CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT: DRUG REPACKAGERS AND RELABELERS Revision Note: Program revised 09/11/2015 to update implementation date, completion date, organizational/procedural changes and program contacts.	IMPLEMENTATION DATE 09/11/2015 COMPLETION DATE 09/11/2016

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry Codes: 50, 54-56, and 60-66 inclusive.	56002B

FIELD REPORTING REQUIREMENTS

Establishment Inspection Reports (EIRs) are to be created and filed electronically using the drug repackers/relabelers specific module in TurboEIR or replacement system that is accessible to both ORA and CDER.

For inspections of routine commercial manufacturing classified as Official Action Indicated (OAI) due to failure to comply with 21 CFR Part 210 and 211 Current Good Manufacturing Practice (CGMP) as they apply to drug repackagers/relabelers, submit advisory, administrative, or judicial action recommendations via MARCS-CMS in accordance with the Regulatory Procedures Manual (RPM).

Districts should immediately report significant issues according to current FACTS, Panorama and CMS procedures. This includes promptly filing and changing OAI notifications.

During an inspection, if you obtain information pertaining to inadequate adverse drug experience (ADE) reporting, unapproved drug issues, or post-approval reporting violations (application supplements, Field Alert Reports (FARs), etc.), report in accordance with directions provided in the applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported under separate Program Assignment Codes (PACs). Expansion of coverage under these programs into a CGMP inspection should be reported under this compliance program.

The Districts are requested to use this compliance program for all drug repackager/relabeler inspections.

PART I - BACKGROUND

The repackaging and relabeling of drugs under Current Good Manufacturing Practice (CGMP) controls has been a problem of long standing. Product mix-up, loss of product identity, contamination and cross-contamination, lack of stability data to support expiration dates and the lack of adequate control systems have been frequently documented.

Drug repackaging and relabeling are manufacturing processes which must be conducted in accordance with applicable CGMP requirements. The repackager/relabeler is performing the operations a formulator would handle if the formulator was packaging the product into consumer-sized containers.

PART II - IMPLEMENTATION

OBJECTIVES

To provide uniform guidance and a means of assessing the operations of drug repackagers and relabelers as they relate to the provisions of the Current Good Manufacturing Practice (CGMP) Regulations, 21 CFR 210 and 211.

To initiate regulatory follow up for operations which deviate from CGMP's?

To identify whether there is a need for specific CGMP's for the regulation of these operations.

To assess the compliance with all labeling requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its implementing regulations for repackaged drugs.

PROGRAM MANAGEMENT INSTRUCTIONS

The program includes, but is not limited to, the following operations:

- repackaging of solid and liquid bulk-dosage forms into smaller packages (may include larger containers such as pints, quarts, half gallons, 1000 tablet bottles, etc.) ;
- repackaging from conveyances (e.g., tank cars) into smaller containers such as drums;
- contract packagers who package expressly for manufacturers of dosage forms;
- repackagers or relabelers of antibiotics; and
- shared services operations (shared services operations servicing HMO's and hospital groups may be extensive operations.)

Exclusions:

- repackagers/relabelers of sterile products, radioactive drugs, and relabelers of compressed medical gases.
- Pre-packagers operating within the practice of pharmacy and distributing (selling) drugs upon receipt of written prescriptions.

DEFINITIONS

Unit of Use: A method of packaging *drug product* into a single container which contains more than one dosage unit, usually sufficient quantity of medication for one normal course of therapy.

Unit Dose: *A method of packaging a drug product into a non re-usable container designed to hold a quantity of drug intended for administration as a single dose directly from that container.*

For the purpose of differentiating whether an establishment is acting as a pharmacy or as a repackager/relabeler, the repackaging of drug products by licensed pharmacists, i.e. filling prescriptions for identified patients is within the regular practice of pharmacy. The repackaging of drug products by pharmacists, or any other entity, for resale or distribution to hospitals, other pharmacies, nursing homes, health care facilities, etc., are beyond the practice of pharmacy and these repackaging/relabeling facilities are thus required to register and list all such drug products with FDA.

