

Analytical Registrants and/ or Analytical Labs Under Manufacturing Registrants

- ◆ Typical Scenario:
 - You work in an analytical laboratory and now your company has started working with controlled substances.
 - What new procedures have to be implemented?
 - What accountability/ records will you be responsible for maintaining?
 - What security issues are involved?
 - Will this be so much work and headache you need another person?
- ◆ What will be the impact on the following key people?
 - Standards Room Supervisor
 - Bench Analyst
 - cGMP Auditor
- ◆ Need to evaluate activity and schedule of CS materials.
 - Will this be a stand-alone analytical registration or done under the umbrella of coincident activity to a manufacturing registration?
 - Is there an existing CS compliance program already in the company?
 - Will there be import/ export of samples to overseas companies?
 - Is the analytical lab part of an existing campus or an isolated operation supporting manufacturing somewhere else?

Analytical Registrants: Standards Room Supervisor

- ◆ Scenario: The standards room is a designated - but not restricted access - area where analysts get columns, reference standards, and samples. Your job includes dispensing materials/ samples and logging projects, as well as inventory. How will CS materials fit into this scheme? You will need to do/ have the following in place:
 - Log books for receipt of CI or CII samples separate from CIII-CV materials and non-CS compounds;
 - Log books for receipt of CIII, CIV, or CV samples (may be combined);
 - Log books for CS reference standards (may all be combined);
 - Restricted access to the CS samples and reference standards (room temperature, refrigerated, and frozen storage)
 - Scheduling sheets for analysts to sign out CS samples/ reference standards
 - Security measures for analytical work that may be unattended for long periods of time
 - SOPs/ procedures for capturing inventory for ARCOS (if the lab operates under a manufacturing registration)
 - Systems for documenting chain-of-custody transfers within the company as it relates to stability, manufacturing, retains, etc.

Analytical Registrants: Standards Room Supervisor (continued)

- ◆ Even though you may be registered to handle $C_I - C_V$ as an analytical lab, it's important to know (1) what quantities of material you can receive and (2) what paperwork is required based on an internal transfer versus shipment from another DEA registrant. Thus, what coincident activities are allowed under an analytical registration? What is not?
- ◆ What can I do under an analytical registration?
 - Manufacture for chemical analytical or instructional activity
 - Distribute for chemical analysis, instructional activity, or research
 - Import/ export for chemical analysis or instructional activity
- ◆ What is outside of my analytical registration?
 - Manufacturing (beyond basic analytical needs)
 - Import/ export for other than analytical or instructional activity
 - Research and/or Instructional Activity
 - Dispensing
 - Narcotic Treatment Program, including compounder

Analytical Registrants: Standards Room Supervisor (continued)

◆ Log Books

- What needs to be recorded and when?
 - Upon receipt, manufacture, or distribution the log book should record:
 - ◆ name,
 - ◆ product form (e.g., powder, granulation, tablet, capsule, solution, etc.)
 - ◆ strength,
 - ◆ quantity (usually expressed as mg anhydrous base),
 - ◆ date received,
 - ◆ name, address, and DEA registration # of supplier,
 - ◆ DEA 222 # if a CI or CII is received from another registrant,
 - ◆ initials of person entering the information, and
 - ◆ NDC code if available (optional).
 - An exception is for drug samples received for evidential analysis
- Do I need separate log books for C_I and/or C_{II} compounds versus the C_{III} through C_V compounds?
 - Yes. Usually, it is organized in the log book by individual compounds -- each new lot having its own page. Some compounds with large numbers of transfers may require a separate book for each compound.
- Should the log book(s) be secured along with the other records?
 - Yes, the log books, unexecuted DEA 222 forms and executed DEA 222 forms -- as well as continuing records -- should have restricted access.

