DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

Indian Fishing—Yurok Indian Reservation (Subsistence Gill Net Fishing)

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Notice.

SUMMARY: The Sacramento Area Director of the Bureau of Indian Affairs is making pre-season changes to the fishing regulations to assure proper management of the fisheries resources of the Klamath River.

DATES: 25 CFR Part 250.9 is amended as follows: The Fall Chinook Management Season shall be during the period of July 14, 1993, 7:01 pm through midnight December 31, 1993. The season is expected to consist of an early season and a late season. The early season is from July 14 through September 1 or 65% of the subarea quota. Fishing during the early season is permitted from Wednesday at 7 pm through Sunday at 7 pm. The late season will begin on September 1 at 7 pm and continue until December 31, 1993, or the remainder of the subarea quotas. Fishing during the late season would be permitted 24 hours a day, 7 days a week, except for a closure on Monday from 9 am to 5 pm. Any subarea allocations that are not harvested during the early season will be added to the late season allocations.

Prior to this season, the River will be closed to all fishing, and all nets must be out of the water between July 12, 1993, 9 am until July 14, 1993, 7 pm.

FOR FURTHER INFORMATION CONTACT: Ronald M. Jaeger, Area Director, Bureau of Indian Affairs, 2800 Cottage Way, Sacramento, CA 95825.

SUPPLEMENTARY INFORMATION: As authorized by 25 CFR 250.12 Indian Fishing: Hoopa Valley Indian Reservation, the Area Director of the Bureau of Indian Affairs is making the following pre-season changes to the regulations to assure proper management of the fisheries resources of the Klamath River. The total Indian allocation level will be 18,500 adult fall chinook salmon. Of this number, 14,800 will be allocated to be taken on the Yurok Indian Reservation. Subsequently, the subarea adult chinook quota would be 8,900 fish in the Management Area 1 (estuary) and 5,900 fish for Management Area 2 (U.S. 101 Bridge to Weitchpec).

Area 1 is from the confluence of the Klamath River and the ocean upstream to the Highway 101 Bridge. A quota of 5,800 adult fall chinook salmon has been established for the early season. A quota of 3,100 adult fall chinook salmon has been established for the late season.

Area 2 is the remainder of the mainstream Klamath River within the exterior boundaries of the Yurok Reservation. A quota of 3,800 adult fall chinook salmon has been established for the early season. A quota of 2,100 adult fall chinook salmon has been established for the late season.

The Blue Creek conservation zone will be closed to gill net fishing ⅛ mile above the upper portion of the Blue Creek delta (bedrock wall) and ½ mile below the lower portion of the Blue Creek delta from September 14 until December 31, 1993.

Dated: July 27, 1993.

Ada E. Deer,

Assistant Secretary—Indian Affairs.

[FR Doc. 93–18387 Filed 8–2–93; 8:45 am]

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federal register

Tuesday
August 3, 1993

Part IV

Environmental Protection Agency

40 CFR Part 141
National Primary Drinking Water Regulations; Analytical Techniques (Trihalomethanes); Final Rule

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 141

[WH–FRL–4542–5]

RIN 2040–AB87

National Primary Drinking Water Regulations; Analytical Techniques; Trihalomethanes.

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is approving two additional methods in 40 CFR 141.30 for monitoring total trihalomethanes (TTHMs) in drinking water for compliance with the maximum contaminant level (MCL). These two EPA methods, Methods 502.2 and 524.2, are capillary column methods and are already approved for the compliance monitoring of eight volatile organic chemicals (VOCs) under 40 CFR 141.24(g)(10)(iv) and (v) and unregulated VOCs under 40 CFR 141.40(g).

DATES: This rule is effective and the methods herein may be used on September 2, 1993. For the purposes of judicial review only (consistent with 40 CFR 23.7), this rule is considered issued at 1 p.m. Eastern Time on August 14, 1993.

FOR FURTHER INFORMATION CONTACT: The Safe Drinking Water Hotline, telephone (800) 426–4791. The Safe Drinking Water Hotline is open Monday through Friday, excluding Federal holidays, from 9 a.m. to 5:30 p.m. Eastern Time. For technical questions, contact Baldev Bathija, Ph.D., Office of Ground Water and Drinking Water (WH–550D), Environmental Protection Agency, 401 M Street SW., Washington, DC 20460, telephone (202) 260–3040.

SUPPLEMENTARY INFORMATION: On November 29, 1979 (44 FR 68642), EPA published a National Interim Primary Drinking Water Regulation for TTHMs in drinking water. This rule became a National Primary Drinking Water Regulation (NPDWR) on June 19, 1986, when the Safe Drinking Water Act (SDWA) was amended. This rule requires community water systems that disinfect and serve 10,000 persons or more to comply with an MCL of 0.1 mg/l for TTHMs. The concentration of TTHMs is the sum of the concentrations of four individual trihalomethanes (trichloromethane, dichlorobromomethane, chlorodibromomethane and tribromomethane). In 40 CFR 141.30(e), EPA approved two methods (501.1 and 501.2) for the analysis of TTHMs in drinking water and for determination of compliance with the MCL for TTHMs.