STRATEGY

The program strategy requires the review of a firm's quality assurance system(s) against CGMP requirements to determine their adequacy, and auditing these systems (including SOPs) during inspections. CGMP inspectional coverage shall be sufficiently complete to assess the adequacy of all significant drug repackaging/relabeling process and control systems. The frequency and depth of inspection should be determined by the firm's history, and/or the technology employed or the kind of product. When a process is inspected for a particular product, the *inspection of* that process may be considered applicable to all products which use it. The program also requires a review of the labeling of the repackaged drugs to determine if they are in compliance with the Act.

The District is responsible for the depth of coverage given to each drug process. The Districts are expected to prioritize and schedule more frequent *inspections, as* appropriate, taking into consideration the firm's compliance history, along with product characteristics.

Consider using inspection teams which include a chemist or microbiologist, particularly to assess a firm's laboratory controls.

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Resolve difficulties in inspectional reporting.

Identify headquarters or field personnel (if other than Home District) who can provide special expertise and arrange for their assistance I the performance of inspections, as necessary.

PART III - INSPECTIONAL

OPERATIONS

Inspections will be conducted in accordance with CP 7356.002 Drug Process Inspections as far as applicable. These will include Unit Dose repackagers and Shared Services operations.

Inspectional Options

This program circular provides two inspectional options: Abbreviated Inspectional Option, and Full Inspectional Option *(For this program, the Full Inspectional Option provides specific policies for Unit-Dose Repackagers.)* To determine which option should be used, an evaluation of the following is appropriate.

1. Review and Evaluation

   a. Determine if changes have occurred by comparing current operations against the EIR for the previous full inspection. The following type of changes are typical of those that would warrant the full inspectional option:

      1. New potential for cross-contamination (see Part III, page 5, item 8) or mix-ups arising through changes in process or product line.

      2. Use of new technology requiring new expertise, significantly new equipment, or new facilities.

      3. A change in the personnel directly involved in the repackaging/relabeling operation.

   b. Review the firm's complaint file, Drug Quality Reporting System (DQRS), etc., and determine if the pattern of complaints (or other information available to the District) as well as the firm's records of internal rejection warrant expanding the inspection to the full inspectional option to look for weaknesses in the firm's processes, systems or controls.

      Review the firm's ANDA and AADA applications and confirm that requirements are being followed.

   c. If no significant changes have occurred and no violative conditions are observed, the abbreviated inspectional option may be adequate.

d. If significant changes have occurred, or if violative or potentially violative conditions are noted, the inspection should be expanded to the full inspectional option to provide appropriate coverage.

e. If an inspection needs to be expanded to the full inspe6tional option, it need be expanded only for the general product or process area in question.

f. Review the firm's labeling for misbranding violations *and determine if the nature and extent of violations warrant expanding the inspection to the full inspection option in order to look for deficiencies in the firm's labeling processes, systems, or controls.*

2. Abbreviated Inspectional Option

This option involves a brief inspection of the repackager/relabeler to maintain surveillance over the firm's activities. An abbreviated inspection as described below is adequate for routine coverage and will satisfy the biennial inspection requirement. The use of this option is designed to save inspectional and clerical resources.

This option should not be used on an initial inspection of a facility, nor when the District's review of information such as, past history, results of sample analysis, complaints, DQRSs, recalls, etc., indicates that an abbreviated inspectional option is not appropriate for a specific firm.

a. Perform an inspection of the firm's repackaging/relabeling facility including master records and batch records for a representative number of products repackaged/ relabeled by the firm. Products with a history of previous labeling problems should be included. *Special note should be taken of the firm's repackaging and relabeling controls.*

For products required to be packaged in tamper-resistant (TRP) packaging, determine the adequacy of the firm's TRP and required labeling statement (see Part VI, References, Page 1, Items F, G, and H).

