Structured Product Labeling and Supply Chain Integrity

122nd AFDO Educational Conference
Drugs, Devices & Cosmetics Committee
Burlington, Vermont
June 11, 2018

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In This Presentation

- Brief review transition to electronic format of data submission to FDA.
- Structured Product Labeling (SPL) standard and integrity within the drug supply chain.
- CDER Direct and common SPL documents used in Supply Chain Management.
- Scenarios of SPL data use in management of supply chain integrity.

History of Electronic Submissions

- The Paperwork Reduction Act of 1995
- Image Solutions, Inc. first electronic submission to FDA in 1997 with Sandoz (Novartis)
- Portable Document Format (PDF)
- Extensible Markup Language (XML)

XML Language


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directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.</paragraph>                    </text>                    <effectiveTime
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</section>        </component>        <component>            <section ID="G770a3473-1aea-48b3-b934-aec685c76bd3">                <id root="a40a840c-aa70-4999-bf21-cd7692f23716"/>                <code
code="34068-7" codeSystem="2.16.840.1.113883.6.1" displayName="DOSAGE &amp;amp; ADMINISTRATION SECTION"/>                <title>DIRECTIONS</title>                <text>                    <list
listType="unordered" ID="Ga2758bb7-fd11-4e70-9926-7649c955a44d" styleCode="Square">                        <item>                            <content styleCode="bold">do not take more than directed</content>
                </item>                        <item>                            <content styleCode="bold">the smallest effective dose should be used</content>                        </item>
<item>adults and children 12 years and over: take 1 capsule every 4 to 6 hours while symptoms persist</item>                        <item>if pain or fever does not respond to 1 capsule, 2 capsules may be
used</item>                        <item>do not exceed 6 capsules in 24 hours, unless directed by a doctor</item>                        <item>children under 12 years: ask a doctor</item>
</list>                </text>                <effectiveTime value="20121022"/>            </section>        </component>        <component>            <section
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                        <item>                            <content styleCode="bold">each capsule contains:</content> potassium 20 mg </item>                        <item>read all warnings and directions before use. Keep
carton.</item>                        <item>store at 20-25°C (68-77°F)</item>                        <item>avoid excessive heat above 40°C (104°F)</item>                    </list>                </text>
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INGREDIENTS</title>                <text>                    <paragraph ID="G8410fc91-0741-4018-93a0-d25f6e34c5e0">FD&amp;amp;C green no. 3, gelatin, light mineral oil, pharmaceutical ink, polyethylene glycol,
potassium hydroxide, purified water, sorbitan, sorbitol</paragraph>                </text>                <effectiveTime value="20121022"/>            </section>        </component>        <component>
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<paragraph ID="G0f32d34f-8af1-4187-85f7-f3ce8aa6bae0">                    <content styleCode="bold">Advil Liqui-Gels</content>                    </paragraph>                    <paragraph
ID="G9ea87f8d-7697-499d-a9a0-76afaa70e231">Solubilized Ibuprofen Capsules, 200 mg</paragraph>                    <paragraph ID="G08de737a-95bf-48b3-8c5a-3a6aaa262401">Pain Reliever/Fever Reducer
(NSAID)</paragraph>                    <paragraph ID="G9af288c4-88d8-464d-939e-0528dd54ace3">80 Liqui-Gels*  *Liquid Filled Capsules</paragraph>                    <paragraph
ID="G10fb614b-648b-4301-98fd-54fb7b0330d6">                        <content styleCode="bold">Liquid Filled Capsules</content>                    </paragraph>                    <paragraph
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                <paragraph ID="G53ff8af5-17af-4642-bac9-819fb6caf91d">LIQUI-GELS is a trademark or registered trademark of Catalent Pharma Solutions.</paragraph>                    <renderMultiMedia
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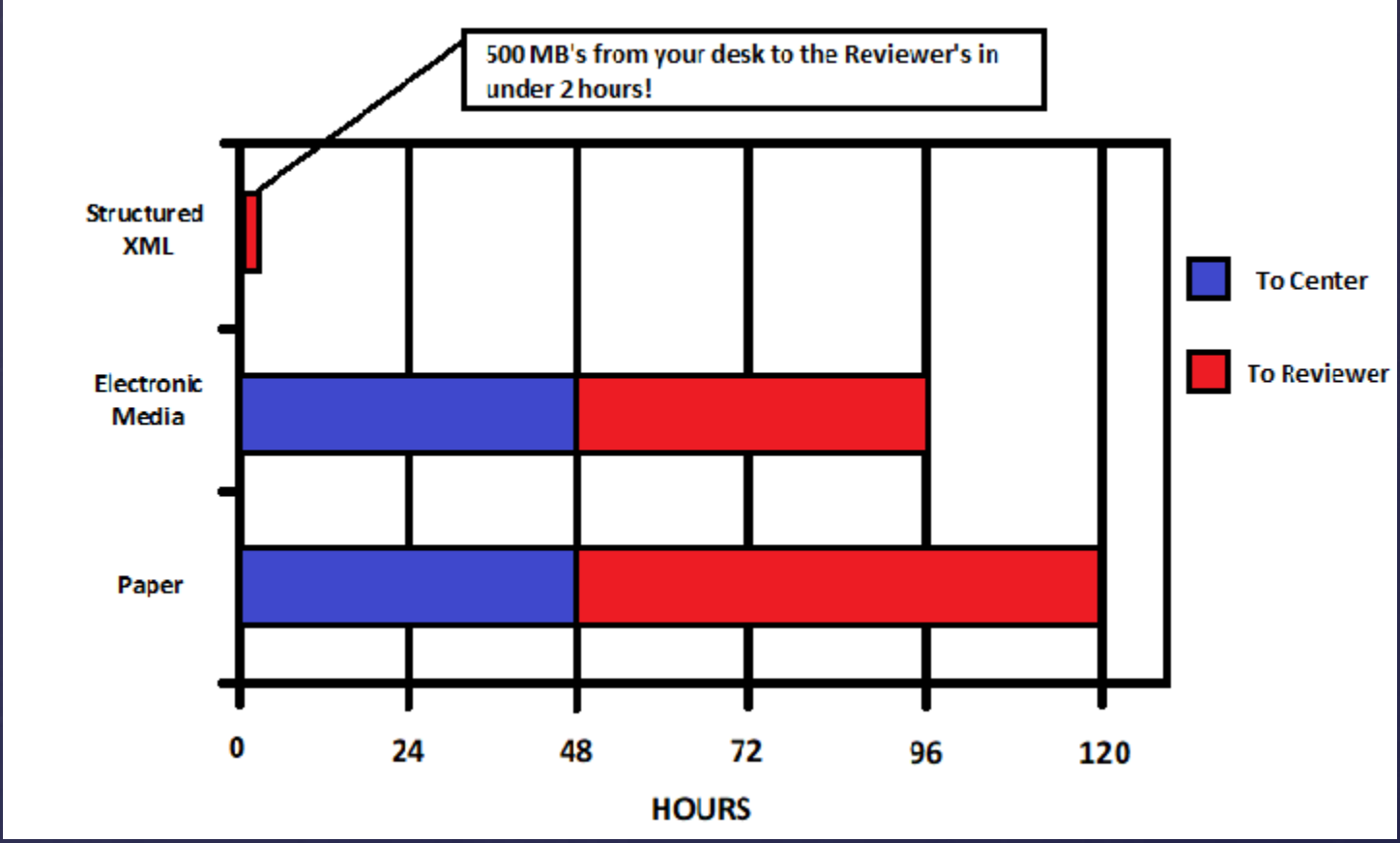
Benefits of Electronic Submission in XML Format