Only July 8, 1987 (52 FR 25690), the Agency published regulations that required monitoring for certain unregulated contaminants by all community water systems and non-transient, non-community water systems. EPA had proposed these regulations pursuant to Section 1445 of the SDWA on April 17, 1987 (52 FR 12876). The rule provided for use of the two capillary column methods for detecting a list of VOCs, but the rule did not establish MCLs for the individual chemicals on the list. This list, at § 141.40(e), includes the four individual trihalomethanes. Section 141.40(g) describes several methods available to monitor for these compounds, including EPA Methods 502.2, "Volatile Organic Compounds in Water by Purge and Trap Capillary Gas Chromatography with Photoionization and Electrolytic Conductivity Detector in Series," and EPA Method 524.2, "Volatile Organic Chemicals in Water by Purge and Trap Capillary Gas Chromatography/Mass Spectrometry." In today's action, EPA is approving use of 502.2 and 524.2 for monitoring compliance with the MCL for TTHMs under § 141.30.

EPA is promulgating today's rule without providing notice and opportunity for public comment pursuant to section 553(b)(B) of the Administrative Procedure Act (5 U.S.C. 553(b)(B)). EPA did provide notice and an opportunity for public comment on the methods in today's rule when the methods were approved for compliance monitoring for VOCs and the detection of unregulated contaminants under SDWA section 1445 (52 FR 12876, 12879, proposed April 17, 1987; and 52 FR 25690, 25702, final July 8, 1987). In the section 1445 rule, the two capillary column methods (524.2 and 502.2) were approved for the detection of the four individual trihalomethanes that are included in the definition of total trihalomethanes—trichloromethane (chloroform), dichlorobromomethane, chlorodibromomethane, and tribromomethane (bromoform). These capillary column methods were approved for determination of compliance with the MCLs for eight VOCs at 40 CFR 141.40(g) on July 8, 1987 (52 FR 25690, 25702). Today's rule approves the use of the two capillary column methods as alternate methods for determination of compliance with the MCL for TTHMs found at 40 CFR 141.30.

Because EPA has already provided an opportunity for public comment on the use of the capillary column methods for monitoring VOCs, including the four trihalomethanes, EPA finds that notice and public comment at this time is unnecessary and therefore good cause exists not to provide for notice and opportunity for public comment (5 U.S.C. 553(b)(B)). Systems may use the two capillary column methods approved in today's rule for determining compliance with the MCL for TTHMs on the effective date of today's rule.

The protocols for the two capillary column methods (502.2 and 524.2) being approved are contained in Methods for the Determination of Organic Compounds in Drinking Water, EPA/600/4–88/039 (revised July 1991). This document is available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161. The NTIS toll-free number is 800–553–6847 and the NTIS order number is PB91–231480.

EPA is encouraging the use of the above methods for all TTHM monitoring. The Agency intends to discontinue technical support for packed column methodology for the analysis of TTHMs and other VOCs (EPA Methods 501.1, 501.2, and 501.3). This means that the Agency will no longer provide technical advice, keep copies of the method after the current stock is exhausted, or resolve technical problems that may develop. However, the Agency will continue to accept data generated with these methods.

Regulation Assessment Requirements

Executive Order 12291

Executive Order 12291 requires EPA to judge whether a regulation is "major" and, if so, to prepare a regulatory impact analysis. A rule is considered major if it has an economic impact of $100 million or more, causes a significant increase in cost or prices, or any of the other adverse effects described in the Executive Order. The objective of this rule is merely to allow the use of additional alternate methods. This does not require purchase of any new equipment by the regulated community or impose any new requirements. As such, this rule is expected to reduce the cost of monitoring by allowing the use of a single method for monitoring both VOCs and total trihalomethanes. In view of this, EPA believes that this action will either have no economic impact or have positive economic impact. Hence it is not a major rule within the meaning of the Executive Order. This notice has been reviewed by the Office of Management and Budget under Executive Order 12291

Regulatory Flexibility Act

The Regulatory Flexibility Act requires EPA to explicitly consider the effect of regulations on small entities. If there is a significant effect on a substantial number of small entities, EPA must seek to minimize the effect.

Pursuant to section 605(b) of the Regulatory Flexibility Act, 5 U.S.C. 605(b), the Administrator certifies that this rule will not have a significant economic impact on a substantial number of small entities. The rule provides laboratories with two additional alternatives for THM testing. Because these methods are optional, and because EPA is not promulgating any new requirement, the Agency believes that this notice will not have any significant effect on a substantial number of small entities.

Paperwork Reduction Act

Today's rule places no additional information collection or record-keeping burden on respondents. Therefore, an information collection request has not been prepared and submitted to the Office of Management and Budget under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq.*

List of Subjects in 40 CFR Part 141

Administrative practice and procedure, Chemicals, Intergovernmental relations, Reporting and Recordkeeping requirements, Water supply.

Dated: July 22, 1993.

Carol M. Browner,

Administrator.

For the reasons set out in the preamble, part 141 of title 40 of the Code of Federal Regulations is amended as follows:

PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS

1. The authority citation for part 141 continues to read as follows:

Authority: 42 U.S.C. 300f, 300g–1, 300g–2, 300g–3, 300g–4, 300g–5, 300g–6, 300j–4, and 300j–9.

2. In § 141.30, paragraphs (e)(3) and (e)(4) are added, and two new sentences are added at the beginning of the concluding text of paragraph(e) to read as follows:

§ 141.30 Total trihalomethanes sampling, analytical and other requirements.