Analytical Registrants: Standards Room Supervisor (continued)

- ◆ Materials have been logged in. Now, how do I track the disposition of materials signed out for analysis? What needs to be recorded and when?
 - The lab must have someone in charge of access to the CS reference standards and samples. This person can sign out the materials for analysis. The information to be recorded is similar to a log book entry (see attached microscheduling sheet on next page):
 - product name,
 - product form (e.g., powder, granulation, tablet, capsule, solution, etc.)
 - number of units or weight/ volume and strength,
 - test being performed,
 - quantity dispensed to analyst
 - analyst initials and date,
 - amount returned (unopened containers),
 - amount returned (opened containers)
 - amount used in testing (calculated),
 - return date and analyst initials, and
 - disposition of any remaining amounts of material.

Analytical Registrants: Standards Room Supervisor (continued)

- ◆ Besides a log record and an analyst sign-out sheet, what other records do I need to keep? For instance, how do I track CS samples going to other sites within the company, such as for destruction? What needs to be recorded and when?
 - You need to have transfer form (e.g., a Controlled Substance Transfer Form) that accompanies samples - a form that provide tracking and audit trail information. The information to be recorded is similar to a log book entry:
 - product name,
 - product form (e.g., powder, granulation, tablet, capsule, solution, etc.)
 - number of units or weight/ volume and strength,
 - quantity,
 - sent by (signature) and date,
 - received by (signature) and date,
 - DEA 222 number (if C_I or C_{II}): NOTE: this transfer form does not substitute for a DEA 222 form.

Analytical Registrants: Standards Room Supervisor (continued)

- ◆ Scenario: The lab is an analytical registrant - separate from the manufacturing registrant across the campus - and routinely gets samples for QC testing. What paperwork needs to be in place for C_{II} compounds - especially with DEA 222 forms required?
 - This is a common problem for campus style facilities with multiple registrations - requiring coordination of sample movement. When transferring a C_{II} compound across registrations, you need a DEA 222 order form properly executed - even when just moving it across a campus facility - or across the hall. It's the same as purchasing from an outside vendor.
 - The problem becomes sticky because the analytical lab is essentially 'purchasing' the C_{II} material from the manufacturing supplier. The lab needs to know how much to 'buy' but the actual sample quantity is only known by the manufacturer. Thus, a **Request for DEA 222 Form** - completed by the manufacturer - allows the lab to identify the quantities needed to complete the form (see next page) and transfer the materials across registrations.

Analytical Registrants: Standards Room Supervisor (continued)

- Scenario: My lab operates under an analytical registration with an address that is different from the cGMP manufacturing registrant. However, all of our campus parcels come through a central shipping/ receiving area at the GMP warehouse. Per the Controlled Substances Act, people can only ship to our lab (registration) address - not the GMP warehouse address, but the parcels can't be delivered here directly without being identified as controlled substances. How do we resolve this?
 - It's a common problem with campus style facilities. You need a signed Memorandum of Understanding from your local DEA office that concurs with this practice. A copy of this letter should accompany your CS purchases so that shippers have something for their files showing they were in compliance shipping to an address other than what's stated on the registration form.

Analytical Registrants: Standards Room Supervisor (continued)

- My lab may perform a CS analysis over more than one shift/ day. How do I account for CS materials logged out during one shift and returned during another?
 - Accountability is best with a documented chain of control or possession. By transferring the material to another analyst without confirming weights, there is the possibility of diversion with more than one person accountable.
 - Sign the (weighed) material in and out to the 1st shift analyst. At the beginning of the second shift, sign out the (weighed) material to the second analyst. Don't worry about in-process samples already diluted in buffers.
 - The second shift analyst can return material to second shift supervisor who may (or may not) have access to CS cage/ cabinet. If not, lock up accordingly until first shift supervisor places it back.

Analytical Registrants: Analyst

- Scenario: I've signed out the materials for analysis. Should all CS work be performed by two analysts for accountability and security purposes?
 - No, DEA investigations have found two people can divert just as effectively as one. At some point, you have to trust the people will do the right thing. The systems are in place to ensure that loss/ diversion is quickly discovered. However, that's no insurance against all diversion. Sometimes, a Draconian approach can be counter-productive.

