Regulatory Education for Industry (REdI): Focus on CGMPs & FDA Inspections

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Packaging & Labeling

Presenters:

Karen Takahashi, Senior Policy Advisor

Division of Regulations, Guidance, and Standards

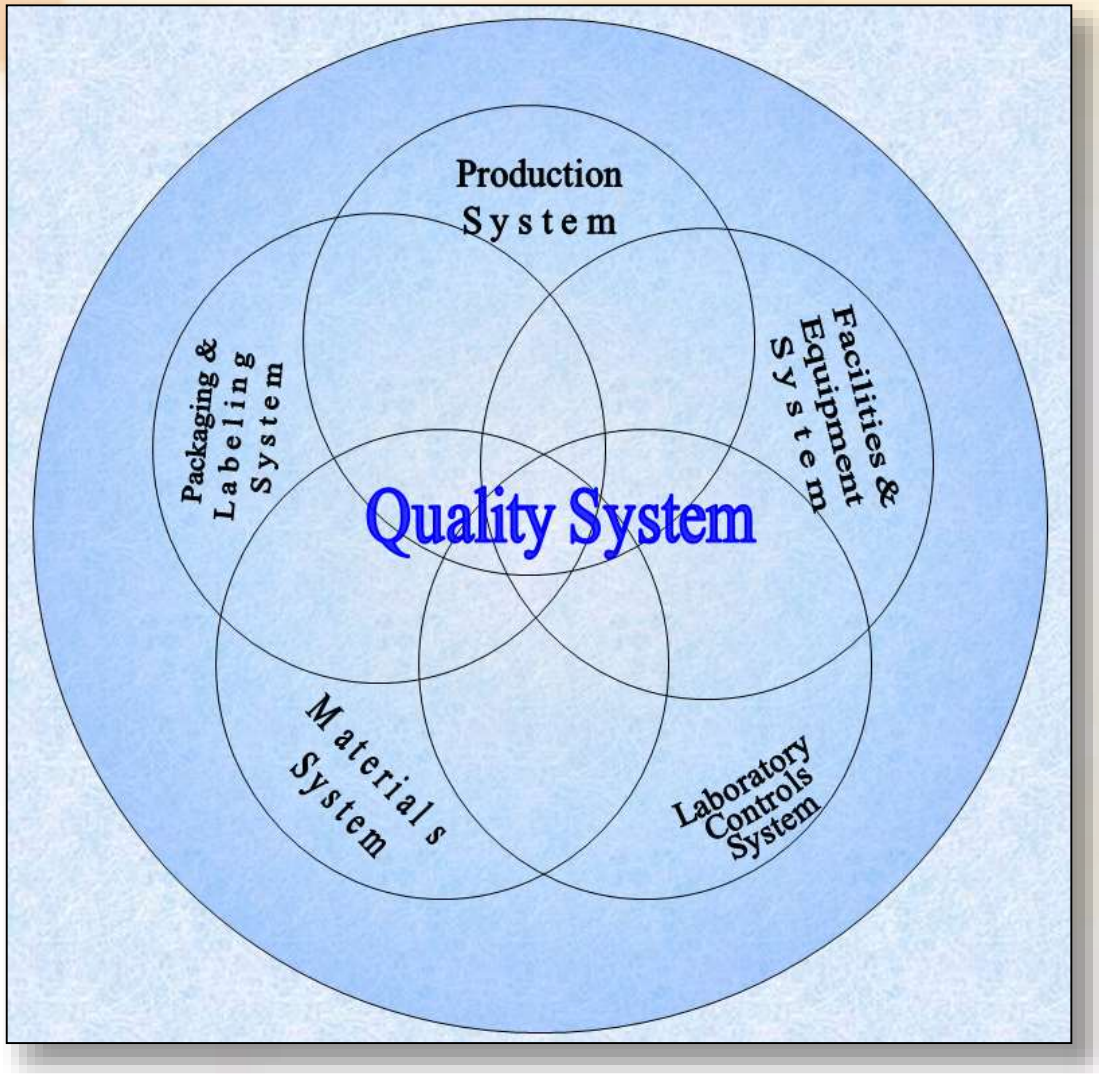
Office of Policy for Pharmaceutical Quality

Allison A. Aldridge, Ph.D., Team Leader

Division of Drug Quality, Office of Manufacturing Quality

The Six Components

- Quality
- Production
- Laboratory
- Materials
- Facilities & Equipment
- Packaging & Labeling