* * * * *

(e) * * *

(3) "Volatile Organic Compounds in Water by Purge and Trap Capillary Gas Chromatography with Photoionization and Electrolytic Conductivity Detector in Series," Method 502.2, EMSL, EPA, Cincinnati, Ohio. EPA Method 502.2 is contained in Methods for the Determination of Organic Compounds in Drinking Water, EPA/600/4–88/039 (revised July 1991).

(4) "Volatile Organic Chemicals in Water by Purge and Trap Capillary Gas Chromatography/Mass Spectrometry," Method 524.2, EMSL, EPA, Cincinnati, Ohio. EPA Method 524.2 is contained in Methods for the Determination of Organic Compounds in Drinking Water, EPA/600/4–88/039 (revised July 1991).

For the methods cited in paragraphs (e)(1) and (e)(2) of this section, see appendix C to this subpart C. The methods cited in paragraphs (e)(3) and (e)(4) of this section are available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (order number PB91–231480.) * * *

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[FR Doc. 93–18226 Filed 8–2–93; 8:45 am]

BILLING CODE 6560–50–M

federal register

Tuesday
August 3, 1993

Part V

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 210 and 211

Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Labeling Controls; Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 210 and 211

[Docket No. 88N–0320]

Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Certain Labeling Controls

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the current good manufacturing practice (CGMP) regulations for human and veterinary drug products to revise certain labeling control provisions. Specifically, the final rule defines the term "gang-printed labeling," specifies conditions for the use of gang-printed or cut labeling, exempts manufacturers that employ automated 100-percent labeling inspection systems from CGMP labeling reconciliation requirements, and requires manufacturers to identify filled drug product containers that are set aside and held in an unlabeled condition for future labeling operations. These changes are intended to reduce the frequency of drug product mislabeling and associated drug product recalls.

EFFECTIVE DATE: August 3, 1994.

FOR FURTHER INFORMATION CONTACT: Tom Kuchenberg, Center for Drug Evaluation and Research (HFD–362), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–295–8046. or Paul J. Motise, Center for Drug Evaluation and Research (HFD–323), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–295–8089.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of June 23, 1989 (54 FR 26394), FDA published a proposed rule to amend the packaging and labeling control provisions of the CGMP regulations. The proposal: (1) Specified conditions for the use of gang-printed or cut labeling, (2) exempted manufacturers that employ 100 percent labeling inspection systems from CGMP labeling reconciliation requirements, and (3) required manufacturers to identify filled drug product containers that are not immediately labeled.

The proposed amendments were based on an agency study of drug product recalls that identified label mixups as the leading cause of recalls involving mislabeled products. An agency analysis of the recalls attributed to label mixups showed that the use of cut labels, labels of similar size, shape, or color, and deviations from existing CGMP labeling requirements were the leading causes of such mixups. In contrast, three label control practices were not involved in any of the recalls attributed to label mixups: (1) the use of labels differentiated by size, shape, or color; (2) the use of dedicated packaging lines; and (3) the use of electronic 100-percent label inspection systems that validate the labeling of each drug product during finishing operations.

The proposed rule was intended to encourage desirable labeling operations and to contribute significantly to preventing drug product mislabeling and associated drug product recalls. The proposal gave interested persons an opportunity to submit written comments by August 22, 1989.

In response to a request for an extension of the comment period, in the **Federal Register** of September 8, 1989 (54 FR 37342), FDA published a notice extending the comment period for submissions to October 20, 1989.

FDA is now issuing a final rule based upon the proposal with changes made in response to public comments. These changes are discussed in the preamble to this final rule.

FDA is continuing to monitor recalls related to mislabeling, and FDA notes that the total number of these recalls for each of 3 fiscal years, 1988 to 1990, exceeded the number of these recalls in any of the 5 fiscal years, 1983 to 1987, that were covered by the agency's recall study. FDA notes also that recalls related to mislabeling are the primary cause of recalls classified by FDA as presenting a significant risk of serious health consequences or death (Class I). In many cases, mislabeled drug products subject to a Class I recall are detected by health care professionals before they are dispensed or by consumers before use. Unfortunately, mislabeled drug products continue to cause consumer injuries.

For example, a 41-year-old woman was hospitalized after becoming comatose from a medication used to lower blood sugar in diabetics that had been mislabeled as a medication to treat a bacterial infection. In another instance, a 6-year-old child was hospitalized after being given a potent liquid tranquilizer that had been mislabeled as a medication used for the treatment of cough and cold symptoms. For 3 fiscal years, 1988 to 1990, recalls related to mislabeling have accounted for almost 50 percent of Class I recalls. Further, for fiscal year 1990, mislabeling-related recalls have accounted for almost 60 percent of Class I recalls. FDA remains convinced that the CGMP regulations must address effectively this disturbing and persistent trend.

II. Comments

FDA received 44 comments on the proposed rule. These comments represented many interests—29 human drug manufacturers, 6 biological drug manufacturers, 2 veterinary drug manufacturers, 2 drug equipment suppliers, and 5 trade organizations representing manufacturers, repackers, and distributors. In general, the comments supported the agency's initiative to modify the CGMP labeling control requirements to reduce the frequency of drug product mislabeling. However, many comments suggested modifications. FDA has carefully considered all comments and suggested alternatives and has adopted those comments that would reduce the burden on manufacturers while at the same time achieving the goal of significantly reducing mislabeling-related recalls. A section-by-section summary of the comments and the agency's responses to them are set out below.