Analytical Registrants: Analyst (continued)

- Must the lab data from the CS analysis be kept in separate lab notebooks too?
 - No, the actual CS sample analytical data can be combined in lab notebooks with non-CS material analyses. Sometimes the lab notebooks refer back to a specific log book note or sign-out sheet, which allows greater tracing of the samples.

Analytical Registrants: Analyst (continued)

- What are some common compliance problems that analysts can avoid?
 - When signing CS samples/ reference standards in and out from the lab supervisor/ scheduling room, it's best to **do quick confirmatory weight checks of the gross container and if possible, witnessed weighing of the sample amounts you need** - then return the vials to the supervisor.
 - **Do not destroy excess or leftover CS materials by combining with hazardous waste.** With the exception of the material that is absolutely needed for the analytical preparation, don't take the remaining grinds/ tablets and dispose of them without some form of witnessed destruction (if allowed by DEA).
 - **Do not accept rush samples from manufacturing, QA, or other people outside of the normal pattern of paperwork.** If working for a contract lab, do not readily accept mailed samples - especially CI or CII compounds that may not have a DEA 222 in place.
 - **Do not leave readily identifiable CS materials/ standards lying about and then go to lunch.** Would you leave \$300 on the lab table and expect it to still be there when you return? Secure them in a desk drawer.
 - **Do not mail any CS samples or reference standards directly to other company departments/ individuals.**

Analytical Registrants: Analyst (continued)

- I work as an analyst in a lab for a List I/ II manufacturer. What are the compliance aspects of this registration type vs. controlled substances?
 - Registration is spelled out in Part 1309 for List I/ II manufacturers, distributors, importers, and exporters. Note that per a proposed rule, some firms that perform these same activities with chemical mixtures containing List I/ II chemicals may be required to maintain certain recordkeeping - unless exempted.
 - Security requirements are also noted in Part 1309 but not as much detail as for controlled substances. Acceptable methods include restricted access by locked storage and tamper-evident seals.
 - Analytical security is not specified, but it's apparent that DEA feels these materials are ripe for diversion. Using some of the same accountability practices outlined for handling CS materials will ensure proper safeguards.

Analytical Registrants: Security

- ◆ My company/ lab has never worked with CS before. What security systems are required?
 - Analytical lab security requirements are same as for a practitioner -- even when those labs registered under a non-practitioner (e.g., manufacturer). Security system requirements are outlined in 21 CFR 1301.75.
 - Securely locked, substantially constructed cabinet (e.g., a file cabinet with lock, but not desk drawer). Could also be a combination safe available at office supply or home improvement stores.
 - Carfentanil, etorphine HCl, or diprenorphine (C_I) must be stored in a Class V safe
 - Employee screening (recommended for non-practitioners)
 - SOPs for handling with limited access and detection of loss/ diversion

Analytical Registrants: Security (continued)

- My lab does analysis for both CS and non-CS materials in the same area. Do I need to isolate or restrict the CS area when analysis is going on?
 - No. The DEA does not specify or require a lab to have the same the level of restriction as a manufacturing environment -- presumably because of the small quantities. However, general controls still do apply, such as limited access, systems to detect diversion/ loss, etc. Accountability is best with a documented chain of control or possession.

Analytical Registrants: Security (continued)

- My lab stores CS samples in both refrigerators and freezers with non-CS materials. What kind of security is required for this situation? Do I need to lock and alarm the units?
 - An alarm is not required. A lot of upright and walk-in refrigeration/ freezer units have locks that make it easier for limited access. If the units do not have locks, consider placing a locking box/ file cabinet within the larger unit and restricting access that way. Be sure to fasten the box/ cabinet in some fashion.
 - Still need to do a log-in/ log-out of the samples to individual analysts (see recordkeeping section for data to collect).

