



Manufacturer Registrants: Overview

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Manufacturer Registrants: Registration

- ◆ **Coincident Activities under a Manufacturing Registration**
 - What can I do under a manufacturing registration?
 - Distribute (for those substances and/or classes covered under registration)
 - **Conduct** chemical analysis (only for registered substances)
 - Preclinical research (only for registered substances)
 - What is outside of a manufacturing registration?
 - Import/ export
 - Clinical research
 - Dispensing
 - Narcotic Treatment Program, including compounder

Manufacturer Registrants: Registration

- ◆ Change in Registration Due to Change in Schedules
 - My facility was a C_{III} - C_V repackager/ relabeller, but now is moving into C_{II} manufacturing. What needs to be done to accomplish this? How long will this take?
 - First off, get your facility in shape to withstand a scrutinizing inspection by DEA (e.g., physical systems, personnel, handling SOPs, destruction, etc.). Finalize as much as time will allow before contacting DEA.
 - Will also need to provide DEA with an information packet that summarizes facility design, security systems, and general aspects of handling materials.
 - Notify the DEA regional office and State representatives of your intention to manufacture C_{II} finished dosage forms and request an inspection of your upgraded security system. Provide copy of information packet.
 - DEA will come out and inspect systems. Turnaround time varies, but it can be within a few weeks. They will schedule visit.
 - DEA inspects facility. If OK, DEA regional office will give 'pass' to DEA registration office which can then receive an upgraded registration DEA 225 or 225A (if close to re-registration).
 - If systems need work, fix and DEA may be back to physically inspect again.
 - Once registration certificate is in hand, apply for procurement quotas to manufacture C_{II} finished dosage forms. Turnaround time is about 4-6 weeks.

Manufacturer Registrants: Registration

◆ Change in Registration

- My company has changed names (legal entity).
 - A change in the legal entity holding the registration = a new registration.
- My lab has changed its physical address, but it still performs the same activities with the same CS schedules.
 - Notify the regional DEA office and State representatives to confirm whether a new inspection is required. If not, a change of address can be handled through DEA registration office at time of change-over. Complete DEA 225A form with new address.
- My lab is now covered under the coincident activities of another registrant. It still performs the same activities with the same CS schedules.
 - Notify the regional DEA office and State representatives of the termination of the analytical registration and inclusion under another registrant coincident to that activity.
 - DEA and/ or State representatives may inspect the lab again as part of the inspection for a manufacturing facility.
- My lab now includes a warehouse that holds samples for our stability program.
 - Warehouses are excluded from registration when they are not involved in distribution. Otherwise, the warehouse may require separate registration.

Manufacturer Registrants: Registration

- ◆ **How do I handle lapses in my registration when I need to receive/ ship CS ?**

Some vendors/ clients will accept copies of the complete re-registration form with the promise (in writing) to provide a copy of the new registration form. Other vendors -- like USP -- do not observe this common practice and it's best to store up reference standards, samples prior to expiration date.

Manufacturer Registrants: Security

◆ Physical Requirements

- My facility has never manufactured CS before and now needs to register for $C_{III} - C_V$. What security systems needs are required?
 - The facility's security system needs to be in compliance with 21 CFR 1301.72(b) which is:
 - ◆ a safe or steel cabinet as detailed in 21 CFR 1301.72(a) or
 - ◆ a vault with an alarm system as detailed in 21 CFR 1301.72(a) or
 - ◆ a building with:
 - perimeter security during working hours,
 - an alarm system,
 - self-closing, self-locking doors,
 - an enclosed cage within the building constructed of not less than # 10 gauge steel fabric (mesh fencing) on steel posts (1" diameter minimum) set in concrete with lay bolts (pinned or brazed) with mesh openings not more than 2.5" wide and securely attached to the ceiling of the building (lighter gauge steel mesh is OK when the ceilings are at least 14' tall), with an alarm system, or
 - ◆ a masonry enclosure with comparable security
- My facility needs multiple storage areas to accommodate different needs. Do they all have to meet the same security criteria?
 - Yes.



Manufacturer Registrants: Security

◆ Physical Requirements

- My facility has only handled $C_{III} - C_V$ before and now needs to register for C_{II} .
What additional security systems needs are required?
 - The facility's security system needs to be in compliance with 21 CFR 1301.72(a) which notes:
 - ◆ a safe (Class V) or steel cabinet
 - rated against 30 man-minutes against surreptitious entry, 10 man-minutes against forced entry, 20 man-hours against lock manipulation, and 20 man-hours against radiological techniques;
 - if less than 750 lbs, is bolted or cemented to the floor;
 - motion detector; and
 - alarmed with a signal directly to a central protection company.
 - or
 - ◆ a vault with
 - walls, floor, and ceiling at least 8" thick of reinforced concrete with 1/2" steel rods (rebar);
 - a door conforming to the same anti-manipulation requirements as for a Class V safe and equipped with contact switches;
 - a self-closing, self-locking door for vaults that remain open;
 - motion detector; and
 - alarmed with a signal directly to a central protection company.



