI Return Drug List, but multiple returns of the same agent for the same patient should be a single line item.


Questions?
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