Analytical Registrants: Security (continued)

- ◆ If the CS safe is on a lab bench top, does the area need to be enclosed?
 - No, but the safe/ cabinet should be securely fastened so it's not easily removed. This is applying the same security measures for non-practitioners to a practitioner registrant (see Part 1301.72(a)(1)(iii)). Although the regulation is intended for CI/ CII compounds, it can be easily applied for all schedules in the practitioner surrounding.
- ◆ How should diluted in-process samples be handled? Should they be locked up and an accountability check at the beginning of every shift?
 - When analytical samples are mixed/ diluted with organic buffers for HPLC or other methods, the contamination with hazardous waste usually eliminates them from being abused (see Destruction Practices). One should consider greater care in handling samples diluted in physiologic buffers (which can be taken via oral, inhalation, or intravenous routes). Accountability checks for each shift should only cover the undiluted powder or solutions that are returned by the analyst.

Analytical Registrants: Security (continued)

- Is hazardous waste -- that contains trace quantities of CS -- required to be stored under the same security conditions as the CS schedule in it?
 - No. Per discussions with DEA, the hazardous waste from a lab environment contains lots of toxic compounds which renders the material from being abused and "destroyed." Thus, hazardous waste containing small amounts can be disposed of through the HAZMAT programs for the facility (see Destruction Practices).
 - However, manufacturing registrants may have large quantities of both CS materials and/or desired List I/II chemicals in a single solvent system, which may offer potential for diversion through purification methods. Thus, those quantities are often stored and handled as CS hazardous waste - according to the CS schedule of the materials - and only shipped to DEA-registered hazardous waste disposal facilities.

Analytical Registrants: Security (continued)

- ◆ What kind of personnel screening should my company perform?
 - Employee screening is recommended for non-practitioners (21 CFR 1301.90), but is usually done for practitioners too (e.g., analytical labs). These include:
 - screening all employees with access to CS;
 - background checks for: (1) conviction of a felony in the last five years, (2) conviction of a misdemeanor in the last two years, or (3) presently formally charged with a criminal offense (written authorization from employee needed); and
 - queries regarding illegal use of narcotics, amphetamines, or barbituates.
 - Drug screening (initial, annual, and/or random) -- while specifically recommended in the CSA -- is common practice in the pharmaceutical industry.
 - There are liabilities in how "random" and "uniformly" some tests are applied. When "probable cause" is a mitigating factor for drug testing, the extent of required evidence -- and how equally it's applied -- can become a potential landmine.

Analytical Registrants: Security (continued)

- ◆ What are some common personnel security issues?
 - How should contractors and security system personnel be handled in the CS areas?
 - If there is construction activity in the lab, you shouldn't be doing any testing -- CS or not. However, most analytical samples are "blinded" to an outside observer just by the alpha-numerical systems used to track the samples. It's unlikely someone could know the contents of the sample without it being labelled as such.
 - Handle/ secure reference standards or marketed products with appropriate care.
 - Security system personnel are usually bonded and have background checks. Although they may have access to certain security codes/ systems, they are missing company passkeys and lab door locks.
 - In a manufacturing environment, the level of security and access is completely different.
 - An employee is convicted of DUI and this person has access to CS. Should they be removed from working with CS?
 - The answer is ?
 - An employee is convicted of a narcotics offense. Although they don't have access to CS, they do work in the same building. Should they be transferred to another building? Fired?
 - The answer is ?

Analytical Registrants: Security (continued)

- ◆ What are some more common personnel security issues?
 - During an investigation of a loss/ diversion, an employee failed to report the finding. Should this person be removed from working with CS?
 - The answer is ?
 - An employee is suspected of involvement in a loss/ diversion but refuses to submit to drug screening. Can this employee be fired?
 - The answer is ... ?