- Paper -> Electronic Media -> XML
- Automated/electronic processing –"computer-readable"
- Electronic validation – validation procedures
- Granular document approach
- Moved between systems and combined with other data sources
- Easy update/revision

Benefits of Structured XML Documents - Time



Health Information Management Technologies Supported by XML

- Electronic Prescribing
- Electronic Health Record (EHR)
- National Library of Medicine (DailyMed) – populated by 101,896 current SPLs in XML
  - Reimbursement
    - Medicare
    - Medicaid
- Additional Downstream Users

Building a Structured XML Submission

- FDA provided to industry as low cost options
  - Pragmatic Structured Product Labeling Editor
  - eSubmitter
  - CDER Direct
- Notepad
- Commercially available customizable software
- Conversion Vendors

Structured Product Labeling (SPL) and the Drug Supply Chain

HL7 INTERNATIONAL

DAILYMED

FDA CDER Direct Electronic Submissions Portal

FDA ESG

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Association of Food & Drug Officials
AFDO
Founded 1896

What is Structured Product Labeling (SPL)?

- Structure Product Labeling –
  - Data standard for submitting, viewing, and exchanging information about products and facilities
  - XML format – extensible mark-up language
- Health Level Seven International (HL7)
- SPL stands for "Structured Product Labeling" but covers product information beyond labeling

Document Types Currently in SPL

ANIMAL COMPOUNDED DRUG LABEL
BLANKET NO CHANGES CERTIFICATION OF PRODUCT LISTING
BULK INGREDIENT
BULK INGREDIENT - ANIMAL DRUG
CELLULAR THERAPY
COSMETIC
DIETARY SUPPLEMENT
DRUG FOR FURTHER PROCESSING
ESTABLISHMENT DE-REGISTRATION
ESTABLISHMENT REGISTRATION
GENERIC DRUG FACILITY IDENTIFICATION SUBMISSION
HUMAN COMPOUNDED DRUG LABEL
HUMAN OTC DRUG LABEL
HUMAN PRESCRIPTION DRUG LABEL
IDENTIFICATION OF CBER-REGULATED GENERIC DRUG FACILITY

Document Types Currently in SPL

INDEXING - BILLING UNIT
INDEXING - BIOLOGICAL DRUG SUBSTANCE
INDEXING - INDICATION
INDEXING - PHARMACOLOGIC CLASS
INDEXING - PRODUCT CONCEPT
INDEXING - RISK EVALUATION & MITIGATION STRATEGIES
INDEXING - SUBSTANCE
INDEXING - WARNING LETTER ALERT
LICENSE BLOOD INTERMEDIATES/PASTE LABEL
LICENSED MINIMALLY MANIPULATED CELLS LABEL
LICENSED VACCINE BULK INTERMEDIATE LABEL
LOT DISTRIBUTION DATA
MEDICAL DEVICE
MEDICAL FOOD
NO CHANGE NOTIFICATION

Document Types Currently in SPL

NON-STANDARDIZED ALLERGENIC LABEL
NDC LABELER CODE INACTIVATION
NDC LABELER CODE INACTIVATION - ANIMAL DRUG
NDC LABELER CODE REQUEST - ANIMAL DRUG
NDC/NHRIC LABELER CODE REQUEST
OTC ANIMAL DRUG LABEL
OTC MEDICAL DEVICE LABEL
OTC TYPE A MEDICATED ARTICLE ANIMAL DRUG LABEL
OTC TYPE B MEDICATED FEED ANIMAL DRUG LABEL
OTC TYPE C MEDICATED FEED ANIMAL DRUG LABEL
OUT OF BUSINESS NOTIFICATION
PLASMA DERIVATIVE
PRESCRIPTION ANIMAL DRUG LABEL
PRESCRIPTION MEDICAL DEVICE LABEL
RECOMBINANT DEOXYRIBONUCLEIC ACID CONSTRUCT LABEL

Document Types Currently in SPL

REMS CONVERSION TO SHARED SYSTEM
REMS RELEASE
RISK EVALUATION & MITIGATION STRATEGIES
STANDARDIZED ALLERGENIC
VACCINE LABEL
VFD TYPE A MEDICATED ARTICLE ANIMAL DRUG LABEL
VFD TYPE B MEDICATED FEED ANIMAL DRUG LABEL
VFD TYPE C MEDICATED FEED ANIMAL DRUG LABEL
WHOLESALE DRUG DISTRIBUTORS AND THIRD-PARTY LOGISTICS FACILITY REPORT
WITHDRAWAL OF WHOLESALE DRUG DISTRIBUTORS AND THIRD-PARTY LOGISTICS FACILITY REPORT

Common SPLs for Drug Supply Chain

- In the order of submissions, SPL in XML is the standard for:
  - NDC/NHRIC Labeler Code Request
  - Establishment Registration
  - Product Listing and Certification

Required by the Regulations

- Establishment registration and drug listing:
  - Section 510 of the Federal Food, Drug, and Cosmetic Act
  - 207 of Title 21 of the Code of Federal Regulations (CFR)
- What?
- When?

Establishment Registration and Product Listing in SPL

- List of all current drug manufacturers
- Current inventory of all drugs in U.S. commercial distribution
- Available to:
  - FDA
  - Public
  - Health care professionals
  - Healthcare industry access

SPL Data Received From Over 80 Countries

- Each establishment in the supply chain registers
- Business operations identified
- Establishment linked to Product NDC

Specific FDA Use of Registration and Listing Data

- Electronic Drug Registration and Listing Database
  - Inspections
  - Imports
  - Post-marketing surveillance
  - Recalls and shortage programs
  - Adverse Event Reporting
- Supply chain security
- Counterterrorism
- And many more

FDA Compliance Procedure for Registration and Listing Data

- Surveillance
- Compliance case
- Deficiency letters
- Data exclusion
- Untitled Letters
- Warning Letters

Supply Chain Integrity Summary

- Current Registration and Listing via SPL provides visibility and traceability
- Encourages interaction between supply chain participants
- Quality Agreements/Defined responsibilities
- Ingredient and product source

