

Corporate & DEA-Specified Recordkeeping: Overview

- ◆ Registration for Controlled Substances
- ◆ Registration for List I Chemicals
- ◆ Good Faith Inquiries
- ◆ Inventories and Reconciliation
- ◆ DEA 222 Forms
- ◆ Quotas
 - Aggregate Production Quotas
 - Manufacturing Quotas
 - Procurement Quotas
- ◆ ARCOS Reports
- ◆ SOPs and Training Records

DEA-Specified Recordkeeping: Registration

- ◆ Registration for Controlled Substances (Part 1301)
 - Registrations for Separate Locations
 - Exclusions for Sales Offices and Warehouses
 - Re-registration
 - Power of Attorney
 - Coincident Activities
 - Fees and Fee Exemptions
 - Action on Applications: Revocation, Suspension, or Hearings
 - Modification, Termination, or Transfer of Registration
 - Security Requirements & Employee Screening
- ◆ Registration for List I Chemicals (Part 1309)
 - Registration of Manufacturers, Distributors, Importers, and Exporters of List I Chemicals
 - Security Requirements
 - Action on Applications

DEA-Specified Recordkeeping: Registration (continued)

- ◆ **Good Faith inquiries for other registrants (Part 1301.74(a))**
 - Registrants required to make a good faith inquiry to determine that a prospective purchaser/ recipient is properly registered to possess the amount and schedule of CS material.
 - NTIS makes available a monthly updated register of all DEA registered facilities; will shortly be adding List I chemical registrants to the NTIS tape. Monthly service is not free, but is available on the WEB for easy access.
 - Need to build in an advance expiry date so you don't ship materials to a routine customer close to the expiration date of their registration.

DEA-Specified Recordkeeping: Inventories

◆ Inventory Records and Reconciliation

- What inventories are required and when (Part 1304.11)?
 - Biennial inventory due within 24 months initial (or latest) inventory; for manufacturing, distribution, etc. - everything on hand - no cut-offs like for analytical sites
 - ARCOS annual inventories performed on December 31st -- if an ARCOS reporter (see ARCOS section) - for only ARCOS-reportable compounds
 - May decide to combine the annual ARCOS inventory and the biennial inventory to consolidate efforts
 - Special inventories during loss/ diversion investigations or with DEA/ State/ or local authorities
- What reconciliation should I perform beyond what's already handled by the materials management group?
 - Need cradle-to-grave reconciliation of material from receipt through destruction. Do flow diagrams for each received lot of drug sub.
 - Do/ complete reconciliation of drug substance (for each lot and each container) as soon as possible after the majority is consumed for manufacturing. If 10 Kg comes in, but only 7.5 Kg are used for manufacture, weigh out the rest, reconcile entire drum against supplier weights and move remainder into smaller, sealed containers for storage.
 - Advantage is reconciling material sooner and reducing storage needs of safe, vault, or room. Some hygroscopic materials may change weight after opening, confusing accountability over long periods

DEA-Specified Recordkeeping: Inventories (continued)

◆ Inventory Records and Reconciliation

- What should be included in the manufacturing inventories?
 - Biennial inventories include the following:
 - ◆ bulk drug substance -- even when the finished product is exempt -- such as chloral hydrate to manufacture brass;
 - ◆ in-process material (specified by lot number, exact counts of dosage units, strength, and containers) unless product is an exempt preparation;
 - ◆ complimentary samples;
 - ◆ other types (e.g., retains, QC samples, materials held for further formulation, etc.);
 - ◆ finished product; and
 - ◆ customer material ordered, but not yet invoiced.
 - ARCOS-reportable compounds are noted in an annual inventory performed on December 31st (see ARCOS notes)

DEA-Specified Recordkeeping: Inventories (continued)

◆ Inventory Records and Reconciliation

- What level of manufacturing reconciliation is allowable? How much constitutes a reportable loss to DEA?
 - DEA has stated the accountability should be $100\% \pm 0.1\%$. Although this is a very high standard, DEA does not feel one can make a blanket statement of NMT 5.0% for all the different types of manufacturing scenarios. Thus, each manufacturer must establish a history for accountability and yield.
 - Usually, 5% or more loss from theoretical yield is scrutinized by DEA.
 - Notify DEA of high manufacturing losses (e.g., 20 - 50%) that may occur from tableting operations or contamination.
 - Do not wait for DEA to find those losses in your batch records during an audit.