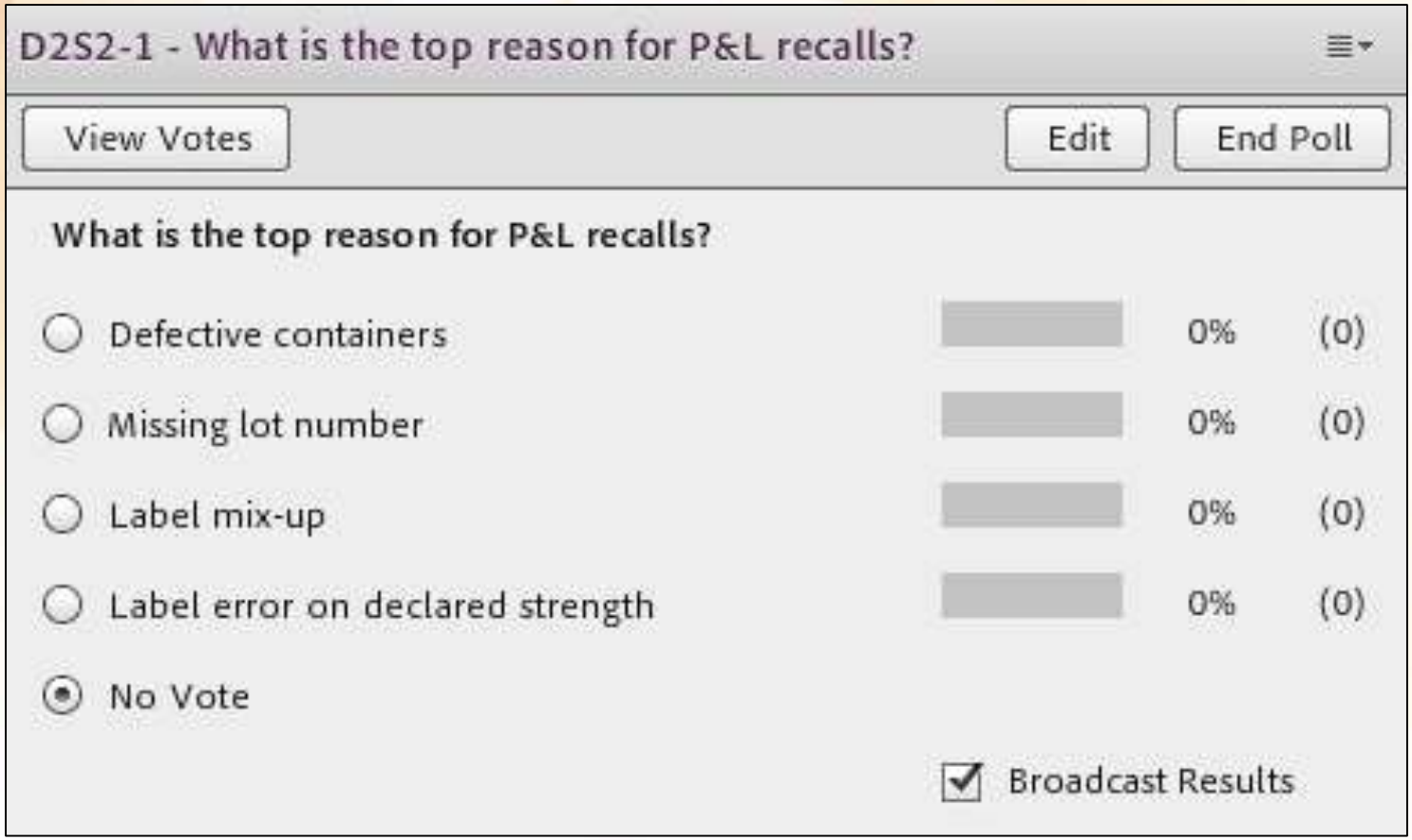


Overview

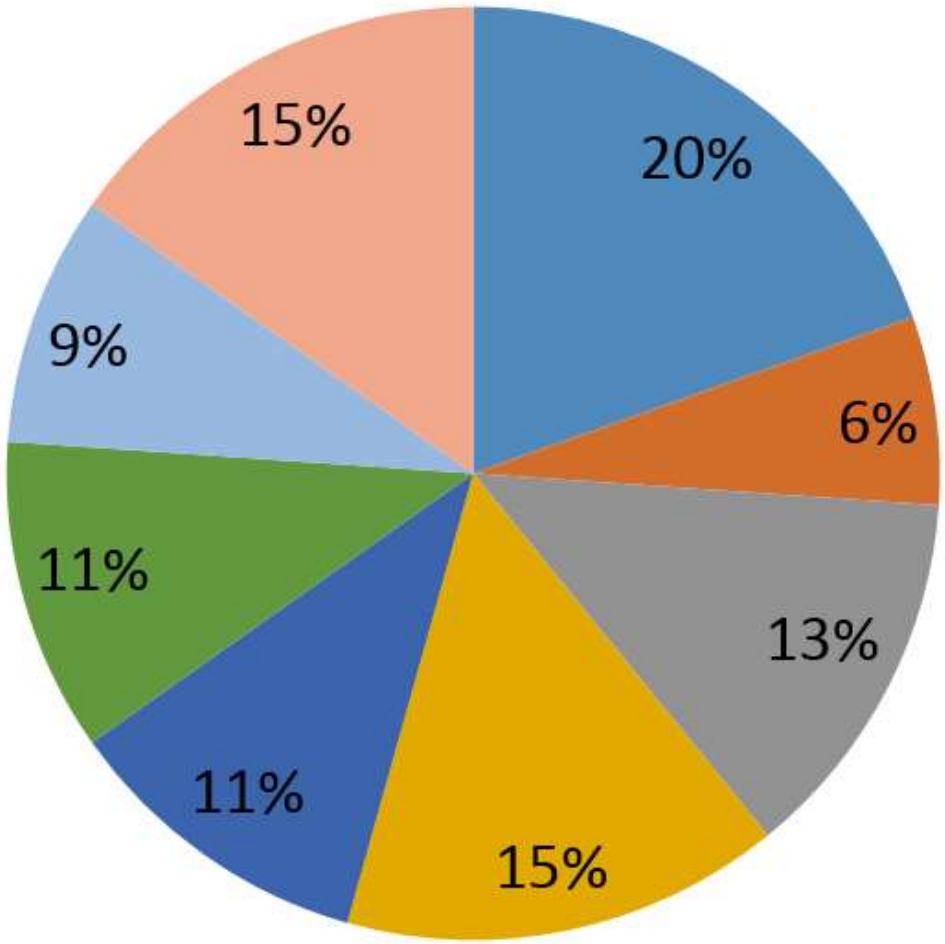
- Introduce the 21 CFR 211 Subpart G:
  - Material examination and usage criteria - § 211.122
  - Labeling issuance - § 211.125
  - Packaging and Labeling (P&L) Operations - § 211.130
  - Tamper-evident packaging - § 211.132
  - Drug Product (DP) Inspection - § 211.134
  - Expiration dating - § 211.137
- Questions

Poll Question

What is the top reason for P&L recalls?



2014 P&L Recall Events



- Defective Container (9)
- Incorrect or missing package insert (3)
- Incorrect/missing lot # (6)
- Error on declared strength (7)
- Label mix-up (5)
- Miscarton or mispackaged (5)
- Presence of undeclared color additive (4)
- Misc. (7)

§211.122 – Materials Examination and Usage Criteria

a) Written procedures for approval and rejection of materials

b) The procedures need to detail:

- Receipt
- Identification
- Storage
- Handling
- Representative sampling
- Examination and/or testing

} Upon receipt and before use

§211.122 – Materials Examination and Usage Criteria

a) Records shall be maintained for each shipment of materials

- Receipt
- Examination or testing
- Whether accepted or rejected

b) Storage area access limited to authorized personnel

§211.122 – Materials Examination and Usage Criteria

c) Separate storage for P&L materials for each different drug
   - Product
   - Dosage form
   - Strength
   - Quantity of contents

d) Obsolete P&L materials shall be destroyed

e) P&L materials not meeting specification shall be rejected

§211.122 – Materials Examination and Usage Criteria

a) Gang-printed labeling is a sheet of labeling that contains more than one item of labeling, for example:

- Different drug products, strengths, or net contents of same drug

b) Gang-printed sheets are prohibited unless well differentiated

- By size, shape, and color

§211.122 – Materials Examination and Usage Criteria

a) Cut labeling - single labels for individual drug products that are “cut” from a sheet or roll of labels