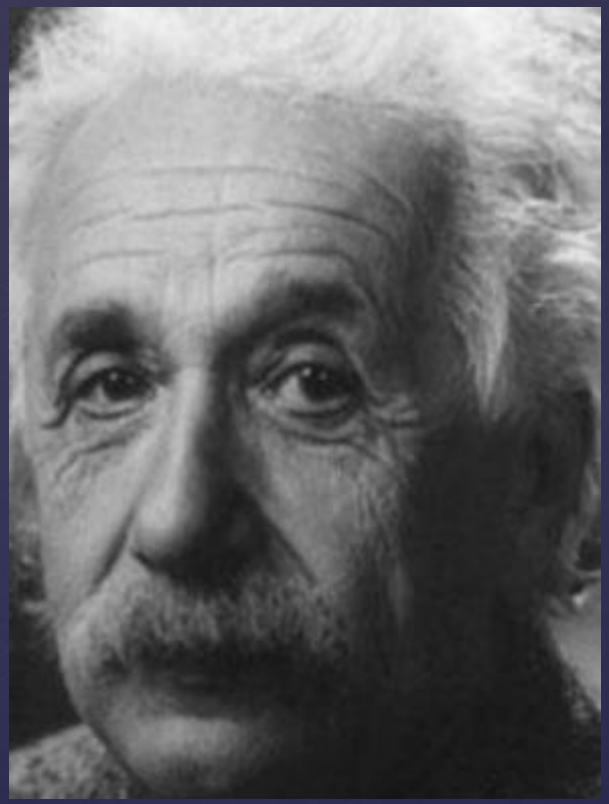
Supply Chain Integrity Summary

- Minimize the end-user's exposure to products that are:
  - adulterated in the traditional sense
  - adulterated due to economic motivation
  - misbranded containing unlabeled ingredients

Supply Chain Integrity Summary

- Minimize the end-user's exposure to products that are (continued):
  - meant for destruction and stolen or diverted
  - expired and relabeled to be sold to end-users
  - not transported and stored according to the environmental conditions stated on the label

Integrity



Whoever is careless with the truth in small matters cannot be trusted with important matters.

— Albert Einstein —

CDER Direct and Common SPL Documents

What is CDER Direct?

- A web based tool for electronic registration and listing
- Create, review, and send SPL submissions
- User-friendly templates to build SPL in XML
- Directly submit to FDA for internal processing
- Initial validations and provides the FDA response to the user

Who Uses CDER Direct?

- Individuals and Businesses responsible for:
  - NDC Labeler Code Requests
  - Establishment Registrations and annual updates
  - GDUFA Facility self-identification
  - Drug Listing
  - Product Listing
  - 503B outsourcing facility
    - Registration
    - Product reporting
  - Wholesale Drug Distributors and Third Party Logistics Providers (WDD/3PL) Report – product transactions – product exchange

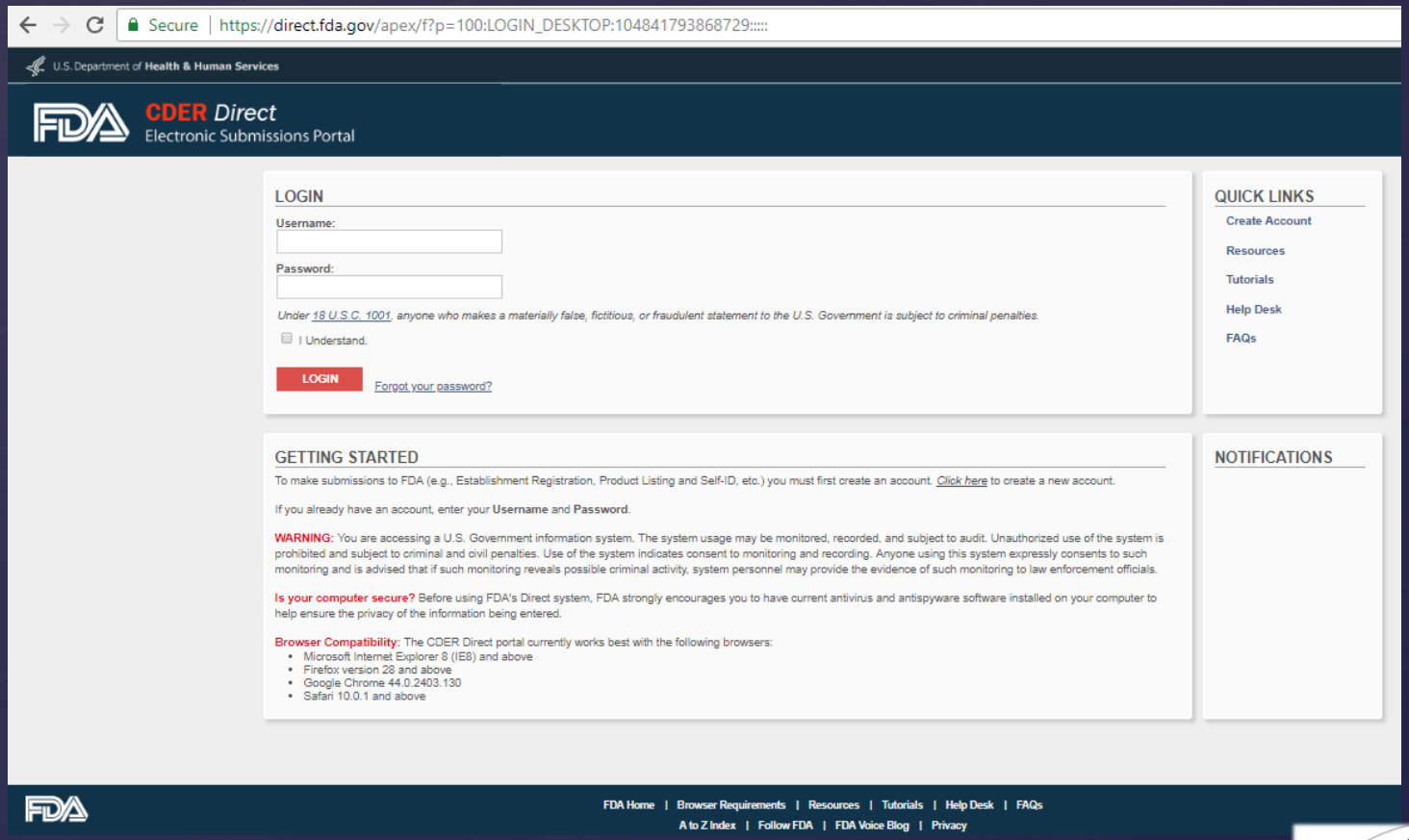
Available SPL Forms in CDER Direct

- Labeler code Request
- Establishment Registration/Update
- GDUFA Self ID
- 503B Outsourcing Facility Registration
- 503B Outsourcing Facility Product Reporting
- Wholesale Drug Distributors and Third Party Logistics Providers (WDD/3PL) Report – transactions and product exchange
- Product Listing and Certification

