

# Drug Listing Highlights

**Vikas Arora, PharmD.**

Consumer Safety Officer

Division of Labeling, Registration, and Unapproved Drugs

Office of Unapproved Drugs and Labeling Compliance

OC | CDER | US FDA

Electronic Drug Registration and Listing (eDRLS) Using CDER

Direct - 2024

# Learning Objectives

- Describe how to properly convert strengths on drug listings
- Describe how to accurately list combination products
- Explain the data inactivation process and how to resolve an inactivated listing

# Strength Conversion in Drug Listings



# Standardization and Compatibility

- Electronic format requires standardization and compatibility with SPL format
  - Dosage form
  - Route of administration
  - Units of measure
  - Active ingredient
  - Labeling
  - Strength

# Standardization and Compatibility

- FDA has adopted USP standards for expressing strength
- Strength cannot be expressed as percentage in SPL format
  - Should align with labeling
  - Must be converted to fraction/ratio
  - Numerator and denominator
  - Automatic validations in place to verify this format

# Strength Conversion

- Numerator strength/unit
  - Weight or volume of active ingredient
  - ex. mg and mL
- Denominator strength/unit
  - Weight or volume of drug base, time
  - ex. mg, mL, hour, tablet

# Strength Conversion Examples

Dosage Form* Type	SPL Numerator Unit	SPL Denominator Unit
Alcohol, Medical Gases, Water	Volume	Volume
Oral Solid (e.g., tablet, capsule, oral film)	Weight	Each
Oral Liquid	Weight	Volume
Oral powder for reconstitution with a known volume	Weight	Volume
Oral powder for reconstitution with a variable volume	Weight	Each
Suppository	Weight	Each
Injectable, liquid (e.g., solution, suspension, emulsion)	Weight	Volume
Injectable, solid intended for constitution/reconstitution	Weight	Each
Inhalation powder (e.g., dry powder inhaler)	Weight	Each

# Incorrect Strength Conversion

- Incorrect strength conversion can cause automated validation errors
- Can result in a compliance case
  - Corrections will require CDER's review and approval prior to a manual override



# Strength Conversion Listing Links

- Strength Conversion in Drug Listing:
  - <https://www.fda.gov/drugs/electronic-drug-registration-and-listing-system-edrls/strength-conversion-drug-listing>

# Identifying Combination Products in Drug Listings



# What are Combination Products?

- Product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product
- For drug listing purposes, they are two or more regulated components consisting of drug/biologic/device
  - Minimum of two different types
    - Drug-device
    - Drug-biologic
    - Drug-device-biologic

# Combination Product Categories

- Categories
  - Single-Entity
    - Two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity
  - Co-packaged
    - Two or more separate products co-packaged together in a single package or distributed as a unit
  - Cross-labeled
    - Two or more products distributed separately that are intended for combined use

# Is my product a Combination Product?

- For products recently approved as NDAs and ANDAs, 356h form can be referenced as sponsors must clearly identify combination products
- If unclear for older approved products or products not subject to FDA approval, contact Office of Combination Products at [Combination@FDA.GOV](mailto:Combination@FDA.GOV)

# Combination Product Listing



- How to identify in CDER Direct?
  - Within the Packaging data section, select the appropriate type on the drop-down listing for combination product:

The screenshot displays the 'PACKAGING' section of the CDER Direct interface. It includes several input fields: 'Check for Deletion' (checkbox), 'Is this a sample package?' (checkbox), 'Package NDC' (text box), 'Package Type' (dropdown menu), 'Quantity' (text box), 'Unit of Measure' (dropdown menu), 'Combination Product Type' (dropdown menu), 'Marketing Status' (text box), 'Marketing Start Date' (text box), and 'Marketing End Date' (text box). The 'Combination Product Type' dropdown menu is open, showing a list of options: '- Select Value -', '- Select Value -', 'Type 0: Not a Combination Product', 'Type 1: Convenience Kit of Co-Package', 'Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)', 'Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)', 'Type 4: Device Coated/Impregnated/Otherwise Combined with Drug', 'Type 5: Device Coated or Otherwise Combined with Biologic', 'Type 6: Drug/Biologic Combination', 'Type 7: Separate Products Requiring Cross Labeling', 'Type 8: Possible Combination Based on Cross Labeling of Separate Products (Temporary Type)', and 'Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)'. At the bottom right, there are buttons for 'PACKAGE', 'DELETE', and 'TO TOP'.

# Combination Product Listing Requirements

- Single-Entity
  - Must be listed with lead center (CDER, CBER, CDRH)
- Co-packaged
  - For drug-device products with a CDER lead, select kit for the dosage form, and then identify each component/part
- Cross-labeled
  - Must be listed with lead center if constituent parts are approved under single application and under multiple centers if separately approved.