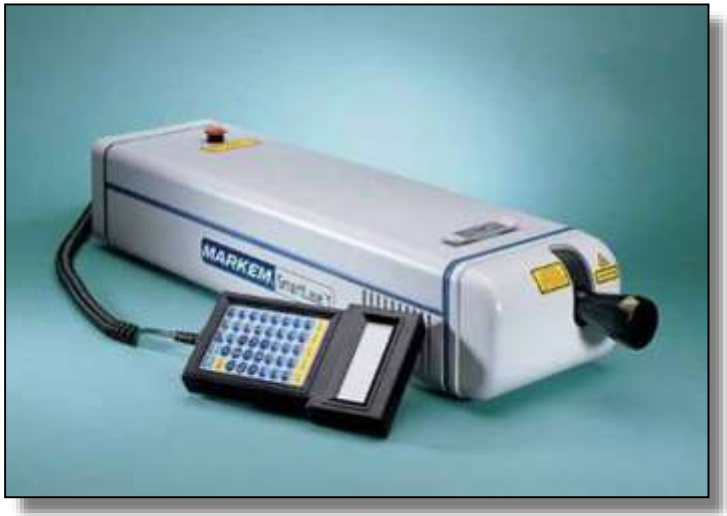
b) Cut labeling operations shall include one of the following:

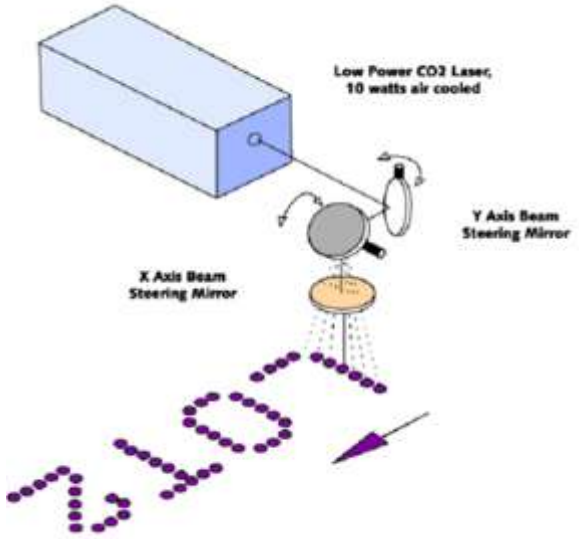
- P&L lines dedicated for each strength of each DP
- Equipment used of to conduct 100% examination
- 100% verified visual inspection for hand-applied labeling
- Automated technology that prevents incorrect labeling

§211.122 – Materials Examination and Usage Criteria

Printing Verification/Control Devices:

- Monitored to assure imprinting conforms to the batch record
- Used for DP, case and carton labels
- Recommended to avoid mislabeled DP





§211.125 – Labeling Issuance

a) Written procedures must be established and followed

b) Strict control over labeling issued for use in DP labeling operations

c) Labeling materials issued for a batch should be examined

- Identity
- Conformity to labeling specified in master or batch production record

§211.125 – Labeling Issuance

d) Label reconciliation procedures that include:

- Quantities used
- Quantities returned
- Evaluation of quantity discrepancies outside narrow preset limits
- Discrepancies shall be investigated
- Waive for cut or roll labeling with 100% inspection

§211.125 – Labeling Issuance

e) All excess labeling with lot or control numbers shall be destroyed

f) Returned labeling shall be maintained in a manner to prevent mix-ups

§211.130 – P & L Operations

a) Written procedures shall incorporate the following features:

- Prevention of mix-ups and cross-contamination
- Identification and handling of unlabeled DPs including:
  - Name
  - Strength
  - Quantity of contents
  - Lot or control number of each container

§211.130 – P & L Operations

a) Written procedures shall incorporate the following features:

- (cont'd)..
- Identification by lot or control number for traceability to manufacture
- Examination of materials for suitability and correctness before production
- Inspection of the packaging line prior to use

Allison A. Aldridge, Ph.D.