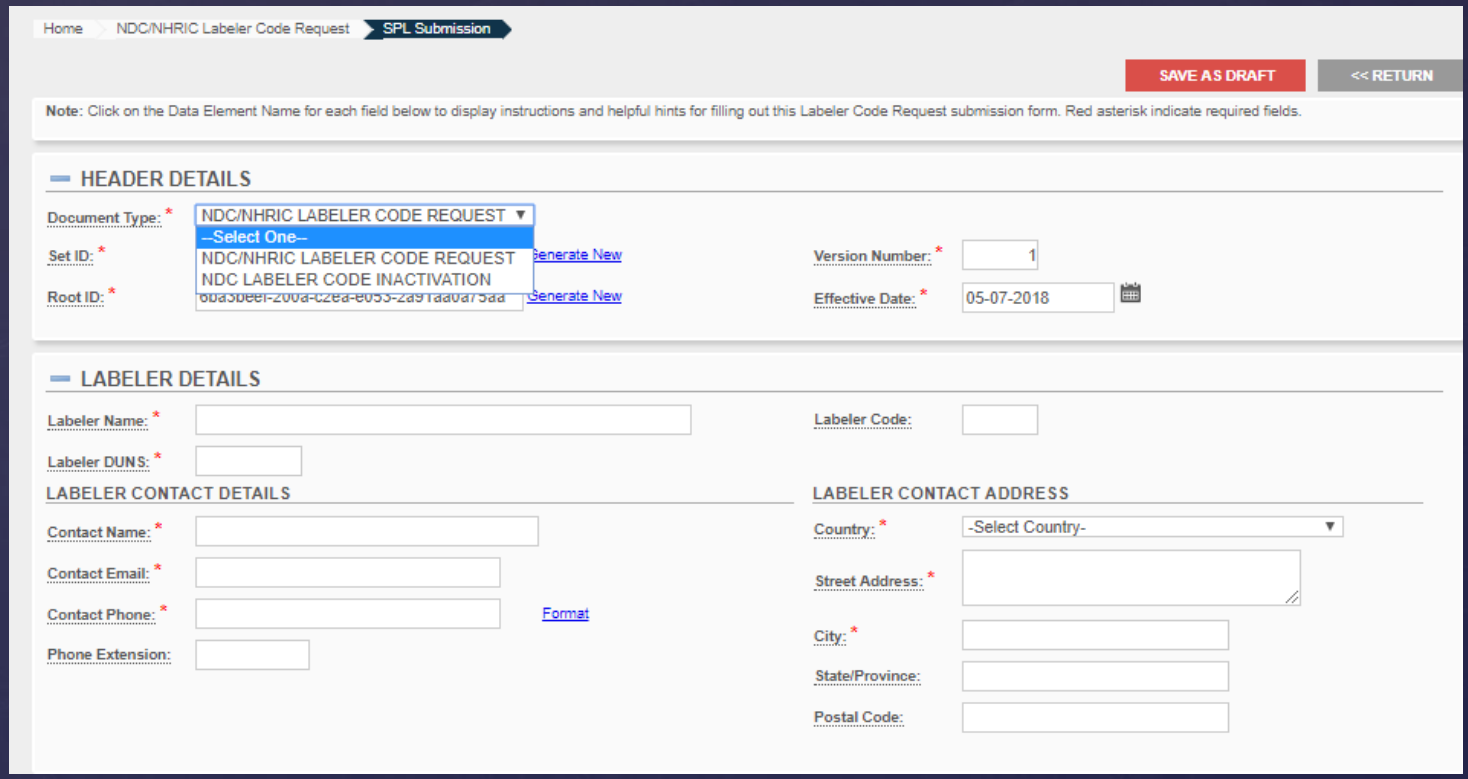
Product Listing and Certification SPLs in CDER Direct

- Bulk Ingredient
- Cellular Therapy
- Drug for Further Processing
- Human Compounded Drug Label
- Human OTC Drug Label
- Human Prescription Drug Label
- Non-Standardized Allergenic Label
- Plasma Derivative
- Standardized Allergenic
- Vaccine Label
- Blanket No Changes Certification of Product Listings (October 1st and December 31st.)

