

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

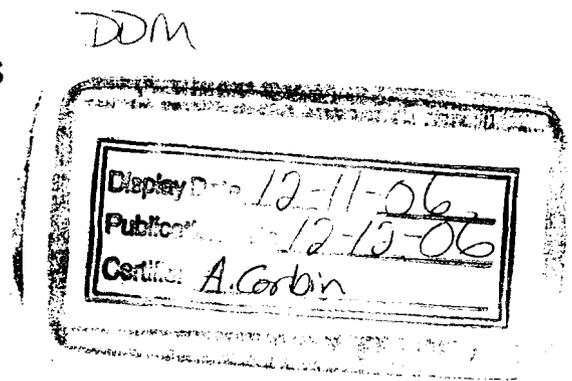
[Docket No. 1998N-0337C]

RIN 0910-AD47

Over-the-Counter Human Drugs; Labeling Requirements; Proposed Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.



SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its final rule that established standardized format and content requirements for the labeling of over-the-counter (OTC) drug products (Drug Facts Rule, codified at 21 CFR 201.66). This amendment proposes a definition and the option of alternative labeling requirements for “convenience-size” OTC drug packages.

DATES: Submit written comments by [*insert date 120 days after date of publication in the **Federal Register***]; written comments on FDA’s economic impact determination by [*insert date 120 days after date of publication in the **Federal Register***]. See section X of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: You may submit comments, identified by Docket No. 1998N-0337C and/RIN number 0910-AD47, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]:
Division of Dockets Management (HFA-305), Food and Drug Administration,
5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the Electronic Submissions portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No. and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of

Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow or Cazemiro R. Martin, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5426, Silver Spring, MD 20993-0002, 301-796-2090.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of March 17, 1999 (64 FR 13254), FDA published a final rule establishing standardized format and standardized content requirements for the labeling of OTC drug products (Drug Facts Rule). Those requirements are codified in 21 CFR 201.66.

Section 201.66(a) states that the content and format requirements in § 201.66 apply to the labeling of all OTC drug products. This includes products marketed under a final OTC drug monograph, products marketed under an approved new drug application (NDA) or abbreviated new drug application (ANDA) under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355), and products for which there is no final OTC drug monograph or approved NDA/ANDA.

In the Drug Facts Rule and in subsequent notices, FDA provided dates by which OTC drug products had to be in compliance with the new labeling requirements. FDA provided a chart in the Drug Facts Rule (64 FR 13254 at 13274) that summarized the time periods within which the various categories of marketed OTC drug products were required to comply with the final rule. Unless otherwise stated, all time periods in the chart began on the effective

date of the final rule. The chart was subsequently updated on June 20, 2000 (65 FR 38191 at 38193) and April 5, 2002 (67 FR 16304 at 16306 to 16307).

In the June 20, 2000, update, FDA clarified the applicable compliance dates in situations where relabeling was required by both the Drug Facts Rule and another rule. In the April 5, 2002, update, FDA delayed the compliance dates for “convenience-size” OTC drug products. Those products are the subject of this proposed rule.

A. Delay of Compliance Dates for “Convenience-Size” OTC Drug Products

FDA’s delay notice of April 5, 2002, postponed the Drug Facts Rule compliance dates for all “convenience-size” OTC drug product packages that do the following: (1) Contain no more than two doses of an OTC drug, and (2) because of their limited available labeling space, would require more than 60 percent of the total surface area available to bear labeling to meet the requirements set forth in § 201.66(d)(1) through (d)(9) and would therefore qualify for the labeling modifications currently set forth in § 201.66(d)(10). “Dose” was defined in the delay notice as the maximum single-serving for an adult (or a child for products marketed only for children) as specified in the product’s directions for use. (See 67 FR 16304 at 16306.)

FDA’s delay does not include single- or double-dose OTC drug packages that do not qualify for the labeling conditions in § 201.66(d)(10) because they can accommodate the Drug Facts labeling required in § 201.66(d)(1) through (d)(9) using 60 percent or less of their total surface area available to bear labeling. Examples of such products include some enemas, disposable douche products, and ipecac syrup products intended for emergency treatment use in poisonings. (See 67 FR 16304 at 16306 to 16307.)