Team Leader

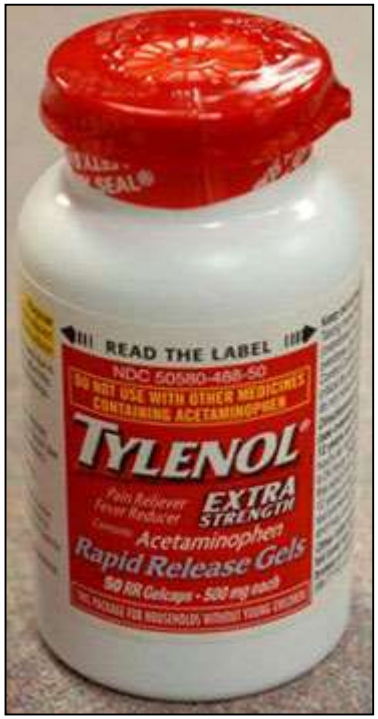
Division of Drug Quality

Office of Manufacturing Quality

Poll Question

What year was the Tylenol® tampering incident?

§211.132 – Tamper-Evident Packaging



§211.132 – Tamper-Evident Packaging

Since 1989,

a) Manufacturers and packers of over the counter (OTC) DPs

b) DPs for retail sale

c) DPs accessible to the public while held for sale

§211.132 – Tamper-Evident Packaging

Labeling requirements include:

- Identifying all tamper-evident features and any capsule sealing technology
- Placing labeling prominently on the package
- Placing labeling to be unaffected if the feature is breached or missing