CDER Direct Log-In



CDER Direct NDCLCR



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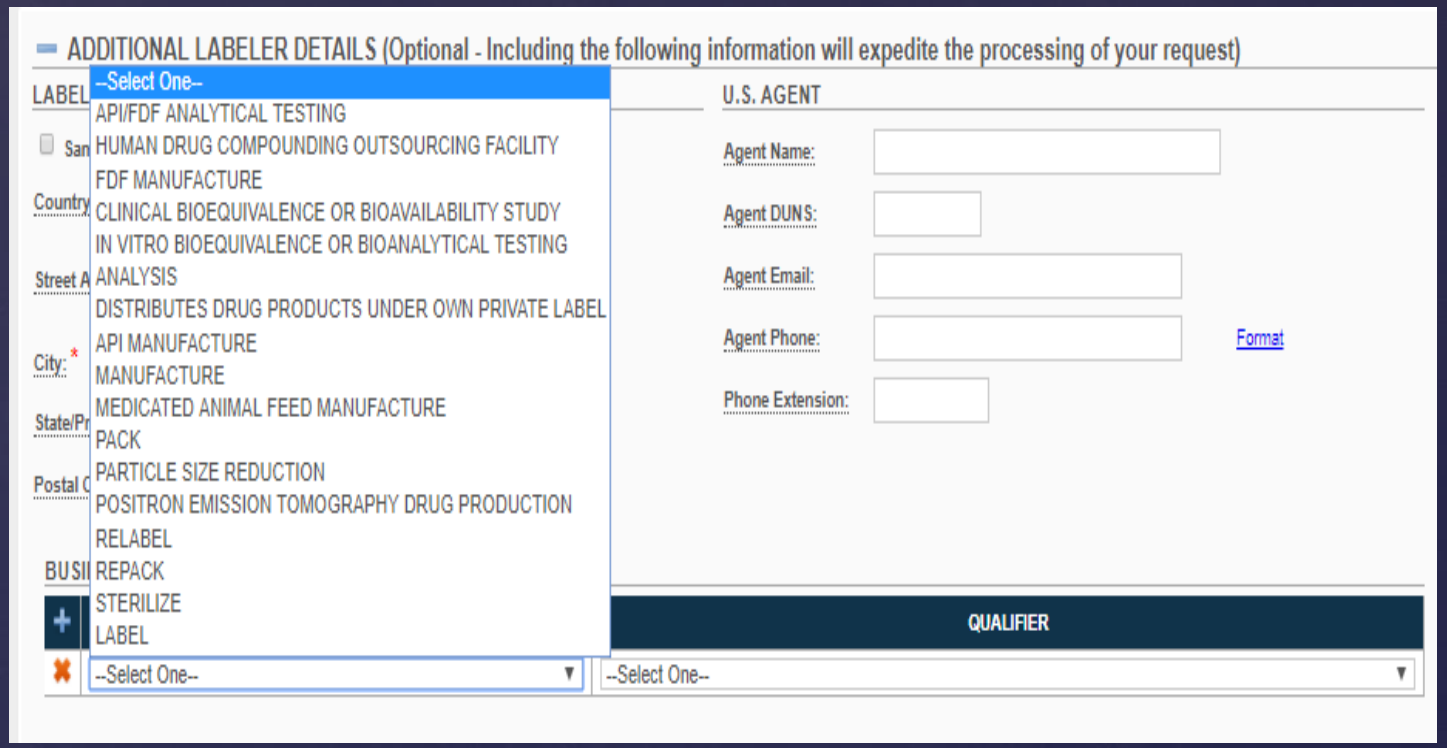
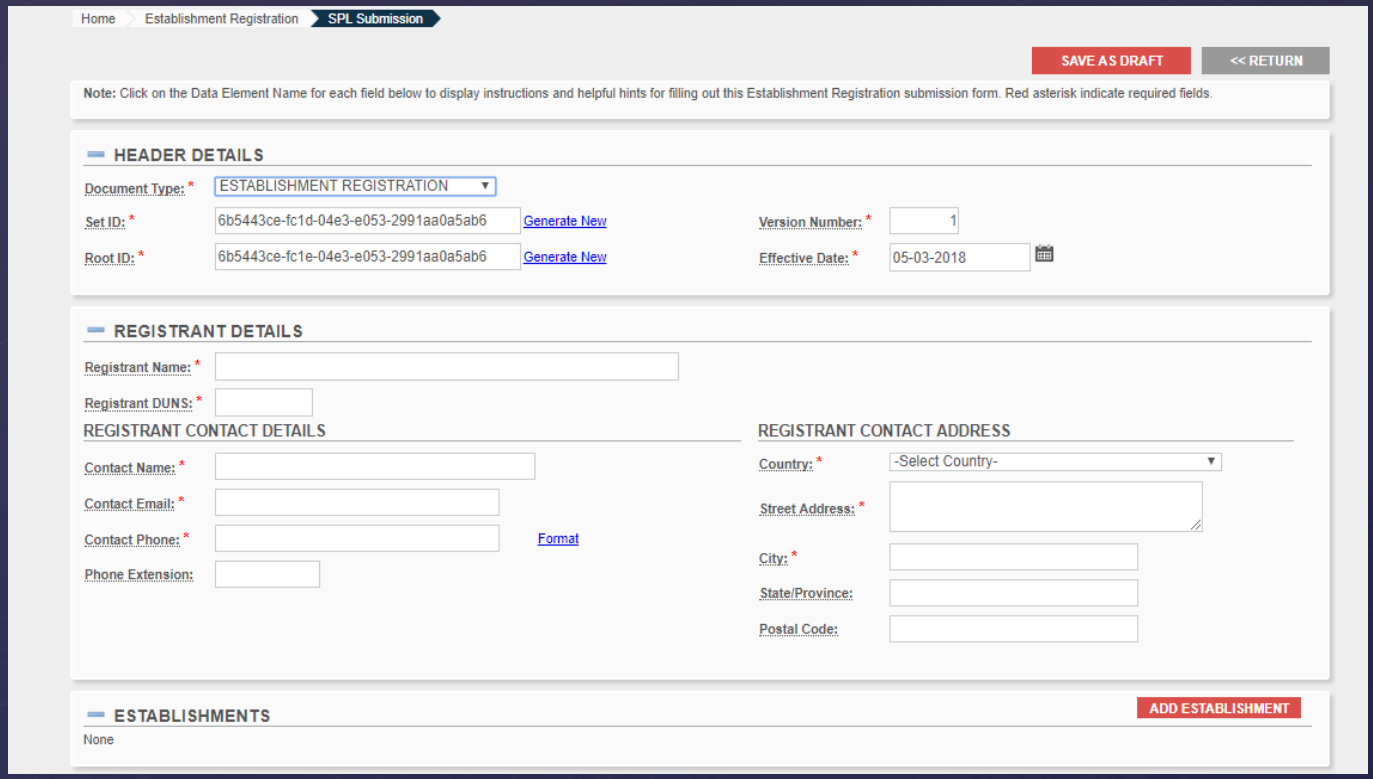


CDER Direct ER



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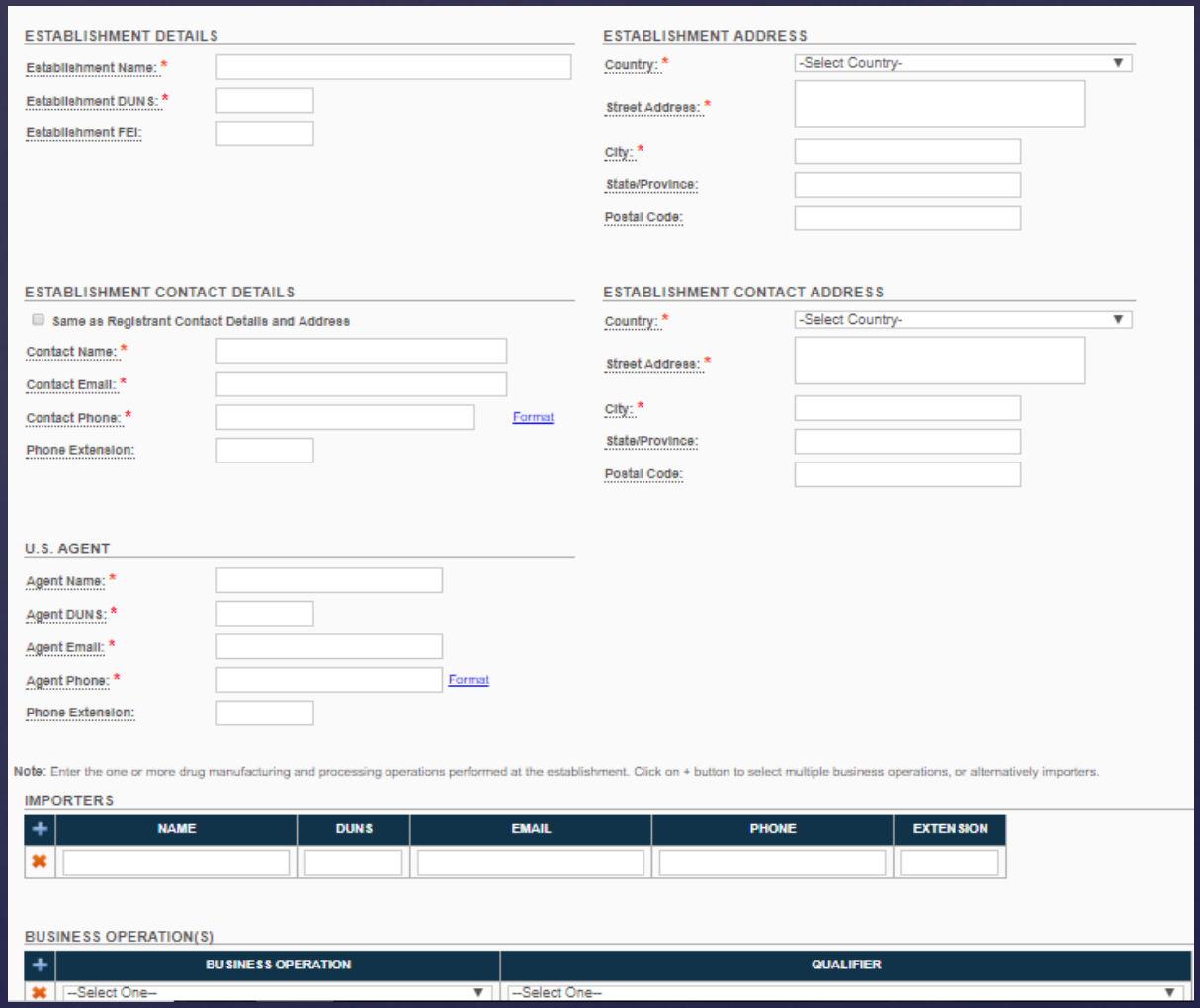