Analytical Registrants: Disposal/ Destruction

- ◆ Destruction Practices - Regulatory Requirements and Limits of Recordkeeping (Part 1307.21)
 - All CS that is destroyed must be recorded on DEA 41 Form
 - Records are held for two years (at registrant site or central recordkeeping site)
 - CS destroyed in analytical testing is exempt from recordkeeping requirements
 - Destruction records include:
 - generic compound name,
 - trade name (if applicable),
 - NDC code (if applicable)
 - quantity,
 - form,
 - purity,
 - date, and
 - name, address, and registration number of site.
 - Destruction records for C_I and C_{II} compounds should be kept separate from destruction records for $C_{III} - C_V$

Analytical Registrants: Disposal/ Destruction (continued)

◆ On-site Destruction

- Can only be performed with prior approval from DEA
- Generally, very rare since destruction can be a significant avenue for diversion of CS and/or solvents
- May be allowed for destruction of C_{III} - C_V samples from formulation studies, but depends on regional differences
- May be accomplished through (1) combination with hazardous waste material already on site or (2) pouring into a chemical treatment pond/ system.
- SOP should be the same as for off-site destruction:
 - collect and inventory materials to be destroyed,
 - notify local DEA office with draft DEA 41 form,
 - schedule destruction,
 - perform destruction on that date,
 - send finalized DEA 41 form to local DEA office for their records.

Analytical Registrants: Disposal/ Destruction (continued)

◆ Off-site Destruction

- Standard industry practice is off-site destruction by incineration and may be done 3 different ways:
 - DEA/ State officer will visit registrant site and confirm CS weights and accompany Sponsor to incinerator to witness destruction.
 - Sponsor notifies DEA/ State officers of target destruction date with draft DEA 41 form completed; sponsor does independent handling of materials and go to incinerator on specific date (no DEA/ State witness)
 - ◆ Notify DEA/ State officers of destruction date with 1-month notice
 - ◆ Specify what materials will be destroyed on a draft DEA 41 Form
 - ◆ DEA may or may not witness destruction; FAX/ mail completed signed off DEA 41 form to officials after destruction
 - Transfer materials to 'reverse distributors' or a HAZMAT incineration facilities also registered with DEA. No DEA 41 form, just "transferred" material (e.g., DEA 222) and let them handle on their records accordingly.

Analytical Registrants: Disposal/ Destruction (continued)

■ Reverse Distributors

The following facilities are registered with DEA for destruction of CS materials:

- BFI Pharmaceutical Services (Conyers, GA) (404) 785-9710
- Capital Returns, Inc. (Milwaukee, WI) (800) 950-5479
(414) 527-9912
- Easy Return Midwest, Inc., d.b.a.
Reverse Management Systems (Center, TX) (800) 797-3837
- Guaranteed Returns, d.b.a.
Devos, Ltd. (East Setauket, NY) (800) 473-2138
- Pharmaceutical Recovery Services, Inc.
(Winter Park, FL) (407) 679-3400
- Reverse Distribution Services, Ltd. (Fort Worth, TX) (817) 868-5300
- SAI Transport (Lakeland, FL) (813) 858-7110

Analytical Registrants: Disposal/ Destruction (continued)

- ◆ Witnesses, DEA 41 Forms, and Other Points to Consider
 - Destruction should be witnessed by two people from company, at least one from management.
 - If there are inventory discrepancies, delay the destruction until those have been reconciled.
 - For C_{III} - C_V bulk tablets, actual tablet count is not necessary -- can approximate using same practices as for inventory. Weigh 100 tablets for an average tablet weight. Approximate number of tablets based on total weight divided by average tablet weight.
 - For C_{III} - C_V powder/ solutions, exact weights can be determined.
 - For C_I and C_{II} materials, exact tablet count is required.
 - For CS materials subjected to microbiological testing (e.g., APE testing, MLT, etc.), may be destroyed by autoclaving as routine biohazardous waste. No DEA 41 Form required for these samples, since entire sample is destroyed by analytical procedure.

