

Import/ Export of Controlled Substances

- Import/ export can quickly become complicated:
 - Some types of CS registrations allow import/ export as coincident activity (e.g., analytical),
 - DEA/ US Customs requirements (e.g., permit vs declaration) vary for different schedules of CS materials - as well as receiving/ exporting countries,
 - There are additional restrictions on material designated for further manufacture and then re-imported or re-exported by FDA & DEA,
 - Labelling differs for marketed product versus investigational material and also for US market versus overseas,
 - Each receiving country has their own import/ export regulations (e.g., Tier 1 versus non-Tier 1 status)
 - Maximal utilization of electronic resources for shipment and logistical tracking:
 - OASIS (Operations & Administration Support Import System) - a FDA-Customs - user interface for imports management
 - TIC (Trade Information Center, International Trade Administration) - export assistance from US Dept. of Commerce

Import/ Export Forms Used for Controlled Substances & Listed Chemicals

- DEA uses the following forms for import/ export of controlled substances, List I/ II chemicals, and/or listed machines:
 - DEA 236: **Import Declaration** for non-narcotic $C_{III} - C_V$ or **Export Declaration** for non-narcotic $C_{III} - C_{IV}$ and all C_V
 - DEA 357: **Import Permit Application Form** for C_I, C_{II} , narcotic $C_{III} - C_V$, non-narcotic listed C_{III} (none to date), and any non-narcotic C_{IV} or C_V listed as a C_I, C_{II} in the Convention of psychotropic Substances (UN Treaty)
 - DEA 35 **Import Permit** issued pursuant to an approved DEA 357 application
 - DEA 161: **Export Permit Application Form** for C_I, C_{II} , narcotic $C_{III} - C_{IV}$, non-narcotic listed C_{III} , and any non-narcotic C_{IV} or C_V listed as a C_I, C_{II} in the Convention of Psychotropic Substances (UN Treaty). Note, there is no export permit required for C_V material.
 - DEA 36 **Export Permit** issued pursuant to an approved DEA 161 application
 - DEA 486: **Import/ Export Declaration** for List I/ II Chemicals and listed machines

DEA 236: Import Declaration

- DEA 236 is a 5-copy declaration form completed in quintuplicate. Brief instructions on its use **for import** are as follows:
 - Copies 1,2, and 3 are forwarded to the foreign shipper
 - Copy 1 is submitted by foreign shipper to foreign governmental authority for issuance of export authorization; Copy 1 accompanies shipment to final destination and retained on file by importer
 - Copy 2 is detached and retained by appropriate Customs official at the foreign port
 - Copy 3 is removed, certified, and signed by US Customs at the port of entry - noting any discrepancies. After signature, Copy 3 is forwarded to ODOI at the Office of Diversion Control, DEA
 - Copy 4 must be furnished to DEA by importer not less than 15 days prior to the proposed date of importation. NOTE: a special waiver of the 15-day time limitation may be requested by importer in emergency or unusual situations.
 - Copy 5 is retained by importer until receipt of Copy 1

DEA 236: Export Declaration

- DEA 236 is a 5-copy declaration form completed in quintuplicate. When used for export, DEA 236 declaration is called a **Special Controlled Substances Export Invoice**. Brief instructions on its use for export are as follows:
 - Copies 1,2, and 3 accompany the shipment
 - Copy 1 accompanies shipment to final destination and retained on file by importer
 - Copy 2 is detached and retained by appropriate Customs official at the foreign port of importation
 - Copy 3 is removed, certified, and signed by US Customs at the port of export - noting any discrepancies. After signature, Copy 3 is forwarded to ODOI at the Office of Diversion Control, DEA
 - Copy 4 must be furnished to DEA by importer not less than 15 days prior to the proposed date of importation. NOTE: a special waiver of the 15-day time limitation may be requested by importer in emergency or unusual situations.
 - Copy 5 is retained by importer for at least two years. NOTE: records retention policies for companies and various State's CS laws may require 5-10 years retention.