ESTABLISHMENT DETAILS

Establishment Name: *

Establishment DUNS: *

Establishment FEI:

ESTABLISHMENT ADDRESS

Country: * -Select Country-

Street Address: *

City: *

State/Province:

Postal Code:

ESTABLISHMENT CONTACT DETAILS

Same as Registrant Contact Details and Address

Contact Name: *

Contact Email: *

Contact Phone: * Format

Phone Extension:

ESTABLISHMENT CONTACT ADDRESS

Country: * -Select Country-

Street Address: *

City: *

State/Province:

Postal Code:

U.S. AGENT

Agent Name: *

Agent DUNS: *

Agent Email: *

Agent Phone: * Format

Phone Extension:

Note: Enter the one or more drug manufacturing and processing operations performed at the establishment. Click on + button to select multiple business operations, or alternatively importers.

IMPORTERS

+	NAME	DUNS	EMAIL	PHONE	EXTENSION
✖					

BUSINESS OPERATION(S)

+	BUSINESS OPERATION	QUALIFIER
✖	--Select One--	--Select One--

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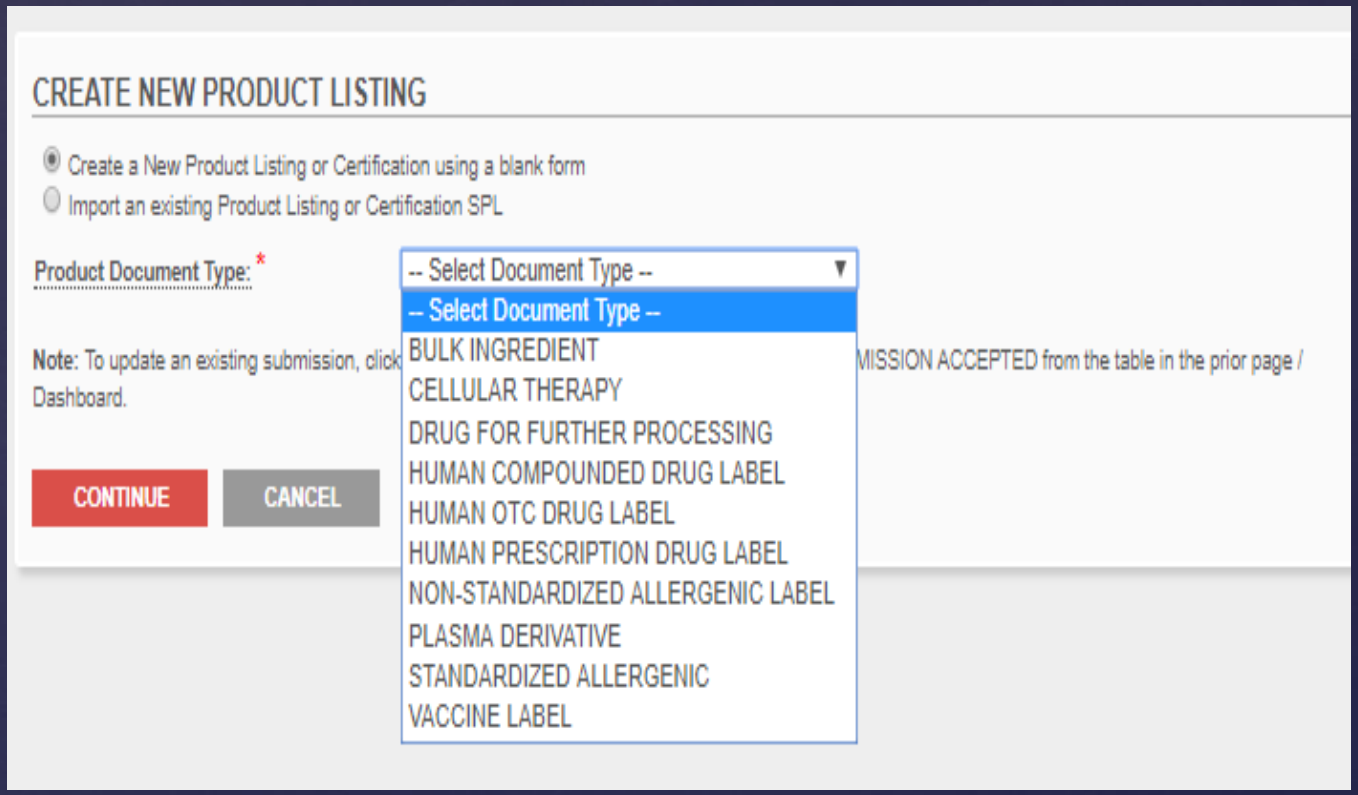
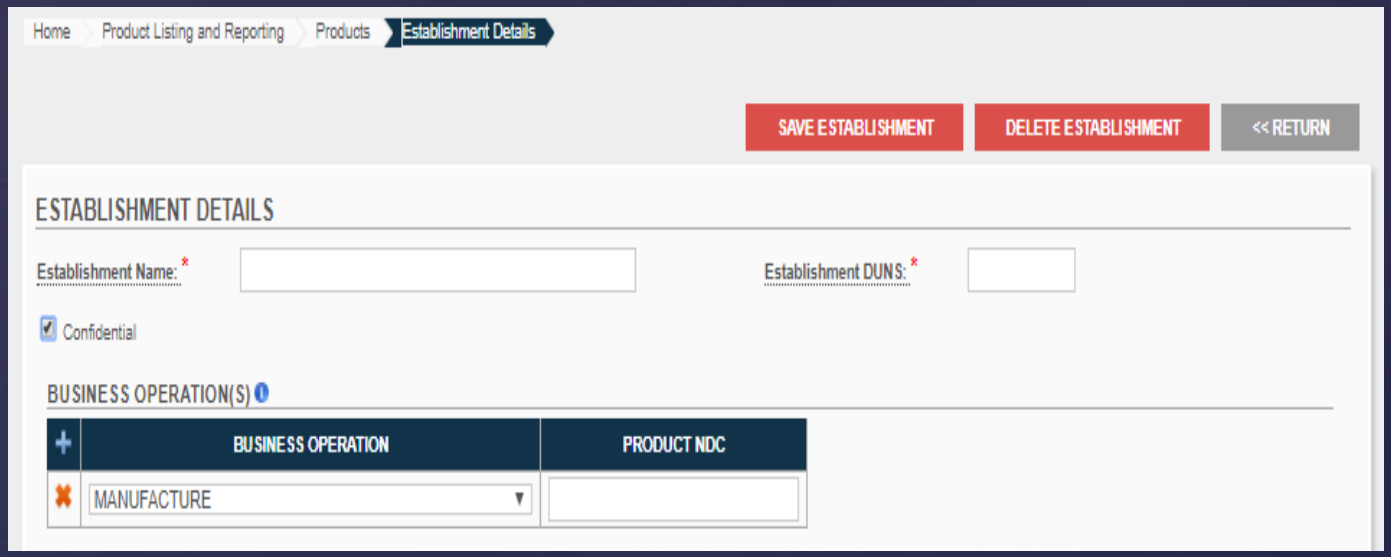
AFDO