B. Citizen Petition Requests Definition

FDA published the notice of delay for “convenience-size” OTC drug product packages in response to a citizen petition (Ref. 1) submitted by Lil’ Drug Store Products, Inc. (Lil’). Lil’ asked FDA to define “convenience-size” OTC drug products and to modify the labeling and content requirements of the Drug Facts Rule with respect to such products. Lil’ proposed that “convenience-size” OTC drug products be defined as packages sold to the public that contain one or two doses of an OTC drug product. Lil’ also proposed that “dose” be defined as a manufacturer’s recommended serving. In addition, Lil’ requested that FDA modify the requirements of § 201.66 for these “convenience-size” OTC drug products by permitting a reduced version of the OTC Drug Facts labeling to appear on the external packaging of such products, while requiring fully compliant Drug Facts labeling to appear on the inside of the package through the use of package inserts or inner-package printing. Lil’ stated that, under its proposal, the labeling on the external packaging would continue to include medically relevant information, would be consistent with the retail environment in which “convenience-size” OTC drug products are sold, and would still adequately enable consumers to make the unique purchasing decision associated with OTC drug use. Lil’ described the “convenience-size” products that it sells as recognized, brand-name, quality OTC drug products packaged in small doses and made available to the consumer at his or her point of need.

Lil’ stated that there were medical and policy rationales for its request centering on the dosing limitations of “convenience-size” packages. Because such packages contain only one or two doses of an OTC drug product, Lil’ reasoned that it is acceptable and appropriate for certain information required

under the Drug Facts Rule to appear inside the packages, either in a package insert or by inner-package printing. Lil' proposed that the outer product labeling of a convenience-size package still contain the complete "Drug Facts" title, active ingredients, purpose, uses, and inactive ingredients, but that it be allowed to abbreviate certain warnings and omit other required information. Lil' also proposed adding the following statement in bold, italic, seven-point Helvetica font: "Please read complete Drug Facts information inside prior to use." Lil' then proposed that the remaining information required by the Drug Facts Rule, including directions for use, certain warnings, and questions or comments, be allowed to appear inside the package, and it provided supporting reasons. (See section III.C of this document for a summary of Lil's suggestions and reasoning.)

In its response (Ref. 2) to the Lil' citizen petition, FDA stated that it had carefully reviewed the data and information in the petition and agreed that some accommodation for "convenience-size" packages might be appropriate. FDA stated that it intended to prepare, for publication in a future issue of the **Federal Register**, a proposed rule that would, if finalized, amend the Drug Facts Rule by defining "convenience-size" OTC drug packages and addressing Drug Facts labeling requirements for such products. The proposed rule would also provide all interested parties an opportunity to comment on the viability, desirability, and impact of the proposed rule, and to respond to specific questions posed by FDA.

II. The Basis for Optional Alternative Labeling for Convenience-Size OTC Drug Packages

FDA believes, from a public health perspective, that convenience-size OTC drug packages may not need to have all of the labeling information required by the Drug Facts Rule on the outer package. This belief is based on the

reduced risks posed by the limited amount of the active ingredient(s) contained in convenience-size packages, particularly because most of these packages do not provide for repetitive dosing. If a package contains only one or two doses of an OTC drug product, FDA believes there is a significantly reduced likelihood of an overdose occurring from consumption of the entire contents of the package. Further, FDA believes there is a corresponding reduction in the likelihood of other adverse side effects.

FDA also believes, as Lil' asserted in its petition, that many consumers who purchase and use convenience-size packages of an OTC drug product do so because they have an immediate need, often in a location away from home, to take a dose or two of the product. These consumers often purchase convenience size drug packages for immediate consumption or other very short-term use and may not be as concerned at the time of purchase about labeled statements regarding when to stop use of the product and ask a doctor for assistance, overdose warnings, directions for continued dosing, or storage information.

Lil' was also concerned that increasing the standardized size of "convenience packages" to comply with the Drug Facts Rule would inhibit the sale of such packages from convenience stores and vending machines, where space is limited and larger packages can not be accommodated.

Thus, given the unique circumstances associated with the purchase and use of "convenience-size" OTC drug products, FDA believes that some modification of the current labeling requirements set forth under § 201.66(d)(10) can be achieved without jeopardizing the public health or undermining the important goals of the act or the Drug Facts Rule. FDA considers such a modification to be especially important if failure to address

this issue means that “convenience-size” OTC drug products will no longer be as available or accessible to consumers.