A. General Comments

1. Several comments objected to specifying a "how to" approach instead of an "objective" approach with respect to labeling control requirements. The comments argued that requiring specific labeling systems or procedures would unduly restrict innovative approaches and technological advances. The comments recommended that the regulations state the objective that is sought and leave the method of attaining that objective to the reasonable discretion and ingenuity of the manufacturer. In contrast, two comments urged that FDA adopt a "how to" approach, stating that the revised requirements should specify acceptable types of "electronic or electromechanical equipment."

The agency agrees with the view that, with few exceptions, it should generally describe "what" is to be accomplished and provide great latitude in "how" a requirement is to be achieved by manufacturers. Indeed, in many instances the CGMP regulations expressly provide manufacturers with considerable latitude to determine the manner in which requirements are to be accomplished. In this instance, because of the continuingand serious problems experienced by the industry in maintaining adequate control over cut labeling, the agency has concluded that somewhat greater labeling control is

needed. While the regulation reflects the agency's view that somewhat greater control over cut labeling is needed to reduce the incidence of drug product mislabeling, the final rule permits manufacturers considerable latitude under § 211.122(g)(1), (g)(2), and (g)(3) of these final regulations in achieving the greater degree of control.

The agency is aware that these regulations apply to a wide variety of drug products, but believes that the regulations are sufficiently flexible to permit technological innovation. Indeed, the rate of technological improvements of automated labeling inspection systems will likely accelerate with the increased use of such systems to comply with these regulations. Therefore, the agency concludes that the proposed regulations are specific enough to address a serious problem effectively while offering regulated industry sufficient flexibility to accommodate a great variety of present and future technologies.

2. Several comments addressed the scope of the proposed regulations. One comment stated that the regulations should not apply to preparation of bulk pharmaceutical chemicals. Another comment claimed that, because clinical supplies (i.e., investigational new drug products) are produced in small lots, there is less chance of labeling errors. The comment urged that such products be exempt from the regulations. Another comment suggested that medicinal oxygen repackers who handle no other compressed medical gases are not likely to experience labeling errors and, therefore, should be exempt from these regulations.

While the good manufacturing practice provisions under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) apply to both bulk and finished drugs, the CGMP regulations set forth in 21 CFR part 211, including the provisions governing labeling controls, apply solely to finished dosage forms, whether or not in packaged form. (See 21 CFR 211.1.) Although the revised labeling control provisions in the CGMP regulations do not apply to the preparation of bulk pharmaceutical chemicals, FDA may use these provisions as a guide in its inspections of the labeling practices of manufacturers of bulk pharmaceutical chemicals.

The revised labeling control provisions apply to the preparation of dosage forms that are under clinical investigation, whatever the size of the product lot. The small size of a product lot does not reduce the need for labeling controls. In fact, in some cases, the manufacture of many small lots may increase the opportunities for mixups and the need for label controls. Furthermore, in cases where firms label both investigational and noninvestigational products, the suggested exemption for investigational lots could create additional difficulties in labeling control for all products on the line. Therefore, the agency does not accept the suggested exemption for clinical supplies.

Finally, the agency rejects the suggested exemption for oxygen repackers who handle no other compressed medical gas. The agency notes that mixups can occur in a facility dedicated to repacking a single product among different lots or different private label distributors for the same product. Such mixups may have considerable public health significance.

3. Two comments addressed the effective date of the final rule. One comment suggested that at least 1 year would be needed, after the date of publication in the **Federal Register**, to acquire and start up new equipment. Another comment requested an 18- to 24-month time period to adopt new electronic systems or to convert from cut to roll labels.

This rule becomes effective August 3, 1994. The agency believes that the 12 months provided gives firms sufficient time to exhaust noncomplying labeling stocks and to make necessary changes to labeling control systems. The period given for compliance in this rule is the same as the period given firms to comply with the final rule requiring tamper-resistant packaging for over-the-counter drug products, a rule which, like these revisions to labeling controls, may have required some firms to install new equipment.

4. Several comments addressed the economic impact of complying with the proposed regulations. The comments argued that costs for new equipment and specially coded labeling could be especially significant for small firms that perform short labeling runs. The comments claimed that compliance would be costly if required for all labeling instead of being restricted to immediate-container labels.

As discussed in comment 13, the agency is adopting as part of the final rule a cut labeling control procedure for hand labeling operations that involves the use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations. Because this alternative can be implemented without new equipment or specially coded labeling, small firms should be able to comply with the new requirements without incurring significant incremental costs.

The agency believes that it is crucial to apply these regulations to package inserts and other pieces of labeling in addition to immediate-container labels. Recalls involving incorrect package inserts and outer/shipping cartons continue to be a problem. The agency does not believe that it is in the public interest to disregard this part of the overall problem of drug product mislabeling. Indeed, some manufacturers already recognize the need to improve controls on all labeling and have instituted bar code control systems for all labeling.

The agency believes that this final rule will bring the regulated drug industry up to the minimum level of current good manufacturing practice necessary for the prevention of drug product mislabeling. The agency agrees that some firms may incur costs in order to adopt suitable labeling control systems, but has determined that the overall cost impact of this final rule is minimal. For those manufacturers that choose to acquire an automated labeling verification system to inspect labeling, estimated cost based on bar-coded or keyhole-coded labeling is between $10,000 and $20,000, an expense that is comparable to the cost of general purpose manufacturing equipment. A more elaborate automated machine vision system for labeling verification may cost approximately $40,000. These equipment expenses will be offset for many manufacturers by the annual cost savings realized by the exemption from the requirement to perform label reconciliation. Further, these costs are considerably less than the costs to manufacturers and the public of label mixups, including the costs of product recalls that may follow a label mixup. Such costs include potential consumer injury and death, the expense of conducting product recalls, loss of goodwill, lost sales, and product liability claims.