Founded 1896

CDER Direct Product Listing



CDER Direct Product Listing



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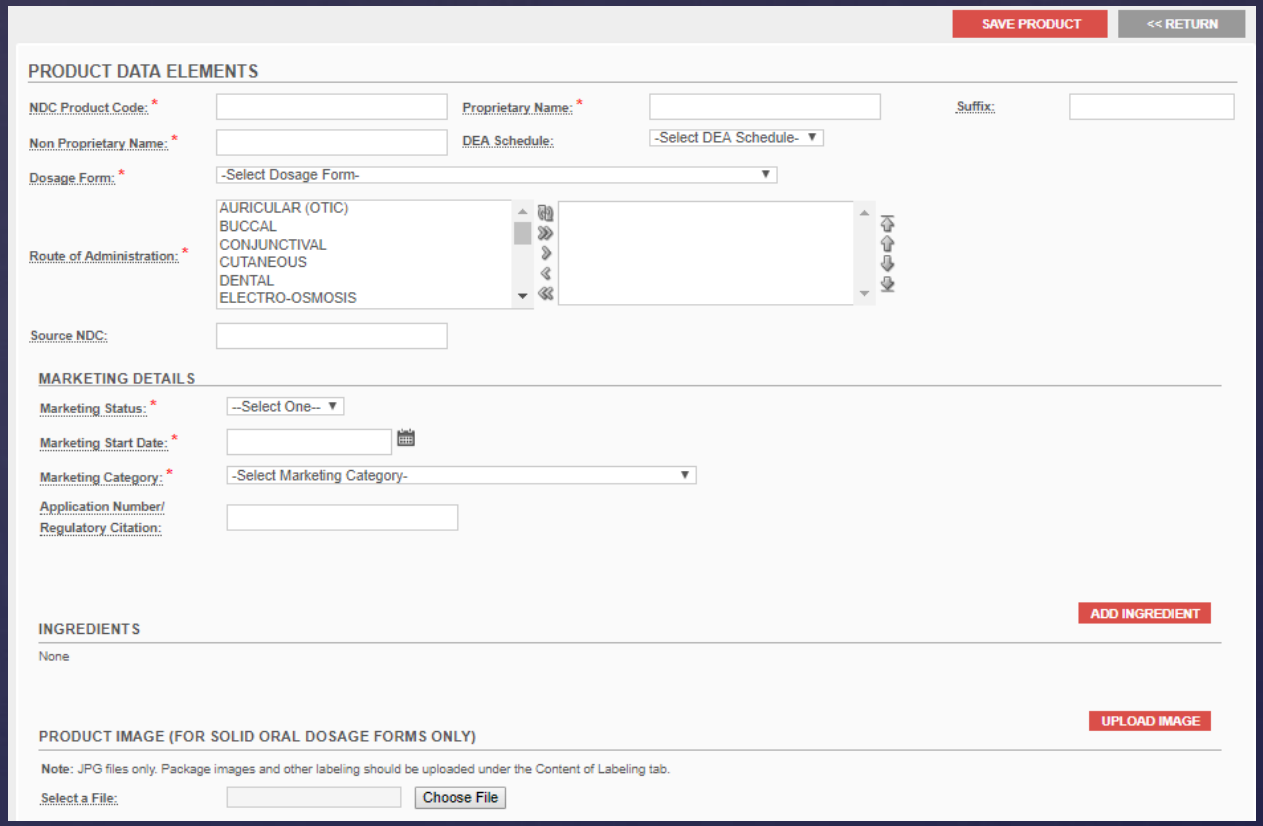
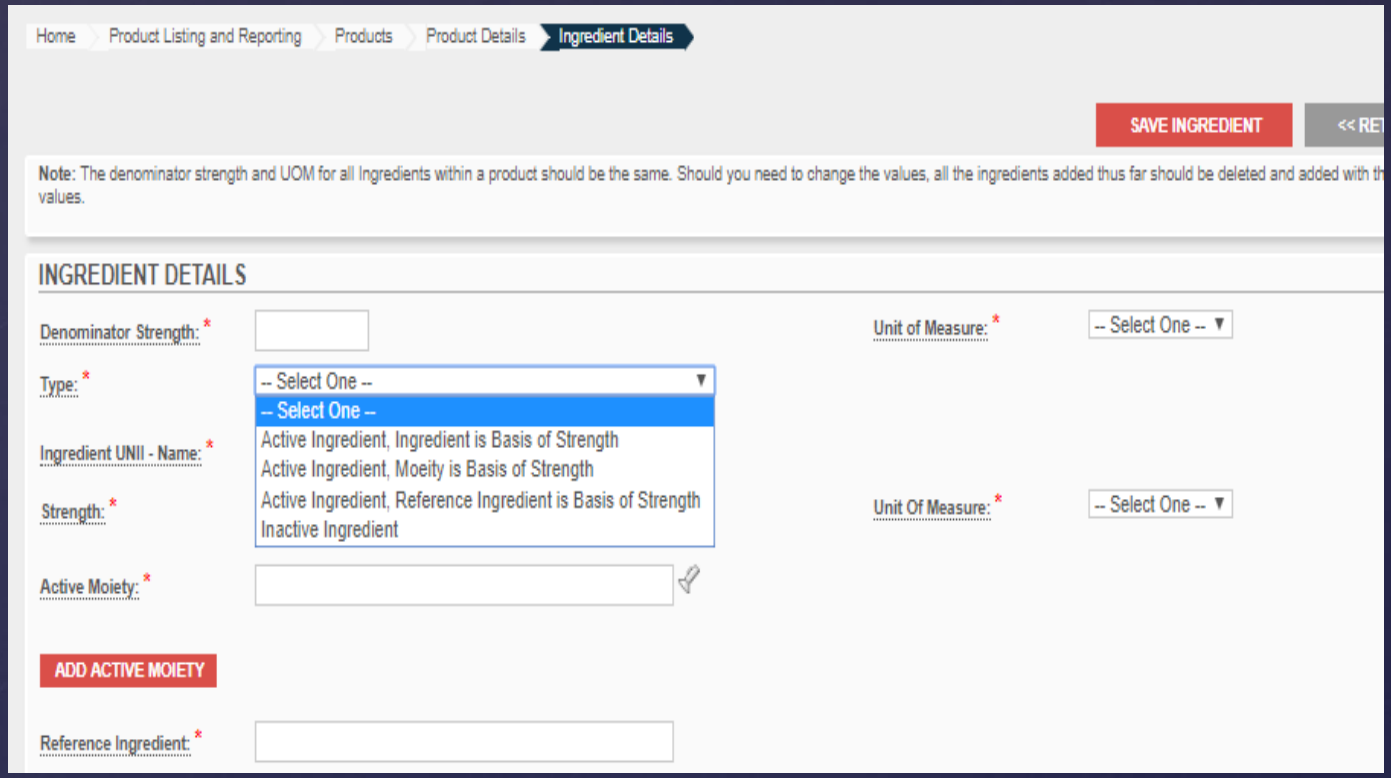
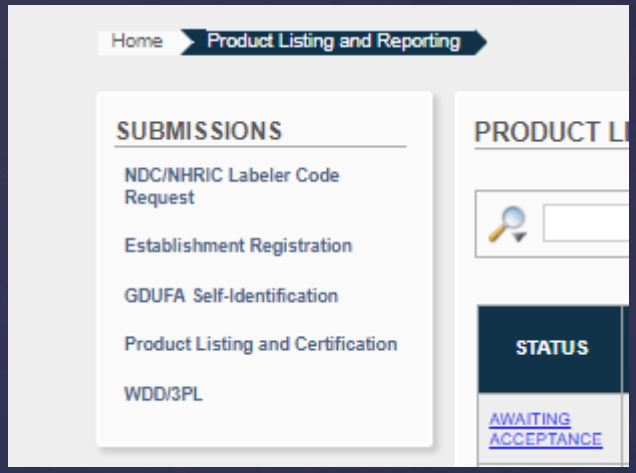
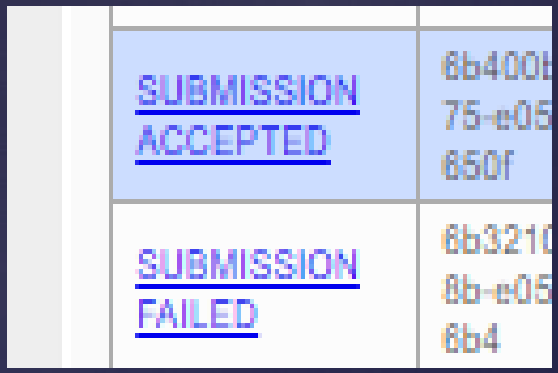