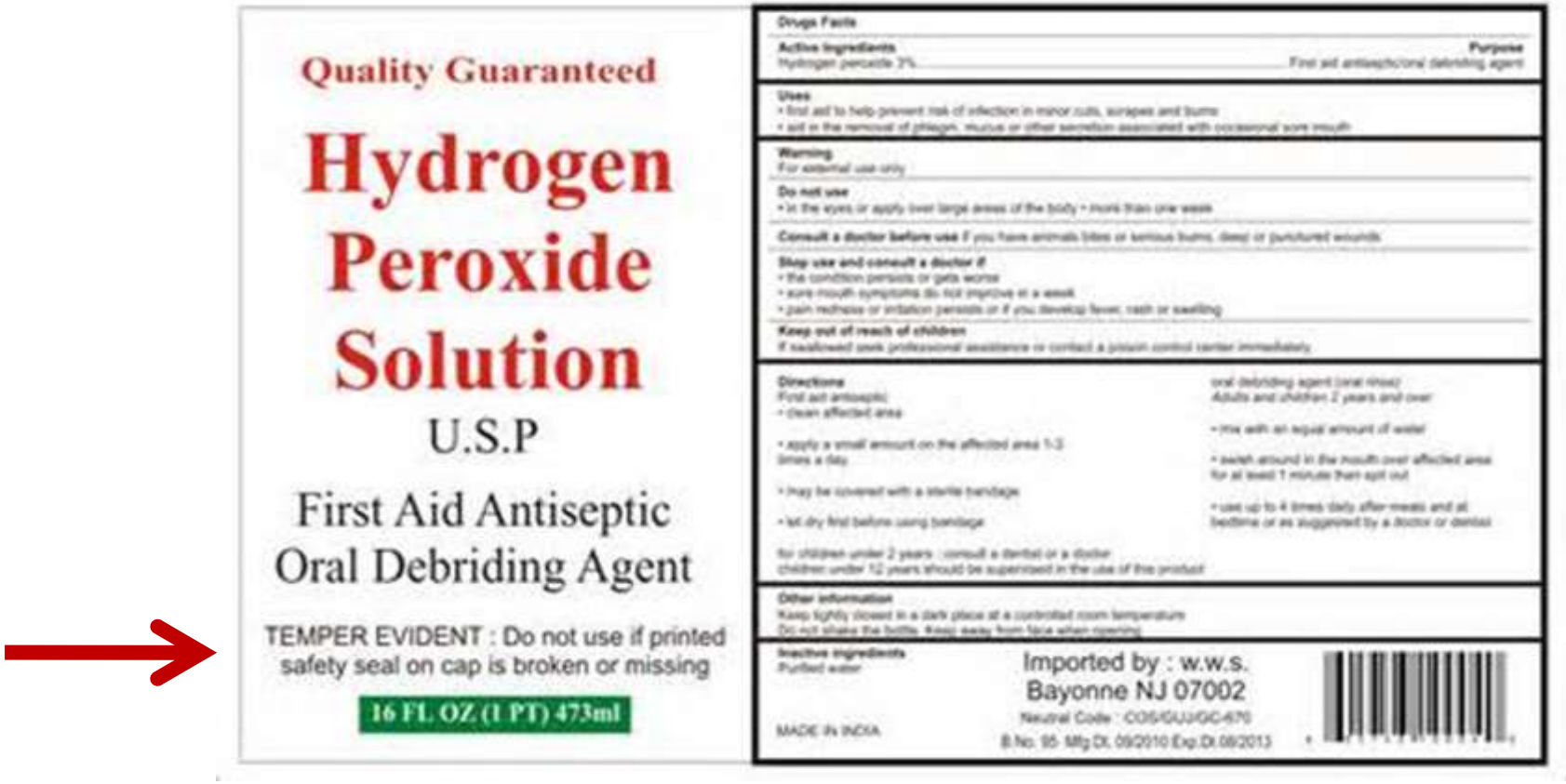
§211.132 – Tamper-Evident Packaging

Labeling requirements include (cont'd):

- Providing one or more indicators or barriers to package tampering
- Ensuring package cannot be duplicated easily - distinctive by design
- Ensuring packaging remains intact during handling up to retail display

§211.132 – Tamper-Evident Packaging

Tamper-evident characteristic is required to be referred to in a labeling statement



§211.132 – Tamper-Evident Packaging

Any two-piece hard gelatin capsule covered must be sealed using tamper-evident technology after the Tylenol® incident of 1982

§211.132 – Tamper-Evident Packaging

a) DPs Exempt from tamper-evident packaging
   - Dermatological
   - Dentrifice
   - Insulin
   - Lozenge

b) Labeling exemptions
   - Ammonia inhalant in crushable glass ampules
   - Compressed gas to expel the contents from the container

§211.132 – Tamper-Evident Packaging

a) Request for exemptions from P&L requirements

- Submit in the form of a citizen petition (CP) under § 10.30
- Label the envelope with “Request for Exemption from the Tamper-Evident Rule”

§211.132 – Tamper-Evident Packaging

b) Citizen petition requirements

- Name of DP or drug class with a list of DPs within the class
- Reasons why compliance is unnecessary or cannot be achieved
- Description of alternative steps available to reduce tampering
- Other information justifying an exemption

§211.132 – Tamper-Evident Packaging

c) OTC DPs subject to approved new drug applications

- Required under § 314.70 to notify the agency of changes in P&L
- Manufacturing changes to capsule sealing require prior FDA approval

d) Poison Prevention Packaging Act of 1970

- § 211.132 does not affect any requirements for “special packaging”

§211.132 – CPG & Packaging Features

Topic:

Tamper-Resistant Pkg. Requirements for Certain OTC Human DPs

Guidance:

1. Policy Guide (CPG): 450.500

Key Points:

- **Acceptable packaging features**
- **Ineffective packaging features**
- **Capsule sealing technologies**
- **Labeling statements**

§211.132 – CPG & Packaging Features

Topic:

Good Packaging Practices

Guidance:

1. **USP General Chapter <1177> GOOD PACKAGING PRACTICES**

Key Points:

- **Containers**
- **Packaging**
- **Environmental issues**
- **Labeling**

§211.134 – Drug Product Inspection

a) Packaged and labeled products examined to assure they have correct label

b) Representative samples of units visually inspected for correct labeling

c) Results of these examinations shall be recorded in the batch production or control records

§211.137 – Expiration Dating

Applies to all labeling

a) Assures the DP is acceptable at the time of use:
   - Identity, strength, quality, and purity
   - Shall bear an expiration date

b) Ensures storage conditions as stated on the labeling

c) Includes labeling information for reconstituted drugs also

d) Includes dates on labeling according to § 201.17

§211.137 – Expiration Dating

Exemptions:

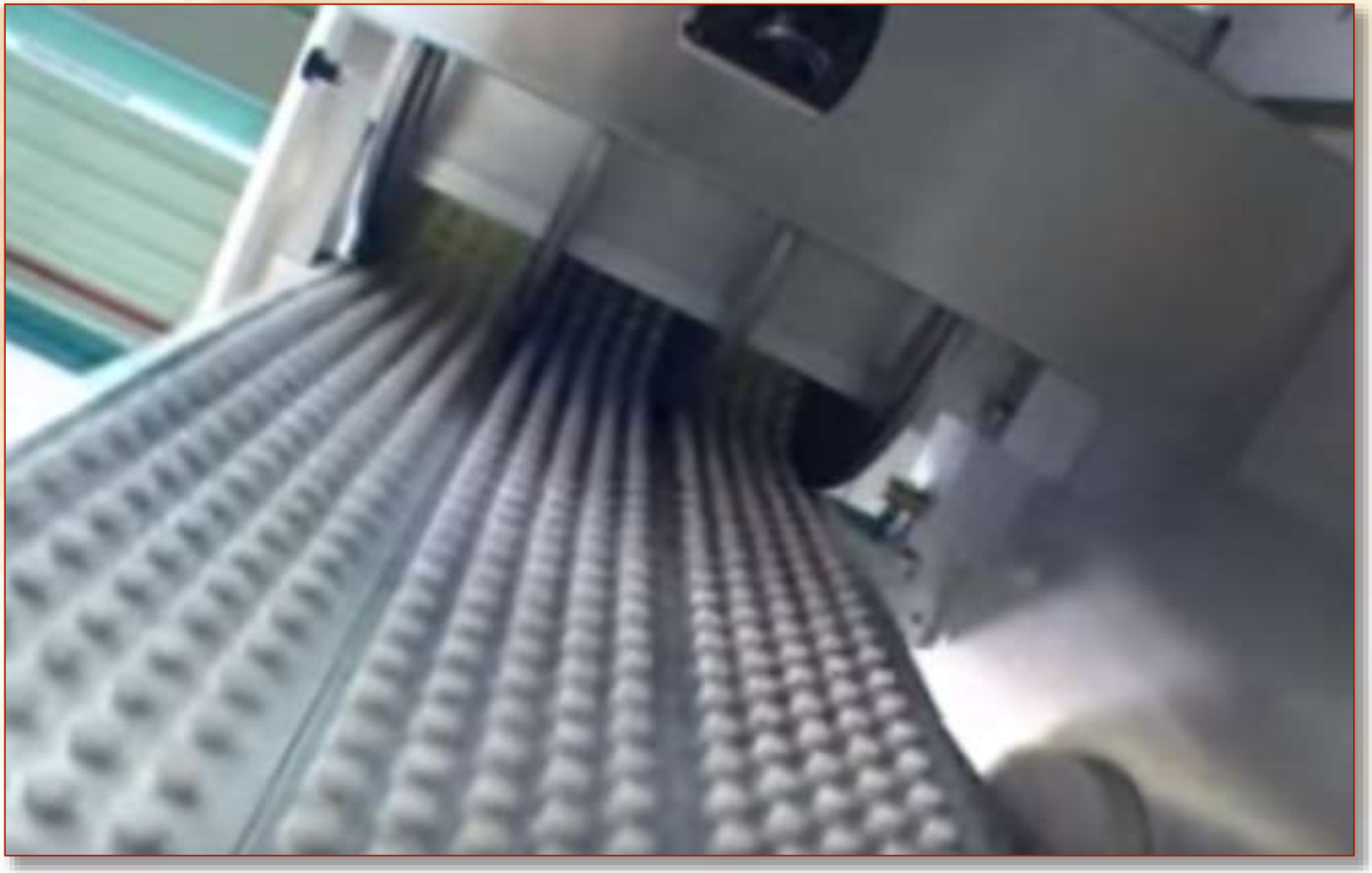
a) Homeopathic DPs

b) Allergenic extracts labeled with “No U.S. Std. of Potency”

c) Investigational new DPs

d) OTCs with no daily dose limitation and they are stable for at least 3 years as supported by appropriate stability data.

Example of Blister P&L Line



Summary

- P&L operations are important because they are a source of recalls
- Materials examination and usage criteria
- Labeling issuance
- P&L operations
- Tamper-evident packaging
- Drug product inspection
- Expiration dating

Take Home Message

A Good P&L System Fosters Excellence

A robust packaging and labeling system:

- **Prevents labeling mix-ups**
- **Ensures effective container closure**
- **Provides traceability information for the lot**

Acknowledgement

- **Jim Dunnie, Consumer Safety Officer, ORA/OO/OMPTO/Division of Medical Products and Tobacco Program Operations**

- **Drew Love, M.S., ASQ-CQE, CQA and CQM-OE, Consumer Safety Officer, Office of Compliance, CDER**

Questions?

Evaluation: surveymonkey.com/r/CGMP-D2S2