Manufacturer Registrants: Security

◆ Physical Requirements

- Can I store CS and non-CS materials in the same area?
 - Yes, but only with prior permission from the DEA regional office. The registrant needs written authorization from DEA that the non-segregated storage does not diminish security effectiveness.
- What about security of CS material during manufacturing or in-process stages?
 - Security controls (for all CS schedules) are outlined in 21 CFR 1301.73 which include:
 - ◆ in-process materials are returned to the storage area at the end of a process, but where processes may last longer than one day, the processing area is secured including tanks, vessels, bins, or other containers, and the entire area is alarmed (e.g., with portable motion detector) and
 - ◆ manufacturing areas are clearly defined with limited access and under the surveillance of a designated employee or employees.

Manufacturer Registrants: Personnel Requirements

◆ Access

- Who should have access? How many are OK?
 - Access should be kept to an absolute minimum of specifically authorized employees. The number with access depends on a number of considerations including:
 - ◆ the number of manufacturing shifts;
 - ◆ should each shift supervisor have access or only the day shift supervisor;
 - ◆ should any management personnel have access when it's unlikely they will ever open up the cage/ room; and
 - ◆ how will CS be handled by materials management personnel versus manufacturing (shared control vs hand-off).

Manufacturer Registrants: Personnel Requirements

◆ Screening

- What additional employee screening/ safeguards should be done for employees with access?
 - Depending on what firms have already done for initial hiring, there may not be much new testing. Instead, some companies may repeat drug screening on an annual or random basis.
 - Some firms may only collect more specific information about those employees and these data sheets are made available to DEA upon request.



Manufacturer Registrants: Detection of Loss/ Diversion

◆ Detection Methods

■ What methods are used to minimize loss/ diversion?

• Some firms:

- ◆ use pocket-less uniforms,
- ◆ observers during manufacturing operations
- ◆ use clear bags for handling materials and samples,
- ◆ inspect all handbags and suitcases/ valises of departing employees after every shift,
- ◆ do random inspections of lockers,
- ◆ do random in-depth accountability for specific operations and investigations of unaccountable losses exceeding manufacturing history/ trend analyses,
- ◆ do audits of systems on a routine, but random basis,
- ◆ change lock combinations when key employees leave,
- ◆ use card in/ card out systems,
- ◆ use eye scan or optical recognition devices for restricted access, and/ or
- ◆ videotape manufacturing operations (compounding and packaging), monitor movement of materials and trash area (since some employees will slap revised labels on active to move it into trash area).

Manufacturer Registrants: Recordkeeping

◆ Power of Attorney/ Power of Revocation

■ Who can be a POA and what are the responsibilities?

- POAs are authorized by the DEA Registrant (for that site or company) to sign DEA 222 forms. They may often have other CS site responsibilities, but those are not conferred by any POA letter -- company by company decision for those. Some key features of POA letters are:
 - POA letter is witnessed by two people, but does not need to be notarized.
 - More than one person can be designated as POA.
 - POA may be designated even if they are not at the registrant site, but forms must be on site -- except for central recordkeeping situations.
 - Copy of POA must be on site
 - POA is not submitted to DEA
 - POA may be revoked at any time by registrant via revocation notice
 - POA expires when registrant ceases legal existence or registration expires
 - A POA cannot authorize another person as POA; only comes from the DEA Registrant for site/ company.



Manufacturer Registrants: Recordkeeping

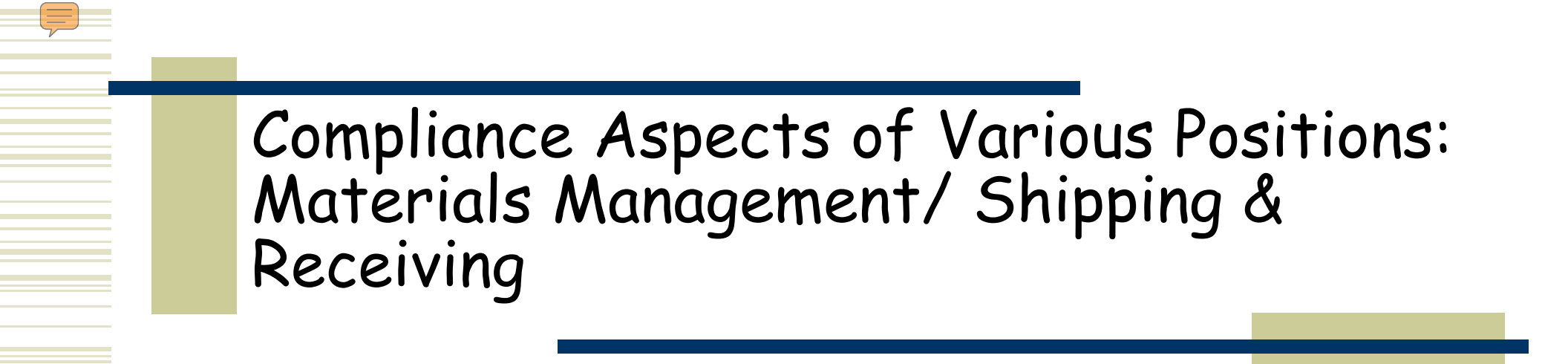
◆ Other Reports: List I/ II Chemicals and Manufacturing Equipment