CDER Direct Product Listing

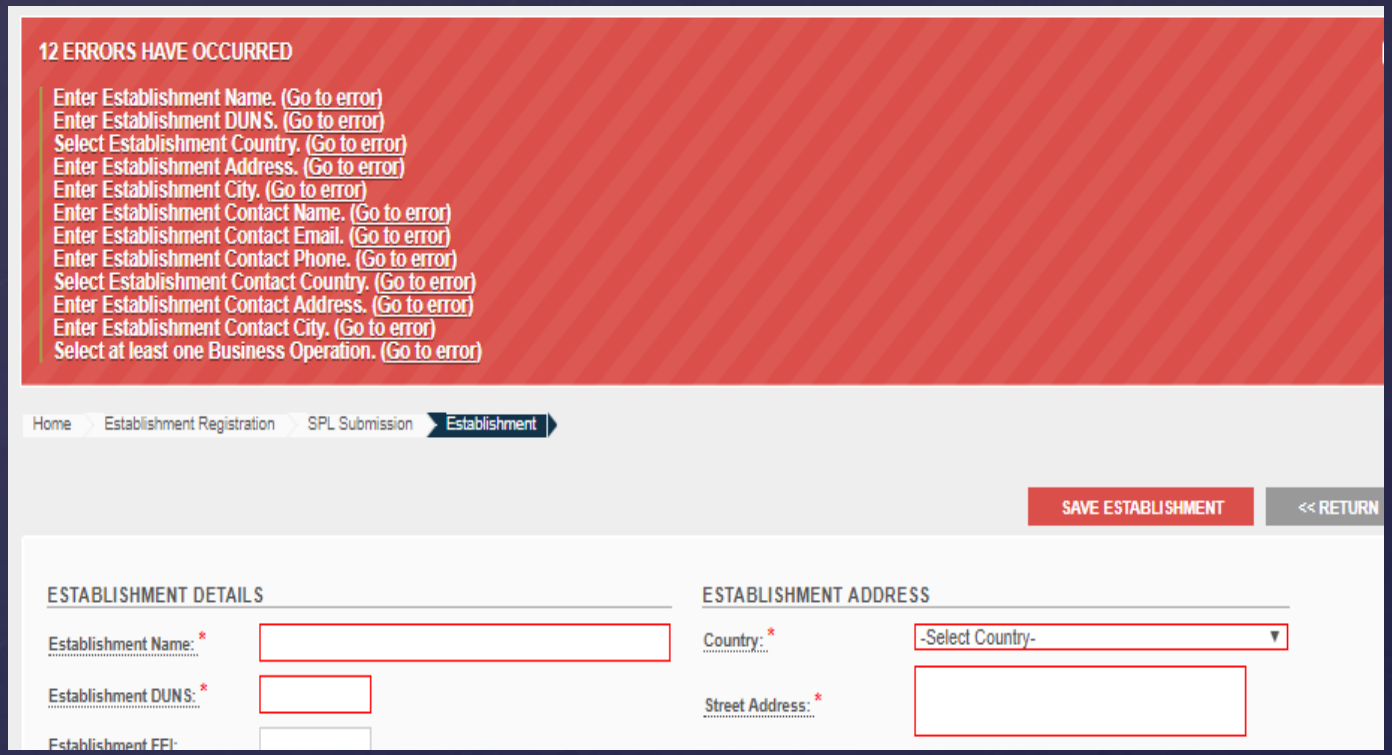


CDER Direct Submission





CDER Direct Errors



Scenarios of SPL use in management of supply chain integrity

Inaccurate SPL Information

- Missing/Incorrect establishment info
- Additional review of ingredients
  - Missing ingredients
  - Strength
  - Application number or monograph
- Comparison of submitted representative package image
- Possibly misbranded

Refusal of Import

- Product held at the port
- Database used by FDA compliance not updated
- Failure of foreign supply chain entity to list under the appropriate marketing category
- Product registered by domestic labeler

Compounding Pharmacy

- 503B reporting
- Validation errors
- Source - active/bulk or finished product used in a compounded product not listed

Questions?