Any observations of inadequate controls or other significant objectionable conditions will indicate that a full inspection should be performed.

b. The minimum reporting required for an abbreviated inspection is described in IOM 593.1. Include a brief summary describing the scope of the inspection, the persons interviewed and any changes which may have occurred since the previous inspection.

3. Full Inspectional Option

This option may involve a complete inspection of all systems and processes or a particular product or process as noted in 1.d. and e. above. A full inspection may also be conducted on a surveillance basis at the District's discretion. It is not anticipated that full inspections will necessarily be conducted every 2 years. They may be conducted at less frequent intervals, perhaps every third or fourth inspection. Also, whenever information becomes known which would question the firm's ability to produce quality products, an appropriate in-depth inspection should be performed.

a. All Repackaging/Relabeling operations

The following applicable portions of the CGMP's must be considered during inspections of repackaging/relabeling operations:

1) Buildings

Evaluate the building facilities employing the standards enumerated in 21 CFR 211.42, 211.44, 211.46, 211.48, 211.50, 211.52, 211.56, and 211.58.

2) Equipment

Evaluate the equipment, equipment cleaning, and maintenance procedures employing the standards stated in 21 CFR 211.63, 211.65, 211.67, and 211.68.

3) Personnel (21 CFR 211.22, 211.25, 211.28, 211.34)

a) Determine the qualifications, background, training and number of personnel engaged in the repackaging/relabeling operations.

b) Where there is a formalized instruction and training program for personnel, determine whether it is an initial or on-going operation.

c) Determine whether there are formalized procedures to fulfill the requirement of 21 CFR 211.22(d).

4) Drugs For Repackaging or Relabeling

a) The firm should carefully examine all incoming drug products for repackaging and relabeling to ascertain that the bulk containers of finished dosage form drug products are received intact, undamaged, and completely and properly labeled as received.

b) Evaluate the procedures employed by the firm in the receipt, handling, and storage of drug products for repackaging or relabeling.

c) *Drugs having a high volatility, such as nitroglycerin sublingual tablets, should not be repackaged. See Compliance Policy Guide 7132b.11 -- Expiration Dating of Unit Dose Repackaged Drugs.*

5) Control Records

Evaluate the control record-keeping system used by the firm for their repackaging/relabeling operations. Use the standards contained in 21 CFR 211.180; 211.182; 211.184; 211.186(a), (b)(1), (2), (8), (9); 211.188(a), (b)(1-13); 211.192; 211.198.

6) Production and Control Procedures

Only one drug product is to be brought into a repackaging area at a time. Upon completion of the repackaging operation, all remaining unused stock and finished stock are to be removed from the area. The packaging machinery is to be completely emptied, cleaned, and inspected before setting the equipment up for the repackaging of another drug product.

a) The following sections of 21 CFR 211 apply in evaluating a repackager/relabeler's adherence to CGMP requirements: 211.100, 211.103, 211.105, 211.110, 211.111, 211.113, 211.122, and 211.130.

b) Where applicable, the term "production" or "manufacturer" includes "repackaging" and "relabeling" operations as contained in 21 CFR 211.100, 211.103, 211.105.

7) Product Containers and their Components

Review the firm's specifications and SOPs regarding selection and handling of containers and closure systems (21 CFR 211.84). Evaluate the suitability of containers and closure systems with regard to 21 CFR 211.94. Report and document deficiencies.

8) Packaging and Labeling

Evaluate the firm's adherence to the following CGMP requirements for packaging and labeling operations. The following criteria of 21 CFR 211 are applicable for the purposes of this program: 211.122, 211.125, 211.130, 211.132, and 211.134.

For products required to be packaged in tamper-resistant (TRP) packaging, determine the adequacy of the firm's TRP and required labeling statement (see Part VI, References, Page 1, Items F, G, and H).