- My firm is an end-user of a number of List I and/or II chemicals. We often exceed the threshold amounts noted (see attached table) for domestic brokers. Do I need to report anything? If so, what and when?
 - As an end user of List I and/or II chemicals, you do not have to file any reports. If you were a manufacturer, distributor, or domestic/ international broker, you would need to register.
 - Note that if you produce a product that contains a List I or II chemical beyond the current threshold for reporting purposes (see legislation overview), then you may have additional reporting/ registration requirements.
- My facility just received a Courtoy tablet press from another facility (in the same company) that was shut down/ phased out. What do I need to inform DEA and how long do I keep these records?
 - If your firm purchased (or sold) this tablet press from (or to) another company, you would need to notify the DEA regional office of this acquisition and you would need to retain the records for five years. Because this is a transfer from within the same company, the transaction is exempt. However, some firms have applied this (DEA notification) standard to tablet/ encapsulation machines acquired from outside their own DEA region -- regardless of whether it came from within the same company or not.



Manufacturer Registrants: Destruction Practices

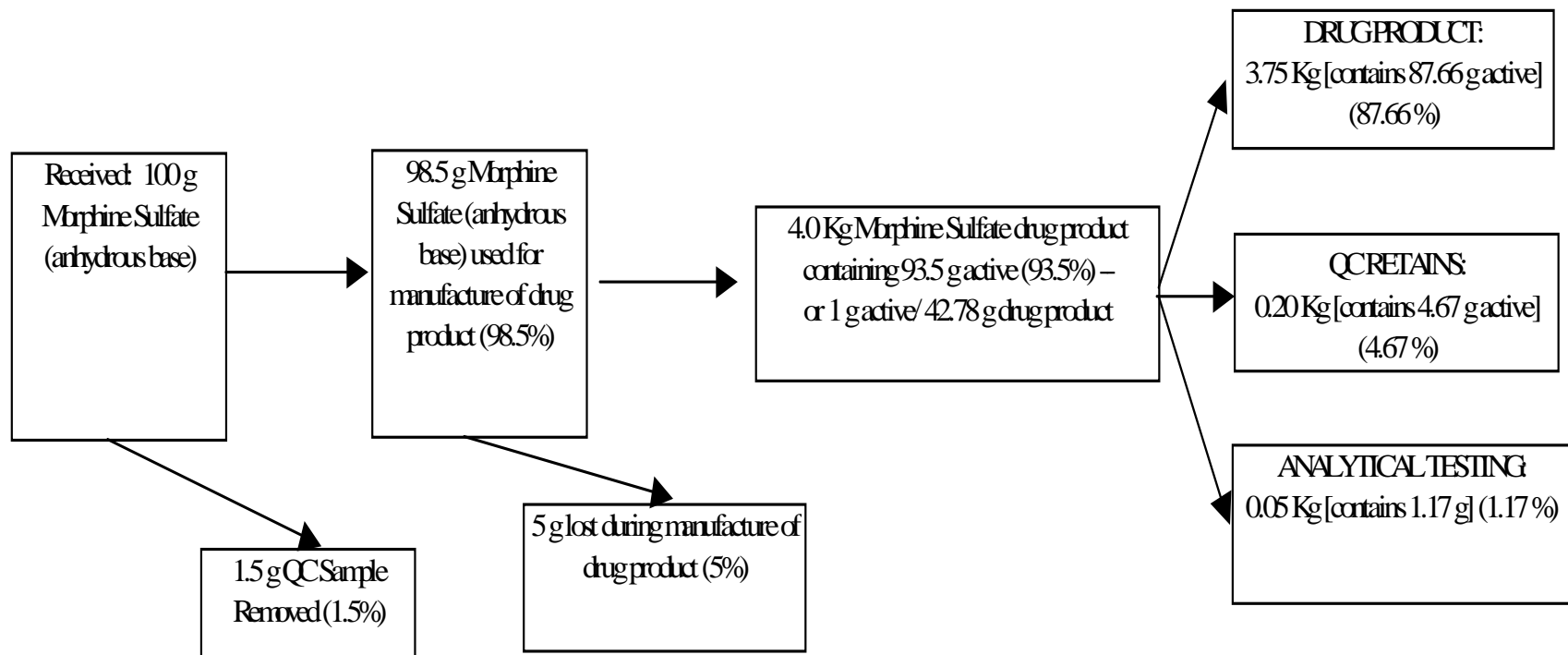
- ◆ **Pharmaceutical versus CS Waste: Types of Materials for Witnessed Destruction and Other Points to Consider**
 - What materials should be considered as pharmaceutical waste?
 - filters (liquid and air)
 - gloves
 - masks
 - gowns
 - paper products used in cleaning equipment/ rooms
 - What materials should be considered as CS waste?
 - bulk drug substance
 - bulk granulation
 - tablets, capsules, gelatin caps, etc. (finished dosage forms marked as reject, retains, set-up, etc.)
 - excess finished dosage forms from packaging runs
 - packaged product (e.g., rejects, retains, set-up)
 - finished product (e.g., rejected, returned, or recalled/ expired product)
 - vacuum cleaner bags from production rooms