DEA-Specified Recordkeeping: DEA 222 Forms

◆ DEA 222 Forms

- What are DEA 222 forms and what are they used for?
 - DEA 222 forms are required for all C_I and C_{II} transactions except:
 - a prescription or dispensed/administered directly to a patient
 - delivery by a common or contract carrier
 - warehouse delivery/shipment
 - movement by a law enforcement officer, civil defense or disaster relief organization, master of a vessel,
 - delivery to analytical lab for anonymous testing
 - export from the US
 - Uniquely numbered with registrant number, schedules allowed, and sequential identifying number
 - Available in limited quantities (2-3 packets) per request, but may get more depending on needs
 - May order with (1) DEA Form 224 (practitioner) or DEA Form 225 (non-practitioner) upon registration or (2) contact DEA office for DEA Form 222D (order form book)
 - A 3-part form with supplier, DEA, and purchaser copies
 - Need to check accuracy of new order forms, since they cannot be altered after issuance (supplier will reject any modified forms)

DEA-Specified Recordkeeping: DEA 222 Forms (continued)

◆ DEA 222 Forms (Part 1305)

- How are they completed and executed?
 - | Complete each line entry with number of units of same description
 - | NDC code recommended, but not required
 - | Unwanted items may be stricken over and "CANCELLED" written beside it -- only acceptable way of modifying order form
 - | Must be signed by registrant or power of attorney
 - | Supplier must fill whole order within 60 days of date on order form; partial shipments must comprise whole order still within 60 days
 - | Supplier completes number of items shipped and date actually shipped
 - | Supplier may cancel portions of order or entire order with erasures, mistakes, or alterations to items noted; form is returned to purchaser
 - | Bulk manufacturer cannot fill order from finished dosage manufacturer unless accompanied by procurement quota letter -- certification per 1303.12(f)
 - | Endorsed order forms: supplier cannot complete order and endorse it to another supplier (see reverse side of Copy 1 and Copy 2)
 - | Lost or stolen order forms: purchaser executes another order along with statement to supplier of lost/stolen order form number(s)
 - | Supplier submits Copy 2 to DEA office monthly

DEA-Specified Recordkeeping: DEA 222 Forms (continued)

◆ DEA 222 Forms

- My manufacturing facility needs to send CI or CII samples for analysis to an analytical registrant within the same company. There is no coincident activity allowed. How do I manage and document this transfer?
 - Basically, the analytical registrant needs to complete a DEA 222 to 'purchase' the samples from the manufacturer.
 - However, the lab has no idea of what to order, when to send in DEA 222, etc.
 - Thus, the manufacturer (the 'supplier') must complete an internal document -- DEA 222 Request Form -- that is sent to the lab specifying what materials to 'purchase.'
 - The analytical lab completes a DEA 222 form for the samples and sends it to the manufacturer registrant who 'supplies' the lab with the materials.
 - The manufacturer (supplier) provides a copy of the executed DEA 222 form to the regional office (on a monthly basis).
 - The DEA 222 Request Forms are part of the manufacturer and analytical registrant continuing record files.

DEA-Specified Recordkeeping: DEA 222 Forms (continued)

- ◆ Special Requirements for Carfentanil, Etorphine, and Diprenorphine
 - How are they completed and executed? What are some additional considerations for these compounds?
 - Orders for carfentanil, etorphine hydrochloride, or diprenorphine can only contain this substance (1305.06(b)).
 - Copies of order forms are stored separately from all other forms (1305.13(d)).
 - Purchaser forwards both Copy 1 and Copy 2 to supplier and retains Copy 3 (1305.16(a)).
 - Supplier confirms registrant is a veterinarian with a zoo or exotic animal practice (1305.16(b)).
 - Manufacturer must forward order forms to DEA on a weekly basis (1305.16(b)).
 - Only reasonable quantities may be shipped -- only to the location on the DEA registration form -- in a package with no outside markings denoting contents.