The manufacture of penicillin must be separate from other drug products, including cephalosporin. The specific requirements for such separation are covered in Sections 211.42(d) and 211.46(d) of the current Good Manufacturing Practice regulations.

There is no specific prohibition against the manufacture or repackaging, of cephalosporin drug products in the same facility as other non-penicillin drug products. However, FDA discourages such practice since there is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and cephalosporins and the subsequent possibility that a patient could be hypersensitive to a cephalosporin received from a contaminated non-penicillin drug product.

At the present time, there is no formal guidance on the separation of cephalosporin from the non-penicillin products beyond the present provisions in the CGMP regulations relating to control of cross-contamination between non-penicillin drug products. However, regulations do require appropriate controls to prevent cross-contamination.

9) Stability

Evaluate the stability testing program. Determine whether stability studies are conducted by the firm, or for the firm, and whether such documentation is, in fact, a part of the record-keeping system maintained by the repackager/relabeler. For program purposes, evaluate on the basis of 21 CFR 211.166(a), (b), (c).

Determine if the firm uses expiration dating periods beyond those used by the manufacturer and, if so, the rationale. Carefully evaluate the basis for any extensions. They must be based on adequate stability data and necessary awareness of any changes in the formula or manufacturing procedures used by the manufacturer.

10) Laboratory Controls

Determine whether the firm has an established and on-going control program. It is not necessary to perform chemical analyses on oral solid drug products in finished dosage form, provided adequate physical identification of the drug to be repackaged is performed *(See Compliance Policy Guide 7132.13).* Determine whether accurate and meaningful test results or examinations are performed by the repackager, such as, organoleptic examinations of incoming bulk drug products, visual inspection of labeling, and, where appropriate, stability data to justify assigned expiration dates. The following 21 CFR 211 criteria are applicable: 211.194; 211.160(a), (b)(1, 3 & 4); 211.170(a), (b) and 211.176.

(For purposes of this program the term "manufacturing" includes "repackaging operations.")

11) Distribution Records

Evaluate the firm's distribution records systems and determine whether the criteria of 21 CFR 211.142 and 211.150 are met.

12) Expiration Dating

Evaluate the expiration dating system as it pertains to stability information under 21 CFR 211.137. Pertinent program criteria are listed in 21 CFR 211.137(a), (b), (c).

The expiration date on the manufacturer's original container may be assigned to a solid oral dosage form repackaged *into a "unit-of-use" or other container /closure system containing more than a single dose,* which is equal to or better than the original container /closure system provided all labeling statements pertaining to storage conditions as specified by the original manufacturer are also used in and on the new labeling. This expiration policy does not apply to liquids, creams, ointments and suspensions.

13) Complaint Files

Criteria are listed in 21 CFR 211.198. Evaluate the firm's system and policy regarding product complaints other than those of an economic nature. Determine whether meaningful investigations are made and proper dispositions are handled in accordance with 21 CFR 211.192.

*b. Unit Dose Repackagers

For this program the full inspectional option provides specific policies for Unit-Dose Repackagers.

The following practices, if completely met, are adequate to allow Unit Dose repackagers to comply with current good manufacturing practices in the specific areas described below. For all other areas, follow guidance in 3a:

1) Expiration Dating for Unit Dose Containers:

A unit dose container is a non-reusable container designed to hold a quantity of drug intended for administration as a single dose, which is to be used promptly after the container is opened.

A firm may repackage solid oral dosage forms into unit dose containers and utilize an expiration date of not more than six months from the date of repackaging without conducting stability studies, provided that all of the following conditions are met:

a) The unit dose container complies with the Class A or Class B standard described in the current revision of the United States Pharmacopeia, Physical Tests, Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets.*

*b) The original bulk container has not been previously opened and the entire contents are repackaged in one operation.

c) The expiration period does not exceed 25 percent of the remaining time between the date of repackaging and the expiration date shown on the original manufacturer's bulk, container of the drug repackaged.