B. Materials Examination and Usage Criteria

5. Nearly all comments supported the proposed revision under § 211.122(f) to the provisions governing the use of gang-printed labeling. One comment favored retaining the existing regulations, contending that the existing regulations already prohibit gang printing. The comment claimed that the proposal would relax existing requirements and fail to reduce the rate of mislabeling.

FDA does not agree. Existing regulations do not prohibit use of gang printing labeling for dissimilar items.

Rather, the existing regulations require that gang printing of labeling to be used for dissimilar items "be minimized," and that gang printing in such cases take place under special control procedures for labeling and packaging operations. As revised, the regulations prohibit use of gang-printed labeling for dissimilar items unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color. As stated in the preamble to the proposed rule, the agency views the change as a positive measure that will contribute significantly to preventing drug product mislabeling.

6. Three comments recommended that the regulations define the term "gang-printed labeling." One comment described a system for label printing that prints labels two to four across on a continuous roll on a sequential basis for dozens of different lots. Identical lots of labels are then separated from the roll for final container labeling. This comment sought to distinguish this printing method from conventional gang printing methods and, thus, exclude it from the proposed restrictions on gang printing. One comment suggested a definition for gang-printed labeling that would exclude sequentially generated computer printed labels. One comment requested the agency to distinguish between sheet-printed and gang-printed labeling.

After considering these and related comments, the agency concludes that a definition of the term "gang-printed labeling" is warranted. Accordingly, the agency is revising 21 CFR 210.3 to define gang-printed labeling as labeling derived from a sheet of material on which more than one item of labeling is printed.

As discussed in the preamble to the proposed rule, the agency has found that labeling mixups related to gang printing frequently arise when the multiple items of gang-printed labeling are insufficiently differentiated by size, shape, or color. Under these conditions, the proximity of the different labeling items to each other is problematic because the items, when cut and separated from gang-printed sheets into individual stacks, are easily mixed up. These proximity-derived mixups may go undetected at the printer, or at the drug manufacturer. Thus, the agency regards even a single sheet of gang-printed labeling (when printed by a manufacturer's computer, for example) to be prone to proximity-derived mixups because separation of similar labeling items may mistakenly include adjacent different labeling items. Likewise, similar labels for different items may be gang printed across roll stock sheets that are subsequently cut into individual rolls. These rolls may be inadvertently spliced onto adjacent rolls of labeling for different items where lack of adequate differentiation can mask the splicing error. The agency considers the continuous roll labeling printing method as gang-printed labeling, and the provisions of § 211.122(f) are intended to apply to roll stock sheets as well as individual stock sheets.

7. Two comments recommended that sequentially generated computer-printed labels, i.e., similar labels for different items that are printed by computer on rolls or flat sheets and separated before application to containers, not be considered gang printing within the meaning of proposed § 211.122(f). One comment asked about the acceptability of printing incomplete identical labels on a single sheet, subsequently separating these labels, and then filling in the blanks with information unique to each different item, as appropriate.

The agency considers the printing system described by the comment to be a type of gang printing within the meaning of § 211.122(f) (see comment 6). The fact that the printing process is controlled by computers is not relevant to the problems attendant to removing individual labels from a roll or sheet, nor does the use of computerized processes reduce the need for special control and handling of individual labels to prevent mixups. At the same time, the agency notes that the use of computer-controlled labeling procedures may make differentiation of labeling by size, shape, or color easier.

Preprinting incomplete identical stock labels on a single sheet or roll is not prohibited under these regulations. The agency advises, however, that labels that have been separated from a roll or sheet are considered cut labels and are subject to the special control procedures for labeling and packaging operations under § 211.122(g) of these regulations.

8. Two comments requested that the regulations allow gang printing of labeling for different items that are not differentiated by size, shape, or color, provided special control procedures are used to separate and control each unique set of labels. One comment argued that, where a firm handles many different products, the printing of distinctive labels for each product is not practical.

The previous regulation under § 211.122(f) permitted gang printing of labeling of the same size and identical or similar format and/or color schemes with the use of special control procedures in packaging and labeling operations, taking into account sheet layout, stacking, cutting, and handling during and after printing. The agency has concluded, through its analysis of product labeling recalls and inspectional findings, that the use of special controls during and after printing cannot be relied on to prevent mixups of cut labeling derived from such gang printing. Therefore, use of undifferentiated labeling derived from such gang printing is prohibited by these final regulations. However, it should be emphasized that the regulation does not require a firm to use labeling that is differentiated by size, shape, or color for each product in a firm's entire line. Differentiation is only required when a single sheet is used for the gang printing of labeling for different drug products, or different strengths or net contents of the same drug product.

9. One comment recommended that the regulations governing the labeling of insulin products be revised to permit product differentiation by the use of color coded labels. The comment claimed that color coding would not only help manufacturers control labeling, but also help consumers distinguish between insulin products.

Color coding of labeling for insulin products is already prescribed by regulation (21 CFR 429.12). The use of color coding to differentiate insulin products is beyond the scope of this final rule. Any person who believes that the color coding of insulin products should be changed may, of course, petition the agency under the provisions of 21 CFR 10.30 to amend 21 CFR 429.12.

