

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

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Packaging & Labeling

Presenters:

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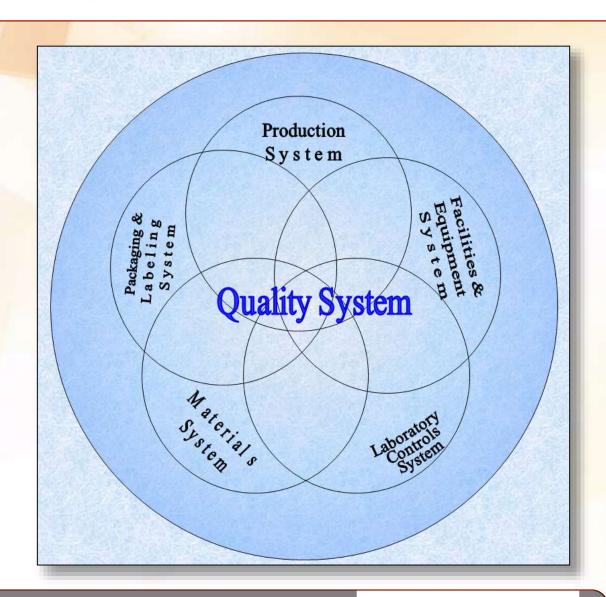
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The Six Components

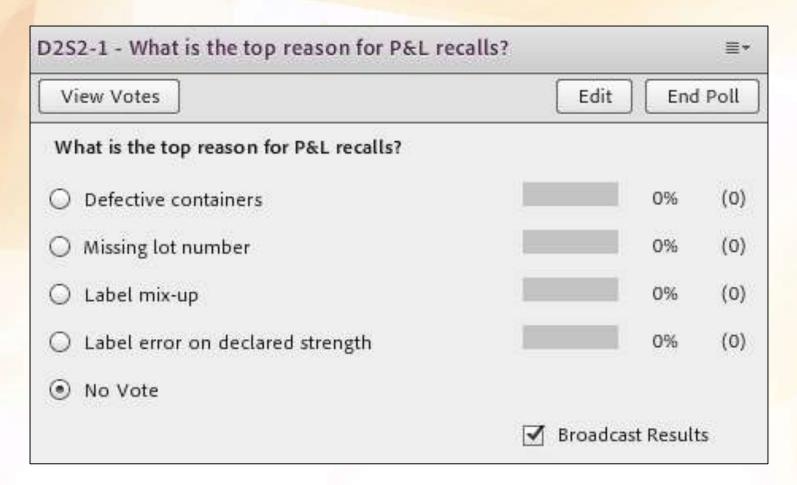
- Quality
- Production
- Laboratory
- Materials
- Facilities & Equipment
- Packaging & Labeling



- 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

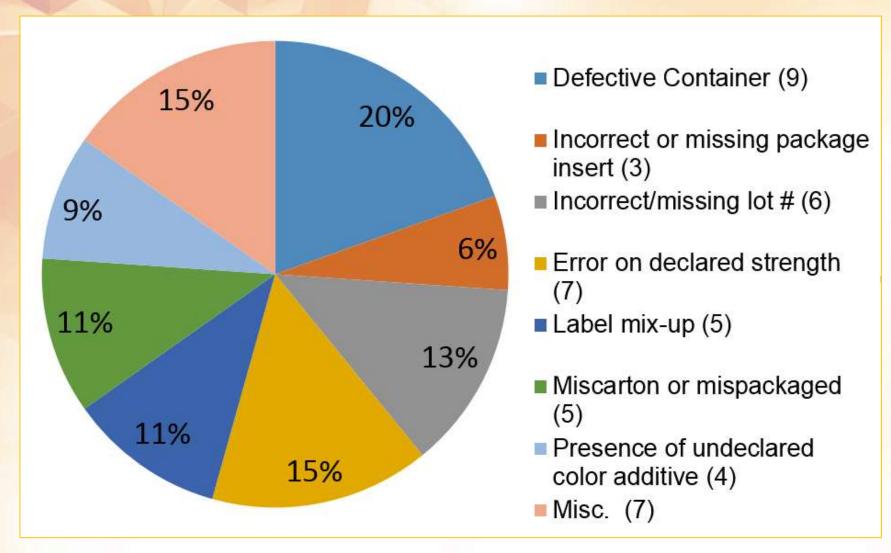


What is the top reason for P&L recalls?





2014 P&L Recall Events





- 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



- 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



- 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



- 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





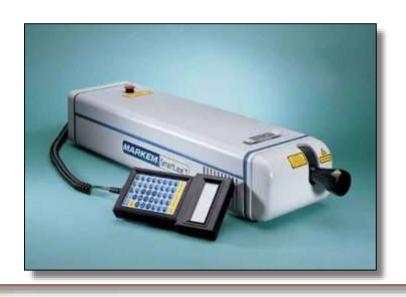
- a) Cut labeling single labels for individual drug products that are "cut" from a sheet or roll of labels
- b) Cut labeling operations shall include one of the following:
 - P&L lines dedicated for each strength of each DP
 - Equipment used of to conduct 100% examination
 - 100% verified visual inspection for hand-applied labeling
 - Automated technology that prevents incorrect labeling

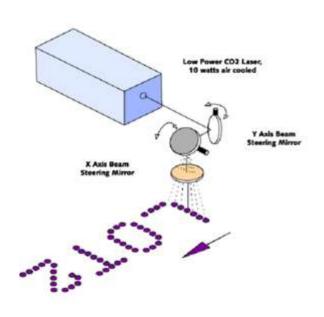




Printing Verification/Control Devices:

- 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

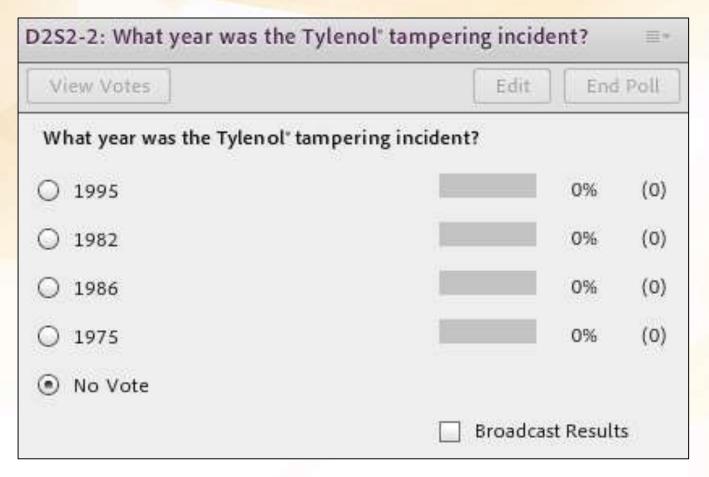
- a) Written procedures shall incorporate the following features:
 - (cont'd)..
 - Identification by lot or control number for traceability to manufacture
 - Examination of materials for suitability and correctness before production
 - Inspection of the packaging line prior to use

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What year was the Tylenol® tampering incident?

















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



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



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



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







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





- 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



- 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"



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



- 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
- 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



- 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



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

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Questions?

Evaluation: surveymonkey.com/r/CGMP-D2S2