FDA has determined, however, that certain critical warnings (e.g., allergic reactions, do not use situations, drug/drug interactions, risks associated with subsequent operation of a motor vehicle or machinery) and other information (e.g., inactive ingredients) must appear on the outer carton of convenience-size packages to allow consumers to accurately assess certain potential risks associated with the selection and use of the drug product at the time of purchase.

Further, FDA believes that complete product information should be provided to consumers with “convenience-size” packages, regardless of whether it is available at the point of purchase. For example, information about repeat dosing need not appear on the outside carton or wrapper of a “convenience-size” package, but it should appear on the inside package labeling in an insert or in inner-package printing for consumers who may purchase more than one package at a time.

Moreover, FDA strongly believes that the labeling modifications it is proposing for convenience-size packages should be narrowly applied and are not appropriate for packages of the same product that contain more than two doses. FDA believes that consumers who buy packages containing more than two doses customarily intend to take the product over a longer period of time than consumers who buy convenience-size packages. FDA believes that consumers who purchase packages with more than two doses should have complete information available at the time of purchase, so they can make fully informed decisions about prolonged use of the product.

For the reasons stated previously, FDA is proposing to modify the Drug Facts labeling requirements in § 201.66 for convenience-size OTC drug products as set forth in sections III.A, III.B, and III.C of this document. FDA believes its proposal will help achieve an appropriate balance between the consumer safety interests of the act and the Drug Facts Rule and the desire to ensure continued access to convenience-size OTC drug products in the marketplace.

III. FDA's Proposal

A. Definition of a Convenience-Size Package

FDA believes that the definition of a “convenience-size” OTC drug package should be a function of both the number of doses contained in the package and the size of the package. FDA’s proposed definition of convenience-size is set forth in proposed paragraph 201.66(d)(5). This definition addresses the number of doses and the package size.

1. Number of Doses

FDA considers a limited number of doses as one of the key criteria in any meaningful definition of “convenience-size.” FDA proposes that the definition of “convenience-size” be limited to OTC drug packages that contain no more than two doses of an OTC drug product. In the notice of April 5, 2002, partial delay of compliance dates, FDA defined a “dose” as the maximum single-serving for an adult (or a child for products marketed only for children), as specified in the product’s directions for use (67 FR 16304 at 16306). FDA is including the same definition in this proposal.

FDA has found that some currently marketed OTC convenience-size drug products have directions for both adults and children. In most cases, the child’s dose is one-half the adult dose. For example, in many products where

the adult dose is two dosage units, the child's dose is one dosage unit. FDA did not address this type of package in the April 5, 2002, partial delay of compliance dates. For safety reasons, FDA is proposing that, for products marketed with directions for use for both adults and children, a "dose" be defined as the maximum single serving based on the child's dose.

Those OTC drug monographs that provide directions for both children and adults generally give manufacturers the flexibility to market the OTC drug package to adults only, or to children only, or to both adults and children, so long as the package labeling bears the warnings that correspond to the age group(s) for whom the product is intended (see, e.g., 21 CFR 341.74(c) and 341.80(c)). Therefore, FDA does not believe that its proposed definition of "dose" will unduly hamper a manufacturer's ability to market convenience size packages to adults, but instead will provide a necessary safeguard against potential overdose in children in those instances where such products are marketed for children's use.

This proposed definition of "dose" would also apply to sample and trial-size packages that contain only one or two dosage units of an OTC drug. It would not apply to trial-size packages, or to any other small package sizes, that contain more than two doses and are sold in a retail setting.

2. Package Size

With respect to package size, FDA proposes that the definition of convenience-size be limited to those packages that qualify for the current labeling modification in § 201.66(d)(10) but which, because of their limited available labeling space, would require more than 60 percent of the total surface area available to bear labeling to meet the requirements set forth in § 201.66(d)(10). Thus, under the proposed rule, one or two dose OTC drug

packages that qualify for, and can accommodate, the current labeling modifications provided in § 201.66(d)(10) with 60 percent or less of their available labeling space would not meet the definition of “convenience-size” package in proposed § 201.66(b)(5). Only those “convenience-size” OTC drug packages that are so small that they cannot accommodate the modified drug facts labeling in § 201.66(d)(10) with 60 percent or less of their available labeling space would be allowed to bear the optional alternative labeling set forth in new § 201.66(d)(11). We note that there are many single-dose OTC products that are packaged in containers that are too large to qualify for the modifications in § 201.66(d)(10) (e.g., most enemas and disposable medicated douche products).