Analytical Registrants: cGMP Auditor

◆ Recordkeeping

- Recordkeeping is critical and evaluated by DEA as a primary area of non-compliance area with CSA for:
 - preparation and maintenance of records
 - taking of inventories
 - filing reports
- Requirements vary for each registrant type and activity:
 - separate records and reports for each location
 - separate records and reports for each type of activity at the same location
 - coincident activity records and reports may be combined
 - separate records for C_I and C_{II} from other CS records
- Records are retained for a minimum of two years, but some states require 5 years. Some List I/II chemical import/ export records are 5 years.
- Records must be kept at actual site or a DEA-authorized central recordkeeping site.
- Exemptions allowed for practitioners (dispensing) and research and training

Analytical Registrants: cGMP Auditor (continued)

◆ General Considerations

- Central recordkeeping is:
 - allowed for financial and shipping records only
 - executed orders forms, prescriptions, inventories, etc. kept at each location unless exempted under 1307.03
 - must notify DEA by registered/certified mail of location, name/address, registration #, type of registration, records type, and manual vs. computer readable systems
 - may begin centralized records system in 14 days after notifying DEA (unless otherwise denied)
 - special equipment or access codes available to DEA
 - must deliver records to registered site within two working days after DEA written notification or allow DEA to inspect at central location without warrant
- DEA may revoke centralized system for non-compliance
- ARCOS centralized recordkeeping also requires notification

Analytical Registrants: cGMP Auditor (continued)

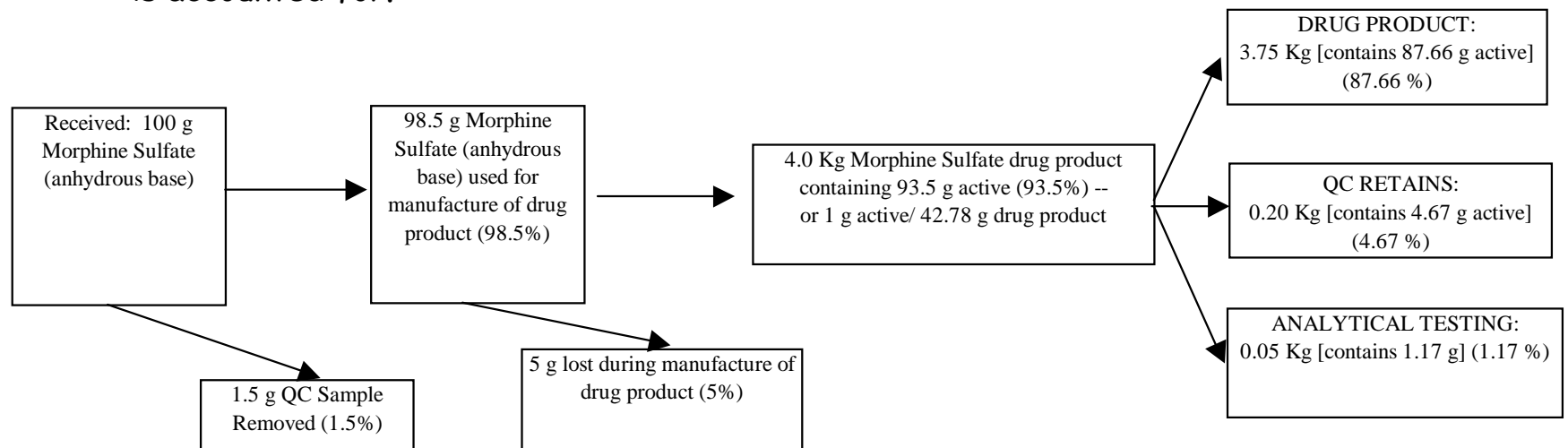
◆ Continuing Records: Cradle-to-Grave

■ What are continuing records? What is recorded and when?

- Continuing records are body of company documents that comprise "a complete and accurate record of each substance manufactured, imported, received, sold, delivered, exported, or otherwise disposed of by [the registrant]." They are completed on a real time basis.

■ What is cradle-to-grave in terms of DEA compliance?