d) The repackaging and storage of the drug product is accomplished in a humidity controlled environment and within the temperature specified in the USP monograph or the product labeling. If no temperature/humidity is specified, a controlled room temperature, as defined by the USP, with a relative humidity not exceeding 75 percent should be maintained. *Documentation must be on file to verify that all the conditions listed above are met.*

2) Labeling:

In addition to the general packing and labeling requirements (see Part III, Page 5, Item 8), all unit dose repackaged products are to be placed into larger containers and each container must be fully labeled prior to removal from the premises.*

LABELING REQUIREMENTS

See Attachment A - Labeling Requirements for Solid Oral Dosage Forms in Unit Dose Containers

See Attachment B - Inspectional Guidance on Label Controls

All the repackaged drugs must be labeled to meet the requirements of the Act and its implementing regulations. *The labeling requirements in Attachment A are for guidance and any deficiencies in labeling should be documented and reviewed by the district compliance office to determine, if a recommendation for regulatory action, to the Office of Compliance, Office of Unapproved Drugs and Labeling Compliance (OUDLC) is warranted.*

SAMPLE COLLECTION

Collect samples to fully document serious deviations from CGMP and the likelihood of product quality problems as well as any labeling violations. Physical samples must be collected in the case of suspected identity, potency, decomposition, contamination and/or labeling problems. The following are areas of concern when deciding whether a physical sample is warranted:

A. Lack of assurance that the incoming drugs are what they purport to be;

B. Lack of assurance that no mix-up occurs between drugs during the repackaging/relabeling operations; and

C. Lack of assurance that the finished product is properly labeled.

IMPORTS

No coverage under this program.

PART IV - ANALYTICAL

See Compliance Program, Drug Process Inspections (7356.002).

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

When non-compliant conditions are identified, voluntary, administrative and/or regulatory options currently available should be initiated (See RPM Part 8). Regulatory recommendations should be based on well-documented and significant CGMP deviations and/or labeling violations.

The following examples may be considered significant deviations if they are not isolated instances, and could reasonably be expected to have an impact on product quality: .

1. Lack of valid stability data for the container/closure system used. Stability data may be accepted by the repackager/relabeler from a suitable source, provided the data can assure the stability of the product in the container/closure system used. This data must be readily available at the repackager/relabeler facility.

2. Lack of control procedures and/or records sufficient to support the integrity of the product, and to identify lots or batches of drug products repackaged or relabeled.

3. Lack of control procedures and/or records to provide assurance that labeling mix-ups will not occur.

The above referenced significant deviations do not represent the only criteria which could adversely impact product quality. In varying factual situations, some of the above may become less significant while conditions not mentioned may become serious failures. All deviations have to be evaluated as to whether there is assurance that the incoming drug is what it purports to be, that there is no product mix-up and that the finished product is properly labeled.

Refer to Part V of the Drug Process Inspection Program for general information on Regulatory Procedure.

If GMP deviations are noted with regard to packaging and label controls, districts should consider issuance of a *warning letter.* If significant deviations are found, the Center will consider additional regulatory action, especially if the firm has had multiple label recalls.

If label/labeling violations are suspected following a label/labeling evaluation based on CPG 7132b.10 and Attachment A, OC/OUDLC should be contacted to determine what course of action to follow. *Before the district concludes an inspection of any

pharmacy supplying repackaged drugs in limited quantities to a health care facility to supplement existing prescriptions from that pharmacy, contact OC/OUDLC(301) 796-3100 for a discussion of the extent of the operation.*

The issuance of *warning letters* which include label/labeling violations must be discussed with OC/OUDLC before issuance. This Compliance Program does not authorize the use of *warning letters* for drug misbranding violations.