DEA 357: Import Permit Application

- DEA 357 is an import permit application form completed in triplicate (see Part 1312.13). Brief instructions on its use are as follows:
 - Original is submitted to DEA for processing
 - Copies 2 and 3 are retained in importer's files until shipment is received. Upon receipt of shipment, information entered into Item 6c.
 - DEA import Permit #
 - Actual quantity shipped and date received
 - Copy 2 is sent to DEA
 - Copy 3 is retained by importer
 - Permits - when issued - are mailed to importer registrant.
 - Import Permit is issued (6-copy form) or the application is returned with reasons for denial (e.g., mistakes, additional data needed, etc.)
 - Distribution of DEA 35 (permit) copies (see Part 1312.14):
 - Copy 1 & Copy 5 sent by DEA to importer - who retains Copy 5 and sends Copy 1 on to foreign exporter.
 - DEA sends Copy 2 to the proper authorities of the exporting country.
 - DEA sends Copy 4 to the US Customs representative for the US port of entry.
 - Copies 3 and 6 are kept by DEA.

DEA 161: Export Permit Application

- DEA 161 is an export permit application form completed in triplicate (see Part 1312.22). Brief instructions on its use are as follows:
 - Original is submitted to DEA for processing
 - Copies 2 and 3 are retained in exporter's files until shipment is sent. Upon shipment, information entered into Item 7c.
 - DEA export Permit #
 - Actual quantity shipped and date sent
 - Copy 2 is sent to DEA
 - Copy 3 is retained by exporter
 - Permits - when issued - are mailed to exporter registrant.
 - Export Permit is issued (7-copy form) or the application is returned with reasons for denial (e.g., mistakes, additional data needed, etc.)
 - Distribution of DEA 36 (permit) copies (see Part 1312.24):
 - Copies 1, 2, & 3 sent by DEA to exporter - who retains Copy 3 for files
 - Exporter presents Copies 1 and 2 to US Customs at port of exportation
 - After endorsement of port of export on Copies 1 & 2, the US Customs District Director will send Copy 1 with shipment
 - Endorsed Copy 2 is sent by US Customs District Director to DEA
 - Copy 4 is sent by DEA to US Customs District Director for comparison to Copy 1; Copy 4 retained by US Customs for their files
 - Copy 5 sent by DEA to officer in foreign country who issued the import certificate
 - Copies 6 and 7 are kept by DEA.

DEA 486: List I or List II Chemicals Import/ Export Declaration

- DEA 486 is an import/ export declaration completed in triplicate. Brief instructions on its use are as follows:
 - Copy 1 is retained by importer/ exporter
 - Copy 2 is sent to DEA
 - Copy 3 is kept by US Customs
 - List I records retained for four years (minimum)
 - List II records retained for two years (minimum)
 - Listed machines records retained for five years (minimum)

Trans-shipments: C_I vs. C_{II} - C_{IV} Requirements

- C_I : Prior Approval
 - can be imported for trans-shipment or trans-shipped within US for immediate exportation provided (see Part 1312.31):
 - Necessary for scientific, medical, or legitimate purposes in country of destination
 - A trans-shipment permit has been issued by DEA
 - An application for trans-shipment must be made to DEA not less than 30 days prior to expected date of importation
 - Each application contains data specified in Part 1312.31(b)
 - Each application accompanied by an export license, permit, or certified copy from the authority of country of origin
 - Each application accompanied by an import license, permit, or certified copy from the authority of country of destination
 - Certification of no re-export and other aspects of 1312.31(d)
- C_{II} - C_{IV} : Advance Notice
 - may be imported for trans-shipment or trans-shipped within US for immediate exportation provided (see Part 1312.32):
 - Written notice to DEA at least 15 days prior to date of importation, transfer, or trans-shipment
 - Each advance notice contains items specified in Part 1312.31(b) and (c).

Re-exportation of Controlled Substances

- CS materials imported into US (via DEA 357 import permit) may not be re-exported (per Part 1312.12(3) and (4))
- CS materials exported from US (via DEA 161 export permit) may not be re-exported (per Part 1312.22(a) and (b))
- CS materials exported from US (via DEA 236 declaration or Special Controlled Substances Invoice) may not be re-exported (per Part 1312.27(5)) ... except for the following circumstances
 - Bulk drug substance can not be re-exported in the same form as exported from the US; must undergo further manufacturing
 - Finished dosage units (if re-exported) will be in commercial package, sealed, and labelled for legitimate medical use in country of destination
 - DEA shall be notified on DEA 236 declaration when materials are designated for re-export. If so, provide information noted in Part 1312.27(5)(iii)
- CS materials exported from US - that are refused by consignee - may be returned to US after (1) US exporter files written request for re-export (along with completed DEA 236) and (2) summary of facts surrounding return of material and (3) DEA authorization.