10. One comment recommended that the agency not apply § 211.122(f) to the use of gang-printed labeling for small labeling lots, e.g., lots fewer than 100 in number.

The agency disagrees. Mixups involving gang-printed labeling can occur in small lots. As noted above, the small size of a lot does not reduce the need for labeling controls. Therefore, the agency declines to accept this recommendation.

11. Two comments requested the agency to define cut labels. One comment asked that cut labels be restricted to "traditional print shop operations." The second comment asked whether labels removed from a roll are considered to be cut labels.

"Cut labels" and "cut labeling" are items of labeling that have been detached from printed stock material prior to being brought to a labeling line. The agency advises that labels printed on a roll but not directly applied to packaging from the roll (i.e., where the labels are removed from the roll for

subsequent storage and handling prior to actual labeling) are cut labels.

12. Two comments recommended that the proposed special control procedures for cut labeling in § 211.122(g) also apply to roll labeling. One comment noted the potential for mixups involving roll labeling when a single roll has items of labeling of similar size, shape, or color.

Although use of roll labels, in itself, does not prevent mixups, the agency has determined that the use of cut labels is much more likely to cause labeling mixups and recalls and that special labeling control procedures for cut labels are justified. Specifically, FDA has found that 76 percent of recalls due to label mixups involved the use of cut labels; only 24 percent of recalls involved the use of roll labels. The agency has determined that individual cut labeling is more liable to result in mixups than labeling that is securely affixed to a roll from the time of printing until immediate application to containers. Therefore, the agency declines to extend special labeling controls to roll labeling at this time.

13. Several comments expressed concerns about the applicability of the proposed requirement regarding cut labels under § 211.122(g) to low volume labeling operations for such products as clinical supplies, bulk pharmaceutical substances, allergenic extracts, veterinary products, and compressed medical gases, and products produced in small lots such as radiopharmaceuticals or orphan drug products. The comments stated that, in low volume labeling operations, labeling is typically applied by hand and claimed that adequate labeling control can be attained by documented 100-percent visual examination by two persons in conjunction with labeling reconciliation. The comments contended that the use of electronic or electromechanical equipment for low volume operations is unwarranted.

The agency has concluded that, for labeling runs of a low enough volume to make hand application of cut labeling practical, visual examination performed by one person with independent verification by a second person of all labeling, in conjunction with labeling reconciliation, provides reasonable assurance of labeling control. Although visual examination is somewhat less effective than electronic or electromechanical examination, differences in effectiveness are insignificant in low volume situations where operators have sufficient time to check the labeling. The agency believes that, by limiting the provision to labeling applied by hand, the labeling control procedure will be confined to reasonably low volume labeling operations where visual checks of all labeling can be both practical and effective. Accordingly, the final regulation is amended to permit as an alternative control for cut labeling the use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Documentation that all products were visually examined for correct labeling must be made a part of the batch production record (see 21 CFR 211.188(b)).

14. Several comments asked whether proposed §§ 211.122(g) and 211.125(c) would apply to labeling other than the immediate container label.

As previously noted, the regulations are intended to apply to all labeling, not just immediate-container labels, and the agency has revised the final regulations accordingly. The agency's experience with product mislabeling recalls continues to show that use of incorrect cartons or inserts constitutes a significant portion of labeling control problems.

15. Several comments requested clarification of the term "dedication" as used in § 211.122(g)(1). Specifically, the comments asked whether "dedication" meant "permanent" or "per job" dedication of labeling and packaging lines. Some comments suggested that a packaging line should be considered to be dedicated if it is physically separated from other lines and if labeling runs for different products on a given line are not conducted concurrently.

For purposes of § 211.122(g)(1), the agency considers "dedication" of a labeling or packaging line to be the exclusive use of a line for a given strength of a given product for as long as that product and its labeling are in a firm's physical inventory or catalog of marketed products. A line may only be rededicated after exhaustion of the product and its labeling from the firm's physical inventory and removal of the product from the firm's catalog of marketed products. Physical or spatial separation of different packaging and labeling lines is already required under § 211.130(a) of the CGMP regulations and is not relevant to whether those lines are considered to be dedicated. Further, the agency has decided that exclusive use for a prescribed period of time as a measure of line dedication would not assure that incorrect labeling is not brought to a labeling or packaging line.

16. One comment recommended that FDA not adopt line dedication as an alternative control for cut labeling because line dedication will not prevent mixups where cut labels are mixed up before delivery to the line.

The agency acknowledges that line dedication alone will not prevent mistakes involving the delivery of labeling to a labeling or packaging line. Compliance with the other pertinent labeling control provisions on the receiving, sampling, inspection, and acceptance of labeling, as well as subsequent storage, issuance, and use of labeling, is still necessary to reduce the risk of mixups before delivery to the line. Line dedication is intended to provide additional assurance that correct labeling is used in labeling and repackaging operations. The agency, therefore, rejects this recommendation.

17. Several comments complained that line dedication is not feasible for firms making many different products, especially where lot sizes are small. Several comments requested that the agency accept as dedicated use of a given labeling and packaging line for different products when sequential packaging/labeling runs are distinguished by a variety of conditions, such as: (1) changes in mechanical equipment on the line; (2) shut down intervals of at least 4 working hours; (3) runs of distinctively different products or identical products having distinctively different net contents; and (4) use of labeling differentiated by size, shape, and color.