PART VI - REFERENCES, ATTACHMENTS AND PROGRAM CONTACTS

REFERENCES

A. Inspection Operations Manual, Sub-chapter 540

B. 21 CFR, Part 210, 211

C. Compliance Policy Guide, 7132.13, "Repacking of Drug Products - Testing/Examination under CGMPs11

D. Compliance Policy Guide, 7132b.10, "Unit Dose Labeling for Solid and Liquid Oral Dosage Forms"

E. Compliance Policy Guide, 7132b.11, "Expiration Dating of Unit Dose Repackaged Drugs"

F. Regulatory Procedures Manual, Chapter 8

G. Compliance Policy Guide, 7132a.17, "Tamper-Resistant Packaging Requirements for Certain Over-the-Counter (OTC) Human Drug Products"

H. Federal Register, Vol. 54, No. 21, pp. 5227-5229, February 2, 1989, Final rule, Tamper-Resistant Packaging Requirements for Certain Over-the-Counter (OTC) Human Drug Products

I. Compliance Policy Guide, 7132.14, "Control and Accountability of Labeling Associated with Tamper-Resistant Packaging of Over-the-Counter Drug Products"

J. Compliance Policy Guide, 7132c.06, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations"

K. Draft Guideline on Repackaging of Solid Oral Dosage Form Drug Products, October 1992

ATTACHMENTS

Attachment A - Labeling Requirements For Solid Oral Dosage Forms In Unit Dosage Containers

Attachment B - Inspectional Guidance on Label Controls

CONTACTS

A. ORA/Office of Operations (OO)

1. Office of Medical Products and Tobacco Operations (OMPTO):

   ORAHQDrugInspectionPOC@fda.hhs.gov

2. Office of Regulatory Science
   Telephone: (301)796-6600

B. Center for Drug Evaluation and Research

CGMP or any Quality-Related Policy Questions
For CGMP or any quality-related policy question, technical or scientific questions or information needs, including questions about this program, please send an email to the following address and it will be handled as a top priority:

CDER-OPQ-Inquiries@fda.hhs.gov

Enforcement-Related Guidance or Policy
For enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice, please send an email to the following address and it will be handled as a top priority:

CDER OMQ Compliance Policy: CDEROMQCompliance@fda.hhs.gov

Labeling Requirements and Policies

Office of Unapproved Drugs and Labeling Compliance, see intranet home page for contacts
[CDER | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

Registration and Drug Listing Requirements
CDER Office of Compliance, see “CDER: Who’s the Lead” intranet page for contacts
[CDER | Office of Communications | CDER: Who’s the Lead]

PART VII - CENTER RESPONSIBILITIES

Office of Compliance/Office of Unapproved Drugs and Labeling Compliance (OUDLC)

Assesses the compliance with all labeling requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its implementing regulations for repackaged drugs.

Office of Product Quality (OPQ)

Addresses CGMP, quality-related policy matters, and technical or scientific issues.

Office of Manufacturing Quality (OMQ)

Identifies the need for enforcement/compliance actions for repackaging and relabeling operations.

LABELING REQUIREMENTS FOR SOLID ORAL DOSAGE FORMS IN UNIT DOSE CONTAINERS

UNIT DOSE LABELING

A. Prescription Drugs (Solid Oral Dosage Forms, e.g. Capsules, Tablets)

The label of the actual unit dose container must bear all of the following information (except item 12 which is not mandatory). However, where the unit dose container is too small to accommodate a label with sufficient space to bear all the information, items 10 and 11 may be omitted from the label. If omitted, they must appear, in addition to all other mandatory items, on the outer enclosing package from which the unit dose container is to be dispensed. If there is insufficient space to do so, then the information must be on a leaflet enclosed with the package.

Note: A firm may not claim an exemption on the basis that the label is too small to accommodate all mandatory information if all available space is not utilized or the label size can readily be made larger, or if the type size on the label can readily be made smaller without affecting the legibility of the information.

1. The established name of the drug, if it contains a single active ingredient.

2. The quantity of the active ingredient, and the quantity or proportion of any ingredient named under Section 502(3) whether active or not.