Compliance Aspects of Various Positions: Materials Management/ Shipping & Receiving

- ◆ **Scenario:** You work in a cGMP facility and are responsible for handling materials from receipt to dispensing for manufacturing. Your job also includes recordkeeping for the CS cage/ vault.
 - You will need to do/ have the following in place:
 - Procedures for inspection and acceptance of CS materials from shippers/ couriers to verify quantities
 - Records for the receipt of raw materials and assignment of tracking code numbers for manufacture
 - Log books for receipt of CI or CII compounds; separate log books for CIII, CIV, or CV compounds (may be combined)
 - CS cage access log that notes who, when, and why entered the cage.
 - Procedures/ forms for reconciliation of empty containers/ depleted lots.
 - Procedures/ forms for continuing records/ chain of custody to transfer materials to analytical, stability, and distribution areas.
 - Procedures/ forms for capturing inventory relating to ARCOS reports
 - Procedures for investigating and rectifying lots with poor reconciliation

Materials Management/ Shipping & Receiving (continued)





Compliance Aspects of Various Positions: Batch/ Line Operator

- ◆ **Scenario:** You are trained for a variety of manufacturing processes such as, blending, tableting, encapsulation, coating, and packaging operations. You will handle materials from receipt to final reconciliation and return to CS storage. Your job also includes batch recordkeeping.
 - You will need to do/ have the following in place:
 - Procedures for inspection and acceptance of CS materials from the Materials Management group to verify quantities
 - Records for the receipt of raw materials and assignment of tracking code numbers for manufacture
 - Initial log books for receipt of CI or CII compounds; separate log books for CIII, CIV, or CV compounds (may be combined)
 - Initial/ sign CS cage access log
 - Assist in reconciliation of empty containers/ depleted lots.
 - Assist in completion of forms for continuing records/ chain of custody to transfer materials to analytical, stability, and distribution areas.
 - Assist in capturing inventory relating to ARCOS reports
 - Assist QA investigations of lots with poor reconciliation



Compliance Aspects of Various Positions: QA/ DEA-Authorized Observer

- ◆ **Scenario:** You are the designated QA/ DEA-authorized observer. You will be responsible for assuring manufacturing operations are not left unattended to the point of diversion or loss of compound. You will observe materials from receipt to final reconciliation and return to CS storage. Your job also includes oversight of accurate batch recordkeeping.
 - You will need to do/ have the following in place:
 - Assure compliance with procedures for inspection and acceptance of CS materials from the Materials Management group to verify quantities
 - Assure accuracy of records for the receipt of raw materials and assignment of tracking code numbers for manufacture
 - May also need to initial/ witness log books for receipt of CI or CII compounds; separate log books for CIII, CIV, or CV compounds (may be combined)
 - May also need to initial/ sign CS cage access log
 - Assure accuracy of reconciliation of empty containers/ depleted lots.
 - Ensure procedures for securing in-process materials are followed
 - Lead/ assist QA investigations of lots with poor reconciliation

Compliance Aspects of Various Positions: cGMP Auditor

- ◆ **Scenario:** You are a cGMP auditor responsible for compliance with current SOPs and CS regulations in the manufacturing operations. You will evaluate performance against a standardized audit checklist (see DEA inspections/ internal audits section for sample).
 - You will need to do/ have the following in place:
 - Audit checklist comprised of CS regulations and SOPs for GMP operations
 - Evaluation of cradle-to-grave reconciliations against raw data sheets and existing records
 - Evaluation of thoroughness of investigations for poor reconciliations
 - Compare various records against each other for accuracy in dates and weights
 - Evaluate compliance with existing SOPs for continuing records maintenance
 - Evaluate inventories and DEA-required reports against reporting deadlines
 - Evaluate effectiveness of QA/ designated observer in assuring quality documentation; recommendations for further training