The agency considers that the effectiveness of using dedicated lines to prevent cut labeling mixups can be achieved only when a given line is used solely for one strength of one drug product, thus minimizing the chance that incorrect labeling would ever be brought to that line. The schemes suggested by the comments would not be, in the agency's view, effective labeling control methods. The agency notes that, under this final rule, use of dedicated lines is not the only option open to manufacturers. Firms may use nondedicated lines if: (1) an automated examination of 100 percent of the labeling is conducted, (2) roll labeling is used; or (3) labeling is applied by hand, if a visual examination of 100 percent of the labeling is conducted. The agency notes that the latter labeling control procedure should be a viable option for small lot sizes. Thus, the agency does not believe it appropriate to delete or qualify § 211.122(g)(1).

18. One comment asked whether a line may be considered dedicated under § 211.122(g)(1) if it is used for the labeling or packaging of several strengths of a single product.

The agency has revised this provision in the final rule to make clear that a

labeling or packaging line may be dedicated only to a single strength of a drug product.

19. Several comments recommended that the differentiation of cut labels by size, shape, or color be included as a special control procedure under proposed § 211.122(g).

Although there is value as a labeling control in differentiation of cut labeling by size, shape, or color, the agency believes that the use of differentiation of cut labeling, in itself, does not adequately assure that a product has been appropriately labeled. Therefore, the agency declines to accept this recommendation.

20. Three comments objected to proposed § 211.122(g)(2) because it requires the use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling. These comments asserted that such equipment is insufficiently reliable and does not guarantee that the correct label will be applied to the correct container.

The agency acknowledges that electronic and electromechanical inspection systems do not completely assure that the correct labeling will be applied to the correct product container. Automated labeling inspection systems are only one part of a total labeling control system. Additional labeling control procedures, including preacceptance inspection, and appropriate storage and handling, are also needed to reduce the risk of labeling mixups. However, the agency thinks that automated labeling inspection systems can serve as a significant safeguard to reduce the chance that cut labeling will be mixed up. The agency is confident that the performance characteristics of automated systems will improve greatly as demand for such systems increases.

The agency is keenly aware of the need to accommodate a wide variety of new technologies in various areas, including technologies applied to labeling controls. The agency is committed to facilitating appropriate use of technologies, consistent with the agency's mandate to protect consumers. Accordingly, any party claiming knowledge of a technology or method of assuring that correct cut labeling is used and which provides at least the same degree of protection against label mixup as the methods specifically stated in the final rule, may submit a citizen petition under 21 CFR 10.30. In addition to the requirements under 21 CFR 10.30, such a petition should be clearly identified as a "Request for Exemption from § 211.122(g) Cut Labeling Control Provisions." The petition shall provide FDA with evidence that the technology or method of labeling control advanced by the petitioner provides protection against labeling mixup either equal or superior to the methods provided for in § 211.122(g)(1), (2), or (3). If FDA agrees with the petitioner, FDA will approve the petition and may propose to amend § 211.122 to add the new control methods.

21. One comment recommended that the term "finishing operations" as used in proposed § 211.122(g)(2) be defined.

Finishing operations include all steps taken by a drug manufacturer to complete packaging and labeling of a drug product. Finishing operations for a solid oral dosage form might include, for example, placing the dosage form in an immediate container; placing a cotton fill and labeling insert in such container; applying a label, cap liner, and cap; placing the immediate container in a carton; applying a labeling outsert; and placing unit cartons in labeled shipping containers. The agency thinks that the term is well understood in the pharmaceutical industry and sees no need for the suggested revision in the definition section.

22. One comment asked whether the process of preparing labeling in an area specifically designed for control of labeling, but separate from the actual packaging operations, is a process that takes place "during or after completion of finishing operations" within the meaning of proposed § 211.122(g)(2).

Although some firms label and package products on contiguous lines, the agency notes that packaging operations may be conducted in areas separate from labeling operations. Section 211.122(g)(2) is intended to cover examination of labeling applied during or after completion of finishing operations. The provision does not pertain to the process of preparing labeling. Thus, labeling preparation is not a finishing operation within the meaning of § 211.122(g)(2).

C. Labeling Issuance

23. Many comments argued that the labeling reconciliation requirement under proposed § 211.125(c) be deleted because labeling reconciliation is not an effective means of label control, either alone or as an adjunct to other procedures. Several comments recommended that the proposed waiver for label reconciliation be expanded to the use of any labeling control procedures, such as dedicated labeling and packaging lines, 100-percent visual examination of hand applied labeling, 100-percent examination of roll labeling by automated systems, or differentiation of cut labels by size, shape, or color. Several comments supported labeling reconciliation as a cost-effective and practical alternative to automated 100-percent labeling examination, especially in low volume situations where labeling is applied by hand and visually examined.

The agency agrees that the proposed waiver of labeling reconciliation should extend to roll labeling which undergoes 100-percent automated inspection, and has revised § 211.125(c) accordingly. The agency does not believe that the other alternative labeling controls suggested by the comments are sufficiently effective labeling control measures to warrant waiver of labeling reconciliation. The agency is convinced that labeling reconciliation has prevented a number of mislabeling incidents. The agency wishes to stress, however, that reconciliation alone will not prevent labeling mixups. Compliance with other pertinent provisions of the CGMP regulations (e.g., on receiving, sampling, inspecting, accepting, storing, issuing, and using labeling) is also required.