Importation Zones: Definitions & Requirements

- Three types of importation through two zones -- **US customs territory** (50 states, Puerto Rico, and DC) and **US jurisdiction** (Virgin Islands, Canal Zone, Guam, American Samoa, and Pacific Territories [Palau])
 - import into US customs territory (Spain to New York);
 - import into US jurisdiction (Spain to Virgin Islands); and
 - import from US jurisdiction into US customs (Virgin Islands to Puerto Rico).
- Registration not required if moving within customs territory of jurisdiction (Puerto Rico to New York)
- DEA requires permits for import/ export of any:
 - C_I or C_{II}
 - narcotic $C_{III} - C_V$
 - non-narcotic C_{III} that DEA has designated (none to date)
 - any non-narcotic C_{IV} or C_V that is listed as C_I or C_{II} in the Convention of Psychotropic Substances (UN Treaty)
- Some CS material imported into US are not allowed for re-exportation
- Rarely can you import a C_I , C_{II} , narcotic C_{III} or C_{IV} into US if a domestic source is available; must be shortage not easily remedied by increased quotas to existing manufacturers.

Import/ Export: Limits of Coincident Activity & Compliance

- Analytical Registrants
 - Allowed to import (and export) small quantities under analytical registration - no need to register as importer/ exporter
 - DEA 357 (import permit): 2-3 week turnaround time
 - DEA 161 (export permit): 2-3 week turnaround time
 - DEA 236 (import or export declaration)
- ♦ Manufacturer Registrants
 - Import/ export is not a coincident activity allowed under a manufacturing registration - must transfer material to a registered importer/ exporter.
 - Import restrictions apply for bringing in non-US sourced C_I , C_{II} , narcotic C_{III} or C_{IV} material when a domestic source is available - even when the US costs are significantly more. This rule does not apply to non-narcotic C_{III} (anabolic steroids), C_{IV} (benzodiazepines), and C_V (codeine).
 - Can import crude opium, medicinal coca leaves, special coca leaves, and poppy straw (bulk or concentrate for further manufacture and export).

Import Scenarios: Issues and Answers

◆ Analytical Registrant

- I need to import a small quantity of a C_{II} drug substance reference standard for analysis. What's needed?
- As a stand-alone analytical registrant, you will need to complete a DEA 357 import permit application form.
- Although there won't be a DEA 222 form in place - since this is a direct import - you need to have the material shipped to the exact same address as on the analytical registration. NOTE: Some analytical registrants may be part of a larger campus operation and they get all their materials shipped to a central warehouse/distribution area.
- When the material comes in, log in as usual for any other C_{II} sample.

Import Scenarios: Issues and Answers

- ◆ Analytical Registrant and Manufacturing Registrant on Campus-Style Facility
 - The Director of R&D wants me to import 1.5 Kg of a C_{II} drug substance for both analysis and formulation development. Is this OK? If not, what limits should a lab apply when acting on behalf of a manufacturing registrant under the same company?
 - You need to apply the same standards as you would for any manufacturer outside of the campus.
 - First off, ordering large quantities for a lab registrant is bound to raise eyebrows in the DEA 357 application; it won't go through and you'll be flagged for greater scrutiny
 - Secondly, the manufacturer needs procurement quotas. Simply transferring them internally via DEA 222 forms does not negate that requirement.
 - Third, as an analytical registrant, you may distribute samples to others for analytical purposes but you can not exceed a reasonable threshold to circumvent the import/ export restrictions of your company's manufacturing registration.
 - Bottom line is if the manufacturer registrant intends to manufacture dosage forms with the material from your DEA 357 import permit application form, that goes outside the coincident activity of your registration import
 - However, if they intend to further manufacture of analytical samples, that's OK.

Import Scenarios: Issues and Answers

- ◆ Analytical Registrant and Manufacturing Registrant on Campus-Style Facility
 - The manufacturing registrant on our campus also has an analytical lab. They have asked me to import samples of European manufactured product for transfer to their lab as part of a method transfer. It's a C_{II} drug substance reference standard and drug product. Is this OK?
 - Yes, the further distribution of analytical samples to a manufacturing registrant for analysis is part of your coincident activity. However, since it's a C_{II} drug substance, the manufacturing registrant must be:
 - Currently registered by both DEA and the State to handle C_{II} drugs in general but for that particular one as well;
 - A properly executed DEA 222 form signed by the DEA Registrant (for the manufacturing registrant) or the Power of Attorney;
 - A copy of the DEA procurement letter stating the allotted quota for the manufacturing registrant for that year; and
 - A copy of the request from the manufacturing registrant noting what remainder of the quota is still available to them (as calculated by orders and existing inventories).