DEA-Specified Recordkeeping: Procurement Quotas

◆ Aggregate Production Quotas

- What are aggregate production quotas? How are they established and used?
 - Quotas restrict the manufacture and procurement of C_I and C_{II} materials to only those manufacturers registered by DEA for (1) control of inventory, (2) limit quantity, and (3) put a ceiling on production.
 - Aggregate (production) quotas:
 - ◆ establish an annual aggregate production tally for all bulk manufacturers,
 - ◆ apportion the production quotas among the individual bulk manufacturers, and
 - ◆ allocate procurement quotas among finished dosage manufacturers.
 - Aggregate quotas are set by:
 - ◆ total net amount of disposal for last three years,
 - ◆ quantities and trends in inventory,
 - ◆ projected demands based on procurement quotas, and
 - ◆ other factors impacting medical, scientific, research, and industrial needs.
 - Aggregate production quotas are set and published in the Federal Register by May of the year that they apply; copy mailed to each bulk manufacturer.

DEA-Specified Recordkeeping: Procurement Quotas (continued)

◆ Procurement and Manufacturing Quotas

- What are procurement quotas? How are they established and used?
 - | Procurement quotas are for bulk drug substance to make finished dosage forms:
 - ◆ DEA Form 250 due by April 1 of the prior year
 - ◆ re-packers/re-labellers now are subject to quotas since activity is defined as manufacturing
 - ◆ quantity calculated as anhydrous base, acid, or non-salt form
 - ◆ may be applied for/revised during production year
 - | Exceptions for procurement quotas include:
 - ◆ registered manufacturers using all the material in manufacturing a non-CS material
 - ◆ chemical analysis
 - ◆ researchers registered in accordance with 1301.22(b)
 - | Manufacturers receiving from another manufacturer must:
 - ◆ have valid procurement quota at transaction time
 - ◆ provide written proof amount does not exceed quota
 - ◆ DEA Form 222 signed by same person as who signed quota certification to manufacturer
- What are manufacturing quotas? How are they established and used?
 - | Individual manufacturing (for bulk drug substance)
 - ◆ quotas set by July 1; DEA Form 189 complete by May 1 of the prior year
 - ◆ separate application for each C_I and C_{II} compound
 - ◆ must be obtained before starting manufacture

DEA-Specified Recordkeeping: Procurement Quotas (continued)

◆ Procurement Quotas

- My company wants to develop a morphine-based (C_{II}) compound for an IND. How do I get a procurement quota and how long will it take to get the morphine in-house?
 - Even though the DEA 250 forms are due by April 1, one can apply for a procurement quota anytime. Written justification for the amount of bulk drug substance (anhydrous base) should be mailed to Ms. Julie Tisinger (DEA, Washington DC).
 - There is about a 2-week turnaround time for the paperwork.
 - You will receive a procurement letter which must accompany each DEA 222 form to purchase the morphine.
 - Purchase of the morphine should be 1-3 weeks turnaround time.
- A contract manufacturer has a C_{II} - C_V registration. A client wants to transfer C_{II} drug substance to them under their (client) quota. Does the contract manufacturer need a procurement quota too?
 - Yes, procurement quotas are not transferable. However, if the C_{II} product was only going to be repackaged/ relabelled, no procurement quota is required. NOTE: Blinding of an active by over-encapsulation is considered manufacturing and thus, a procurement quota for the number of finished dosage units is required.