D. Packaging and Labeling Operations

24. Several comments recommended that the word "immediately" be deleted from the phrase "not immediately labeled" under proposed § 211.130(b) because it does not take into consideration reasonable holding times between filling and labeling operations. Additionally, these comments stated that this requirement should not apply to situations where there are normal processing delays, such as employee rest breaks and product flow holding times between filling and labeling operations.

The intent of the proposed requirement was to require manufacturers to identify unlabeled filled containers that are set aside and held for future labeling operations. The proposed identification provision was not intended to apply to situations where there are reasonable delays between filling and labeling and where containers are otherwise identified during the production process by their phase of processing, as currently required under § 211.105 of the CGMP regulations. The final regulation has been revised accordingly.

25. Several comments argued that identification of unlabeled drug product containers under proposed § 211.130(b) need not include the expiration date because the inclusion of this information will not help the manufacturer identify the product. Several comments also stated that, for certain biological drug products, the

expiration date is based upon potency assays, which are not always available when containers are filled.

The agency agrees and has revised the final regulation accordingly.

26. Many comments stated that proposed § 211.130(b) would be unreasonable if the intention of this provision is to require that each unlabeled filled drug product container be uniquely identified with its name, strength, quantity of contents, lot or control number, and expiration date. These comments recommended that only groupings of such unlabeled containers need to be identified and that instead of including these specific identifiers, a system of identification, such as use of lot numbers or color coding traceable to each drug product's name, strength, quantity of contents, lot or control number, and expiration date, would suffice to prevent mixups.

The agency did not intend to require that the identifying information be affixed to each unlabeled filled drug product container. The agency's intention was to require manufacturers to incorporate into their written procedures provisions for the proper handling and identification of unlabeled containers so as to preclude mislabeling. Any identification system that permits the manufacturer to determine all of the required information is acceptable. This identification system may apply to secure groupings of containers provided that there is no question as to the correct identity of each container in the group. The final regulation has been revised to clarify the agency's intention.

Therefore, the agency is amending the CGMP regulations for human and veterinary drug products to revise certain labeling control provisions by amending § 210.3 by adding new paragraph (b)(22), by amending § 211.122 by revising paragraph (f), by redesignating paragraph (g) as paragraph (h), and by adding new paragraph (g), and by amending § 211.125 by revising paragraph (c).

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(10) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Economic Impact

The agency has analyzed the potential economic impact of the final rule and has determined that it requires neither a regulatory impact analysis as specified in Executive Order 12291, nor a regulatory flexibility analysis as defined in the Regulatory Flexibility Act (Pub. L. 96–354). Specifically, the final rule establishes additional conditions for the use of certain types of labeling and for the control of packaged drug products that will be labeled at a later date. In addition, the final rule provides an exemption from an existing label control requirement when certain conditions are met. The agency believes that the overall cost effect of this final rule is minimal.

As stated in both the 1989 proposal and the agency's economic assessment of this final rule, a significant number of firms already take advantage of electronic or electromechanical equipment to inspect all labeling. This final rule would result in cost reductions to those firms by exempting them from the current label reconciliation requirement. Also, most firms that choose to install automated, 100-percent labeling verification systems would achieve annual cost reductions that exceed the annualized acquisition costs of new equipment. Finally, the final rule provides for a cut-labeling control procedure for hand labeling operations that many small firms already use. Therefore, the agency believes that most firms, both large and small, will experience either unchanged or reduced regulatory costs because of these requirements. The 1989 proposal and the agency's economic assessment of this final rule are on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

In summary, the agency concludes that the final rule is not a major rule because the labeling control revisions do not result in a significant overall cost to manufacturers. Moreover, the final rule is intended to reduce the likelihood of mislabeling-related recalls and in many cases will reduce the industry's regulatory burden by relieving industry from certain CGMP labeling reconciliation requirements. For these reasons, therefore, the agency has determined that this final rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that this final rule does not have a significant economic impact on a substantial number of small entities, as defined by the Regulatory Flexibility Act.

V. Effective Date

To allow for sufficient time for necessary changes to labeling control operations and the consumption of existing labeling stocks made obsolete by labeling conversions, manufacturers are given until August 3, 1994 to comply with the new requirements.

List of Subjects

21 CFR Part 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 210 and 211 are amended as follows:

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS;GENERAL

1. The authority citation for 21 CFR part 210 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 506, 507, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374).

2. Section 210.3 is amended by adding new paragraph (b)(22) to read as follows:

§ 210.3 Definitions.

* * * * *

(b) * * *

(22) Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

3. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 506, 507, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374).

4. Section 211.122 is amended by revising paragraph (f), by redesignating paragraph (g) as paragraph (h), and by adding new paragraph (g) to read as follows:

§ 211.122 Materials examination and usage criteria.

* * * * *

(f) Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

(g) If cut labeling is used, packaging and labeling operations shall include

one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

* * * * *

5. Section 211.125 is amended by revising paragraph (c) to read as follows:

§ 211.125 Labeling issuance.

* * * * *

(c) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with § 211.122(g)(2).

* * * * *

6. Section 211.130 is amended by redesignating paragraphs (b), (c), and (d) as paragraphs (c), (d), and (e), respectively, and by adding new paragraph (b) to read as follows:

§ 211.130 Packaging and labeling operations.

* * * * *

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

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Dated: March 30, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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