Import Scenarios: Issues and Answers

- ◆ Manufacturing Registrant on Campus-Style Facility
 - The manufacturing registrant needs to import samples of European manufactured product for transfer to their lab as part of a method transfer. It's a C_{II} drug substance reference standard and drug product.
 - Since import is outside the coincident activity of a manufacturer, it needs to be handled by an importer registrant - which could also be on the campus facility or a separate broker.
 - The importer must be registered to handle the schedule and quantity of product you're importing.
 - Since it's a C_{II} drug substance, the manufacturing registrant must be:
 - Currently registered by both DEA and the State to handle C_{II} drugs in general but for that particular one as well;
 - A properly executed DEA 222 form signed by the DEA Registrant (for the manufacturing registrant) or the Power of Attorney;
 - A copy of the DEA procurement letter stating the allotted quota for the manufacturing registrant for that year; and
 - A copy of the request from the manufacturing registrant noting what remainder of the quota is still available to them (as calculated by orders and existing inventories).

Export Scenarios: Issues and Answers

- ◆ Analytical Registrant and Manufacturing Registrant on Campus-Style Facility
 - The manufacturing registrant on our campus wants to export finished dosage forms (stability samples) to our European analytical lab. They propose to transfer product to my analytical registrant for easier export. It's a C_{II} drug substance reference standard and drug product. Is this OK?
 - Yes, since the samples are only meant for analytical testing, this is consistent with the coincident activity of your lab as well as the European analytical lab. However, since it's a C_{II} drug substance, the lab must be:
 - Currently registered by both DEA and the State to handle C_{II} drugs
 - Have properly executed DEA 222 form signed by the DEA Registrant or the Power of Attorney
 - Properly executed Controlled Substance Transfer Form
 - The lab will complete a DEA 161 application permit; when approved, ship samples.

Export Scenarios: Issues and Answers

- ◆ Manufacturing Registrant on Campus-Style Facility
 - The manufacturing registrant needs to export marketed product/ investigational product (a C_{II} drug) to European sites.
 - Manufacturer will ship C_{II} drug product to US domestic exporter registrant via DEA 222.
 - Exporter will complete DEA 161 export applications; **since no re-export allowed, must ship to individual countries.** Upon receiving export permits, ship product.
 - NOTE: company may have both import and export registrations on campus facility too. If so, make sure importer/ exporter registrant records accurately reflect inventories of dates received and shipped.
 - The importer/ exporter must be registered to handle the schedule and quantity of product you're moving.
 - Since it's a C_{II} drug substance, the manufacturing registrant must confirm the exporter registrant is:
 - Currently registered by both DEA and the State to handle C_{II} drugs in general but for that particular one as well;
 - A properly executed DEA 222 form signed by the DEA Registrant (for the manufacturing registrant) or the Power of Attorney;

Import/ Export of List I or II Chemicals

◆ Import/ Export

- How do I import or export a List I or List II chemical?
 - Imports/ exports of listed chemical require DEA notification (15-day advance) via DEA Form 486
 - For established importers, a waiver of the 15-day notification requirement may be obtained
 - Regardless, DEA must have FAXed form by day of importation
 - End-users of List I or List II chemicals do not have to register separately with DEA as a List I/ II Chemical importer/ exporter -
 - However, finished dosage forms containing more than impurity levels of List I or List II chemicals - which are distributed for market or further manufacture - can trigger one to become a Listed Chemical registrant and/or certain recordkeeping requirements
 - See Parts 1309, 1310, and 1313 for details on registration, records/ reports, and import/ export, respectively.

Import/ Export Compliance Problems

- What are some common compliance problems associated with import/ export permits?
 - Permits run into trouble when there are:
 - changes in port of entry or exportation,
 - wrong calculations of quantity (not based on anhydrous weight),
 - amounts exceed stated permit quantity (e.g., wrong conversion factors due to rounding errors),
 - changes in carriers, or
 - changes in dates of shipment.
 - Other compliance problems include:
 - Import/ export outside of the allowable coincident activity,
 - Attempting to import/ export large quantities without procurement quotas in place