DEA-Specified Recordkeeping: ARCOS Reporter

- ◆ **ARCOS (Automated Reports and Consolidated Orders System)**
 - **What is ARCOS and who is required to be a reporter?**
 - DEA database for inventory management and tracking of manufacturing, returned goods, theft, and destruction for:
 - ◆ manufacturers of bulk or finished dosage forms for all C_I or C_{II} compounds, ARCOS-listed narcotic C_{III} , and ARCOS-listed psychotropic C_{IV} compounds,
 - ◆ distributors of any C_I or C_{II} or ARCOS-listed narcotic C_{III} compounds, or
 - ◆ re-packers/ re-labellers of any C_I or C_{II} or ARCOS-listed narcotic C_{III} compounds.
 - **What reports are required? Is anyone exempt from reporting?**
 - All transactions to and from another DEA registrant that involve sale, purchase, destruction, loss/ theft for any ARCOS-reportable compounds:
 - ◆ reports are monthly or quarterly, depending upon reporter's preference
 - ◆ annual inventory required to be taken December 31st of all ARCOS-reportable items on hand
 - Persons/ registrants not required to report include:
 - ◆ physicians, hospitals, clinics, or pharmacies
 - ◆ analytical labs
 - ◆ teaching institutions
 - ◆ researchers
 - ◆ maintenance units, compounders, and/ or detoxification units
 - ◆ importers/ exporters

DEA-Specified Recordkeeping: ARCOS Reporter: Transaction Codes

- ◆ Four major categories of transaction codes: inventory, acquisition, disposition, and miscellaneous
 - Inventory
 - Code 1 = Schedule Change Inventory
 - Code 3 = Year-End inventory
 - Code 4 = Year-End In-Process Inventory (Manufacturers only)
 - Code 5 = Special Inventory
 - Code 8 = No Year-End Inventory
 - Acquisition
 - Code P = Purchase or Receipt
 - Code R = Return
 - Code V = Unsolicited Return
 - Code G = Government Supplied
 - Code W = Recovered Waste (Manufacturers only)
 - Code M = Manufactured (Manufacturers only)
 - Code L = Reversing (Manufacturers only)
 - Code J = Return of Sample to Inventory (Manufacturers only)

DEA-Specified Recordkeeping: ARCOS Reporter: Transaction Codes

- Disposition
 - Code S = Sale, Disposition, or Transfer
 - Code Y = Destroyed
 - Code T = Theft
 - Code Z = Receipt by Government (seizures, samples, etc.)
 - Code N = Nonrecoverable Waste (Manufacturers only)
 - Code U = Used in Production (Manufacturers only)
 - Code Q = Sampling (Manufacturers only)
 - Code K = Used in Preparations (Manufacturers only)

- Miscellaneous
 - Code 7 = No ARCOS Activity for Current Reporting Period
 - Code F = Reorder DEA Form 333
 - Code X = Lost-in-Transit

DEA-Specified Recordkeeping: ARCOS Reports: Electronic Records

- **Isn't there an electronic ARCOS spreadsheet available from DEA for use in electronic filing? If so, what type of electronic validation issues surround this?**
 - Yes, there is an electronic spreadsheet that can be obtained from DEA. The issues surrounding validation will stem from what type of data input systems are used and how those data will be calculated to generate reports. If the data input is entirely manual and the spreadsheet is not linked to other database collection or calculations, then the level of validation is minimal.
 - However, if you are linking these spreadsheets to other inventory software, you would need to validate that database collection in much the same manner as any FDA-reviewed system.
 - Although DEA doesn't have the same type of validation issues codified (in the CSA) as the FDA does in 21 CFR Part 11, many of the issues will probably be the same.
 - Inventory systems may be paper-driven or electronic or a combination of both. One firm uses a bar-code tracking system.

Corporate Recordkeeping: SOPs and Training Records

- **What types of SOPs are generated for CS programs? Does DEA pay attention to the training records surrounding these?**
 - Yes, DEA will audit training records against the in-house SOPs. A list of proposed SOPs is provided below:
 - DEA 222 Forms
 - ARCOS Reports (if applicable)
 - Investigations: Loss/ Diversion
 - DEA-Authorized Observer (if applicable)
 - Corporate Overview
 - Schematic of logistical flow of materials
 - Schematic of people by location
 - Applicable SOPs by location and activity
 - Good Faith Inquiries
 - Registrations
 - Power of Attorney
 - Security Systems
 - Overview by Location
 - OQ/ PQ per System Component
 - Inventories
 - CS Transfer Forms
 - Returns/ Complaints
 - Disposal/ Destruction
 - Procurement Quotas (if applicable)
 - Training