3. The expiration date.

4. The lot or control number.

5. The name and place of business of the manufacturer, packer, or distributor as provided for in 21 CFR 201.1.

6. For official drug products, any pertinent statement required by the compendia (e.g., refrigerate).

7. If more than one dosage unit is within the unit dose container, the number of dosage units per container should be specified (e.g., two capsules rifampin; each capsule contains 300 mg.).

8. Special characteristics of the dosage form (e.g., sustained release, enteric coated sublingual, chewable, need for special storage conditions).

9. The statement - "Warning: May be habit forming" where applicable, the controlled drug substances symbol required by DEA, and the name and proportion of any substance as required by Section 502(d).

10. If a combination drug, the established name and quantity of each active ingredient, and the quantity or proportion of any ingredient named under Section 502(e) whether active or not.

11. The prescription legend.

12. The National Drug Code designation is recommended, although this is not mandatory.

In addition to all of the above (except item 12), the following information must appear on the outer package from which the unit dose container is dispensed:

1. The number of unit dose containers in the package. If more than one dosage unit is within each unit dose container, this should also be stated (e.g., 11100 packets; each packet contains two tablets," or 11100 packets of two tablets each").

2. Full disclosure information, as detailed in 21 CFR 201.100. Where unit dose repackaging is performed by a single facility for a closed membership or group (e.g. "shared services") a current package insert bearing adequate directions for use, located on the premises of each member to whom the repackaged goods are shipped is sufficient to satisfy this requirement. The absence of such a current package insert on the premises of a member to which a drug is shipped will cause that drug to be misbranded.

B. Non-Prescription Drugs (Solid Oral Dosage Forms, e.g. Capsules, Tablets)

The label of the actual unit dose container must bear all of the following information (except item 10 which is not mandatory). However, where the unit does container is too small to

accommodate a label with sufficient space to bear all the information, item 9 may be omitted from the label. If omitted, this information must appear, in addition to all other mandatory items, on the outer enclosing package from which the unit dose is to be dispensed. If there is insufficient space to do so, the information must be on a leaf let enclosed within the outer package.

Note: A firm may not claim an exemption on the basis that the label is too small to accommodate all mandatory information if all available space is not utilized or the label size can readily be made larger, or if the type size on the label can readily be made smaller without affecting the legibility of the information.

1. The- established name of the drug if it contains a single active ingredient; and the quantity or proportion of any ingredient as required by Section 502 (e) , and when required, pursuant to Section 502 (g) by a monograph of an article recognized in an official compendium, (e.g., Aspirin Tablets).

2. The expiration date.

3. The lot or control number

4. The name and place of business of the manufacturer, packer, or distributor as provided for in 21 CFR 201.1.

5. For official drug products, any pertinent statement required by the compendia (e.g., refrigerate).

6. If more than one dosage unit is within the unit dose container, the number of dosage units per container should be specified (e.g., two tablets A.S.A.; Each tablet contains 325 mg.).

7. Special characteristics of the dosage form (e.g., sustained release, enteric coated, chewable, etc.).

8. The statement - "Warning: May be habit forming" where applicable, and the controlled drug substances symbol required by DEA, and the name and proportion of any substance as required by Section 502(d).

9. If a combination drug, the established name of each active ingredient, and the quantities of those ingredients (whether active or not) specifically named in Section 502(e).

10. The National Drug Code designation is recommended, although this is not mandatory.

In addition to all of the above (except item 10), the following information must appear on the outer package from which the unit dose container is to be dispensed:

1. The number of unit dose containers in the package. If more than one dosage unit is within each unit dose container this should also be stated (e.g. 11100 packets; each packet contains two tablets" or 11100 packets of two tablets each") .

2. The enclosing package or the leaf let enclosed within the package must bear adequate directions for use as provided for in 21 CFR 201.5 and should include:

   a. Statement of all conditions, purposes, or uses for which the drug product is intended. ,

   b. Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and conditions.

   c. Frequency of administration.

   d. Duration of administration.