"Import for Export" Rule

- ◆ FDA Export Reform and Enhancement Act of 1996 (effective April 26, 1996)
 - Eliminated export restrictions on drugs and devices unapproved in US but which were approved in other countries (e.g., Tier 1 vs. non-Tier 1)
 - *Federal Register* (63) 226: 64930 (11/24/98) contained proposed rule about additional reporting and recordkeeping for products "imported for re-export after further processing."
 - Basis was to ensure that violative components were not being used to manufacture US-based/ marketed pharmaceuticals (e.g., anti-counterfeiting).
 - Written comments due by 2/8/99
 - Per 801(d)(3) of the Act, consignee must submit statement that any portions not used or exported will be destroyed or re-exported.
 - This can cause problems if the time-limits for the 801(d)(3) action become an FDA issue. For instance, how long can a company keep excess 801(d)(3) material and still be in compliance?
 - For some schedules of CS materials, re-export is not allowed under UN treaties and DEA regulations, so will companies be compelled to destroy valuable bulk material?

Shipment of Investigational Clinical Supplies (IND Materials)

- ◆ Labelling of Clinical Trial Material
 - Regulations for Commercial Product
 - Regulations for Clinical Trial Material
 - Export Considerations
- ◆ Scheduling of Materials
 - Automatic Scheduling
 - Exempt Preparation: Request and Contingencies

Handling of IND Materials: Labelling of Clinical Trial Material

- ◆ Regulations for Commercial Product (revised in 1997)
 - Revised regs (Part 1302) removed CS symbol size and location criteria on label. Now, "symbol shall be prominently located" and "clear and large enough to afford prompt identification." Gives sponsors more flexibility in label design.
 - Label regulations apply to all product imported into US customs and/or jurisdictional territories, but not for export from US jurisdiction.
 - Tamper-evident seals/ devices required for each commercial container for C_I , C_{II} , narcotic C_{III} or C_{IV} for import and export (US jurisdiction). (NOTE: commercial is defined as for dispensing or use, not "for sale.")
- ◆ Regulations for Clinical Trial Material
 - CS symbol not required for material used in single-blind or double-blinded studies.
 - Tamper-evident seals/ devices required for CS schedules of IND materials as noted for "commercial containers," prudent to use for all CS schedules.
 - CS recordkeeping requirements are generally exempt under IND regulations, but accurate accounting of clinical trial material is still part of current Good Clinical Practices (cGCPs).

Export of IND Clinical Trial Material

- Prior to FDA Export Reform and Enhancement Act of 1996, exports of unapproved investigational drugs/ devices were done per 21 CFR 312.110 (for clinical investigations not done under a US IND (312.40)).
- Now shipments of unapproved drugs performed on a notification basis as long as drug/ device complies with laws of importing country and has been approved for marketing in a Tier 1 country.
- FDA charges \$175 per export certificate issued.
- For IND materials with CS, there are additional re-export limitations that complicate using a central distribution center. Can't ship all supplies to England or Germany (e.g., to a CRO) and have distribution from there. Need to anticipate shipping site supplies to each country for distribution to various country sites. Need to have export permits for all countries.
- Individual countries have CS regulations mirroring US -- import permits, etc. Need to anticipate requirement and timing for permit to import any C_I , C_{II} , narcotic C_{III} or C_{IV} .
- US Customs may inadvertently rearrange your randomized trial material during inspection. While not required, it's good idea to tamper-evident seal any site-specific medication packets to ascertain if they have been disturbed.
- May also be delays in clinical trial material getting to site by additional identity testing requirements for several countries (e.g., UK, Germany). May be able to avoid this by shipping to Belgium and transporting from there to clinical site.

Handling of IND Materials: Automatic Scheduling of Materials

- ◆ Automatic Scheduling
 - Under *CSA*, there is automatic scheduling of derivatives of classes of compounds. Even though there is no listing of your specific compound, it's assumed to possess same *CS* qualities as parent class until demonstrated otherwise.
 - Complicates movement of materials based on *CS* schedule and not real activity.
- ◆ Exempt Preparation: Request and Contingencies
 - May request exempt preparation status or change in schedule depending upon supporting data. Includes the following:
 - name, address, registration number of sponsor/ applicant,
 - trade name, generic name, chemical name(s) of drug product and active ingredient(s),
 - formulation and composition of drug product,
 - summary of justification for exempt preparation status (e.g., human studies, psychological/ dependence studies in animals, lack of demonstrated pharmacology to parent compound, etc.).
 - Request is published in Federal Register for comment.
 - DEA may modify or waive any portion of exempt status in the future.