- The registrant should have virtual accountability of all product from receipt through destruction. Although DEA does not require (or state) a "cradle-to-grave concept" in the records, it is implied. This approach is a useful internal audit tool to ensure that all product is accounted for.



Analytical Registrants: cGMP Auditor (continued)

- ◆ Inventories (Part 1304.11)
 - What needs to be recorded and when?
 - A complete and accurate inventory of everything “on hand” = under the registrant’s control (e.g., warehouse, CS ordered by customer but not invoiced). Requirements vary considerably for registrant type.
 - Key inventory dates include:
 - ◆ initial [done on date activity starts, not registration date or application date];
 - ◆ biennial [done on second anniversary of initial inventory]; REVISED per CSA rewrite -- just within 2 years of last inventory.
 - ◆ 4-day grace period [allowed around biennial inventory]; DELETED
 - ◆ 6-month variance [allowed for moving inventory date to coincide with other company inventories] -- but no more than a total of 24 months from last inventory; DELETED
 - ◆ open or close-of-business day notation required for when inventory was done;
 - Coincident activity does not require separate inventories.
 - Do I need to notify DEA of when I change an inventory date?
 - Yes under old regs. REVISED. Now, no more.
 - Do I send DEA copies of my initial/ biennial inventories?
 - No, they are kept on file at the registrant site.

Analytical Registrants: cGMP Auditor (continued)

◆ Inventories

- What needs to be included in analytical registrant inventory?
 - Analytical registrants have very lax inventory requirements compared to manufacturers. They do not need to record:
 - ◆ any quantity of LSD less than 0.5 g,
 - ◆ any quantity of a hallucinogenic C_I less than 20 g, or
 - ◆ any quantity of any other CS less than 1.0 Kg.
 - Be sure to include warehouse quantities for any CS stored under an analytical registrant.
- If my analytical lab is under a manufacturer registrant, do the above analytical cut-offs apply?
 - No, the lab inventory is then considered part of the manufacturing registrant's inventory (e.g., QC samples/ retains)

Analytical Registrants: cGMP Auditor (continued)

◆ Inventories

- What happens if I discover an unaccountable loss in the inventory versus my audit records?
 - Inventory variations (due to weighing variability) or unaccountable losses (from reconciliation calculations) discovered during an inventory should not be filed on a DEA 106 form. This form should be restricted for use of suspected loss/diversion.
 - However, if the inventory discrepancy does reveal significant quantities missing that suggest loss/ diversion, you should fill out the DEA 106 per corporate SOPs.
 - Need to provide a copy of DEA 106 to the regional DEA administrator as soon as possible (e.g., not more than one week). Don't wait for a conclusion to the investigation before sending DEA the form; the report can be amended later.
 - Also may need to contact local authorities to begin an investigation per corporate policy.

Analytical Registrants: cGMP Auditor (continued)

◆ Inventories

- Where do I keep the inventory records for a warehouse?
 - If the warehouse is exclusively for the analytical registrant, records are kept at the analytical registrant site. If the warehouse has shared distribution activities, there may be a need to separate inventories (and registrations).
- How do I handle an inventory for a compound that was recently scheduled or rescheduled?
 - The notice of CS scheduling/ rescheduling of a compound will be published in the Federal Register. The effective date of that scheduling should be the date an initial inventory is taken (see Part 1304.11(d)).

Analytical Registrants: Summary of Key Points

- CS management is a combination of physical security, diligent and current recordkeeping, and personnel training.
- Compliance problems arise when SOPs are poorly written (not specific enough) and there are inconsistencies from handling of one department versus another.
- DEA relationships can be strained with poor in-house accountability practices and/ or a history of loss/ diversion without adequate notification or follow-up.
- Analytical labs have lots of activity - often accompanied by poor control over access to materials - and without consistent application of security features, materials will eventually end up missing/ stolen.
- Security features are designed to protect against outside intrusion and inside/ employee theft.