Where unit dose repackaging is performed by a single facility for a closed membership or group (e.g., shared services) a current package insert, bearing adequate directions for use, located on the premises of each member to whom the repackaged goods are shipped is regarded as satisfying this requirement. The absence of such a current package insert on the premises of a member to which a drug product is shipped will cause that drug product to be misbranded.

INSPECTIONAL GUIDANCE ON LABEL CONTROLS

Inspectional Follow-up to Recalls

Follow-up inspections of all incidents such as recalls should not be limited to a determination that the recall is being adequately handled, but should also include a thorough inspection of the firm's basic controls to determine the underlying cause of the problem, where possible. Inspectional coverage should not be limited to the lot recalled. During the investigation of a recall, it should be determined if the problem is a product mix-up or a label mix-up. When reporting these recalls, it is important to be specific as to the cause and to avoid the use of the general term "labeling mix-up."

Inspection of New Registrants

Newly registered drug repackagers or manufacturers should have their labeling controls examined carefully to determine if the firm is in compliance with CGMPs. Special attention should be given to new unit-of-use repackagers. Unit-of-use is a method of repackaging a medication into a single container which contains more than one dosage unit (as opposed to unit dose), usually a sufficient quantity of medication for one normal course of therapy. The general level of competency of employees in these firms should be evaluated as well as the firm's training program for new employees. New employees should be trained to be familiar with all parts of CGMPs. Those employees working in packaging and labeling departments need special training in 21 CFR 211.122 through 211.134.

Labeling Coverage During Routine Inspections

During routine drug GMP inspections, additional emphasis should be placed on coverage of label controls if the firm uses cut labels or roll labels that are similar in color, shape, and size for different products or different potencies of the same product. Routine inspections sometimes reveal recalls carried out by firms but not reported to FDA. For drugs which are subject to NDAs or ANDAs firms are required by 21 CFR 314.81 to report labeling problems in a “field alert" to the district office. During routine inspections and follow-up investigations a determination as to whether the firm is in compliance with this requirement should be made.

The use of labels which are similar in size, shape and color for different products has been a factor in recalls. Cut labels were involved in 76 percent of recalls in recent years. The use of gang printing of cut labels should be minimized as required by current regulations. The use of cut labels which are similar in appearance and do not have some type of 100 percent electronic verification system for the finished product have a serious potential for mix-ups and should be considered inadequate control over the labeling operation.

Roll labels are known to have less potential for labeling problems. However, a complete evaluation of the firm's controls of the roll labeling operation is necessary as problems still arise due to splicing, failure to adequately review, etc. Again, use of similar labels without a 100 percent verification system should be avoided. *(NOTE: New labeling requirements under 21 CFR 211.122(f) and (g), 211.125 (c) and 211.130, published 8/3/93).*

If the firm uses outside contractors to print labeling, it is important that they have detailed information as to how the printer controls the printing process. An audit of the printer should be performed by the firm on a regular basis, and the drug firm must adequately examine the labeling upon receipt from the printer. Sampling and inspection should be statistically based; examining one label per box or roll is not considered adequate. The same would apply to inspection of finished product for correct labeling.

Use of Multiple Private Labels

Special inspectional emphasis should be placed on firms which package products under a number of private labels since this type of firm was involved in the majority of the mislabeling recalls, including both label and product mix-ups. Controls over storage of unlabeled stock should be evaluated to determine if they are adequate to prevent mix-ups. Label controls should be evaluated to determine if they are adequate to prevent labeling errors.

Unless each unlabeled individual finished product container is identified as to the product and potency that it contains, or the unlabeled finished product containers are stored in closed/sealed cases, or other bulk cartons identified with a solidly affixed label, this should be considered a significant deviation from GMPs.

Firms with Multiple Mislabeling Recalls.

Special emphasis should also be placed on any firms which have had multiple mislabeling recalls in the past few years because a correlation has been shown between previous recalls and the probability of additional recalls.