# Combination Product Type Definitions



Type	Description	Common Example(s)
1	<p>Convenience Kit or Co-Package</p> <p><i>Drug and device are provided as individual constituent parts within the same package</i></p>	Drug or biological product vials packaged with device(s) or accessory kits (empty syringes, auto-injectors, transfer sets), first aid or surgical kits containing devices and drugs
2	<p>Prefilled Drug Delivery Device/ System</p> <p><i>Drug is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver drug</i></p>	Prefilled drug syringe, auto-injectors, metered-dose inhalers, dry powder inhalers, nasal-spray, pumps, transdermal systems, prefilled iontophoresis system or microneedle "patch"
3	<p>Prefilled Biologic Delivery Device/ System</p> <p><i>Biological product is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver biological product</i></p>	Vaccine or other biological product in a prefilled syringe, autoinjector, nasal spray, transdermal systems or microneedle patch pre-loaded with biological product
4	<p>Device Coated/ Impregnated/ Otherwise Combined with Drug</p> <p><i>Device has an additional function in addition to delivering the drug</i></p>	Drug pills embedded with sensors, contact lens coated with a drug, drug-eluting stents, drug-eluting leads, condoms with spermicide, dental floss with fluoride, antimicrobial coated catheters/sutures, bone cements with antibiotics
5	<p>Device Coated or Otherwise Combined with Biologic</p> <p><i>Device has an additional function in addition to delivering the drug</i></p>	Live cells seeded on or in a device scaffold, extracorporeal column with column-bound protein
6	Drug/Biologic Combination	Antibody-drug conjugates, progenitor cells combined with a drug to promote homing
7	Separate Products Requiring Cross Labeling	Light-activated drugs or biological products not co-packaged but labeled for use with a specific light source device
8	Possible Combination Based on Cross Labeling of Separate Products	Drug/biological product under development utilizes a device, but unclear whether the final product will require that the two be cross-labeled
9	<p>Other Type of Part 3 Combination Product (e.g., Drug/Device/ Biological Product)</p> <p><i>Combination product not otherwise described</i></p>	All 3 articles are combined in a single product (e.g., a prefilled syringe containing an antibody-drug conjugate), device to manufacture a biologic also includes a drug or biologic in the kit, or the product contains two different combination product types (e.g., Type 1 and Type 2 are provided together)



# Combination Product Listing Links

- Office of Combinations Products page
  - <https://www.fda.gov/combination-products>
- Combination Product contact information:
  - [Combination@fda.gov](mailto:Combination@fda.gov)
- Definitions of combination product codes:
  - <https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types>
- SPL page for combination product types:
  - <https://www.fda.gov/industry/structured-product-labeling-resources/combination-product-types>

# Data Inactivation Process



# Data Inactivation FR Notice

- Federal Register Notice published on August 14, 2019
  - Announced FDA's intent to inactivate outdated drug listings
- Two annual inactivation periods for different violations:
  - January
  - July

# Data Inactivation Notification

- Notification e-mail is sent to the labeler point of contact with the estimated date of inactivation if no updates are made
  - Verify that the Labeler Code SPL has the most updated contact information

# Annual Certification Requirement

- 21 CFR 207.57(b)(2)
  - After initial electronic listing, registrants may satisfy the listing update requirement with respect to unchanged listing information by making a single “no changes” certification during the annual registration update under §207.29(b) applicable to all of the registrant's listed drugs for which no changes have been made since the previous annual registration update
- If drug listing was updated during current calendar year, you are certified

# January Inactivation

- Drug listings not updated during calendar year with a new version of an updated SPL or missing the annual certification period
- If you receive an inactivation notification e-mail, a new version of the drug listing SPL must be submitted to reactivate/correct the data depending on the situation

# July Inactivation

- Drug listing files that remain active and certified after the June listing update, but contain at least one establishment not duly registered with FDA
- 21 CFR 207.57(b) states “Registrants must review and update their drug listing information each June and December”
  - If updates are not made by the June requirement, those drug listings which are still linked to an unregistered establishment are inactivated in July

# Consequences of Inactivation

- Removal from FDA databases
- Flagged in DailyMed
- Possible CMS reimbursements issues
  - Listing inactivation dates are transmitted through the NDC SPL Data Elements (NSDE) file



## Resolving Inactivation

- Once inactivation has occurred, a new version of SPL is required to be submitted
- Can take 24-48 hours for a successful submission to be reactivated and take additional time for downstream publications to be updated

# Data Inactivation Links

- Drug Registration and Listing Requirements:
  - <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-207>
- Federal Register: Drugs Intended for Human Use That Are Improperly Listed Due to Lack of Annual Certification or Identification of a Manufacturing Establishment Not Duly Registered With the Food and Drug Administration; Action Dates:
  - <https://www.federalregister.gov/documents/2019/08/14/2019-17436/drugs-intended-for-human-use-that-are-improperly-listed-due-to-lack-of-annual-certification-or>

# Summary

- Be vigilant when converting strengths from labels into the standardized strengths formats in the SPL
- For combination product listings, it is important to accurately describe the type of combination product in your listing as well as list your product with the correct center
- Be aware of the data inactivation timelines that occur in January and July and certify or update your listings accordingly

# Challenge Question #1

**True or False: The strength of an oral drug product that is a powder intended for reconstitution with variable volume should be described in the SPL as “Weight” in the SPL numerator and “Each” in the SPL denominator in the drug listing.**

**True**

**False**

## Challenge Question #2

**True or False: Co-packaged drug-device products with a CDER lead, must select kit as a dosage form when listing the product.**

**True**

**False**

## Challenge Question #3

**If a manufacturer referenced in a drug listing has been deregistered in February of a calendar year due to no longer manufacturing drug product for commercial distribution, when must the drug listing be updated?**

- A) February**
- B) June**
- C) December**
- D) Never**

# Questions?

[edrls@fda.hhs.gov](mailto:edrls@fda.hhs.gov)