FDA invites specific comment on the following issues:

1. Whether the definition of “dose” should be different from that proposed and, if so, why. For those suggesting that the definition of dose be either expanded or narrowed, please explain the precise rationale for such a suggestion and explain how your proposed definition could be implemented to be meaningfully limited;

2. Whether the criteria regarding package size in proposed § 201.66(b)(5) should be different and, if so, why. For those suggesting that the size criteria be either expanded or narrowed, please explain the precise rationale for such a suggestion;

3. Whether there are any data or evidence to support Lil’s assertion that increasing package size to accommodate all of the information currently required under § 201.66(d)(10) will force traditional OTC convenience-size drug products out of the retail marketplace and/or reduce consumer access to such packages;

4. The relative public health risks associated with use of OTC convenience-size drug packages and the types of labeling information that must (or need not) be available at the point of purchase to ensure the safe and effective use of such products;

5. How the proposed definition of “dose” (or any other suggested definition of “dose”) might apply to topical products and how it might be possible to include OTC “convenience-size” topical drug products within this proposed labeling modification;

6. Whether there are any data to support Lil’s assertion that most OTC convenience-size drug products are purchased for an immediate need to take a dose or two of the drug (as opposed to repeat dosing); and

7. Whether there are reasons to oppose any labeling modification for OTC convenience-size drug products. For those opposing any modification to the Drug Facts Rule for OTC convenience-size packages, please explain the precise rationale for your position and provide evidence, if any, to support your concerns.

B. Exceptions to the Proposed Definition

For public health reasons, FDA proposes to exempt from the definition of “convenience-size” several OTC drug products used for poison treatment that are marketed in single-dose containers. These include syrup of ipecac and activated charcoal. Syrup of ipecac is limited by regulation (21 CFR 201.308(c)) to 1 fluid ounce (30 milliliter (mL)) packages for OTC sale. The usual dosage is one tablespoon (15 mL) in persons over 1 year of age (§ 201.308(c)(3)). FDA has proposed that the dosage be revised to 2 tablespoonsful (30 mL) for adults and children 12 years of age and over and to 1 tablespoonful (15 mL) for children 1 to under 12 years of age. (See proposed § 357.54(d), 50 FR 2244

at 2261, January 15, 1985). Activated charcoal is usually marketed in packages containing a minimum of one dose of 20 grams. (See proposed section 357.52(d)(1), 50 FR 2244 at 2261).

FDA considers it important that all of the labeling information for these products be available to consumers at the time of purchase. FDA also believes that, unlike most convenience-size OTC drug products, poison treatments are not purchased for immediate use, but are often acquired for subsequent access within the home in case of an emergency. FDA is therefore concerned that if some of the important information for using these products only appeared on a package insert and that insert got separated from the package before the product was used, the consumer would not have the necessary information at the time the product was needed, possibly resulting in serious health consequences. Those single dose OTC syrup of ipecac and activated charcoal packages that qualify for the labeling modification in § 201.66(d)(10) may still be labeled according to the modifications set forth in that section. However, for the reasons stated above, FDA proposes to exclude them from the definition of “convenience-size” in § 201.66(b)(5) and the additional labeling modifications proposed in § 201.66(d)(11), regardless of package size.

Because there currently is no final monograph for OTC poison treatment drug products, FDA does not know how many manufacturers, repackers, and distributors of these products have attempted to develop Drug Facts labeling for these products. FDA invites comment, especially from companies that prepare labeling for these products, about how the labeling proposed in § 357.52 and 357.54 (50 FR 2244 at 2261) would best fit on the immediate and outside containers when converted to the new Drug Facts format. Interested parties are invited to submit draft labeling in response to this

proposed rule for FDA to evaluate. FDA also invites specific comment on whether there are other OTC drug products that should not be eligible for the proposed “convenience-size” labeling format, even if such products otherwise meet the definition set forth in proposed § 201.66(b)(5).

C. Optional Alternative Labeling for Convenience-Size Packages: Discussion

FDA agrees with Lil’ that certain Drug Facts information must fully appear on the outer product labeling of a convenience-size OTC drug package, regardless of the size of that package. This information includes the “Drug Facts” title, active and inactive ingredients, purpose(s), use(s), certain warnings, and some of the other information required by § 201.66(c)(7). FDA considers this information an essential part of § 201.66 that must be available to all consumers at the point of purchase. FDA also considers the warnings in § 201.66(c)(5)(i), (c)(5)(ii), and (c)(5)(iii) essential information that should appear in full on the outside of all OTC convenience-size packages because these sections contain especially important warning information that might influence a consumer’s purchase decision at the point of sale. Regarding the other applicable warnings and directions, FDA has the following comments:

1. Section 201.66(c)(5)(iv): This section requires the warning subheading “Ask a doctor before use if you have” and includes warnings for certain pre-existing conditions and warnings for persons experiencing certain symptoms. Lil’ pointed out that the warnings under this heading are those intended only for situations in which consumers should not use the product until a doctor is consulted. Lil’ contended that the information, while important, becomes less so given the low dosage being consumed and the unlikely negative side

effects of such a low dosage, and this information can be safely included inside the outer carton of a convenience-size package.

FDA disagrees. Information under this subheading would include disease conditions such as diabetes, glaucoma, high blood pressure, heart disease, thyroid disease, and trouble urinating due to an enlarged prostate gland. Consumers who have these conditions need to be informed at the point of purchase that the product may have an undesired effect because of the pre-existing condition(s). This potential problem for an adverse side effect exists whether the consumer is taking a single dose from a convenience-size or multiple doses over time from a larger package.

2. Section 201.66(c)(5)(v): This section requires the warning subheading “Ask a doctor or pharmacist before use if you are” and is followed by all drug-drug and drug-food interaction warnings. Lil’ suggested this information need not appear on the outside of the carton because there are generally no pharmacies located in the retail environment in which most OTC convenience-size packages are sold.

FDA disagrees. FDA believes that this information must appear on the outside of the carton to ensure it is accessible to consumers at the point of purchase. For certain OTC drug products, the warnings under this heading inform consumers not to take the product if they are taking sedatives or tranquilizers. FDA believes that most consumers will know if they are taking a sedative or tranquilizer and, thus, can make the informed decision to avoid a product that has this warning, even when the purchase occurs in a non-pharmacy outlet.

3. Section 201.66(c)(5)(vi): This section requires the warning subheading “When using this product” and provides information on the side effects that

may occur and substances or machinery to avoid when using the product. FDA believes, as Lil' suggested, that all information about potential drowsiness, avoiding alcohol, and using care when driving a motor vehicle or operating machinery must appear in the external package labeling.

However, FDA acknowledges there may be other information that appears under this subheading that could appear on the inside package labeling of convenience-size packages without jeopardizing public health or undermining the basic purpose of § 201.66. Examples include information about not using the product at certain times or certain side effects that may occur (e.g., stomach discomfort, cramps). FDA invites specific comments and suggestions, with supportive reasons, about other information under this subheading that could appear on the inside package labeling or should remain on the outside of the package.

4. Section 201.66(c)(5)(vii): This section requires the warning subheading "Stop use and ask a doctor if" and provides information on any signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product. Lil' stated that, based on the dosing limitations of convenience-size packages, this information could be adequately addressed inside the carton.

FDA generally agrees. Most of the signs of toxicity described in this section are expected to occur when the product has been used for more than one or two doses. However, for some products, this section requires a specific warning about potential allergic reactions that could occur even after one or two doses and informs consumers to seek medical help right away. FDA believes this allergy warning information describes a condition that may be serious and that could influence a consumer's decision at the point of purchase. Therefore, FDA

is requiring that any warning information about allergic reactions required under this subheading must continue to appear on the outside package.

5. Section 201.66(c)(5)(viii): This section requires warnings that do not fit within one of the paragraphs in § 201.66(c)(5)(i) through (c)(5)(vii), (c)(5)(ix), and (c)(5)(x). An example of such a warning is “* * * Do not puncture or incinerate. * * *” for drugs in dispensers pressurized by gaseous propellants set forth in 21 CFR 369.21. Lil’ suggested that this section could be addressed case-by-case using the same criteria as used for the other sections. FDA believes that there is little labeling in this category that would apply to convenience-size packages and that most, if not all, of the information that would appear under this heading could appear on the inside package labeling. There may be instances, perhaps in the future, in which a warning required under this section should appear on the outside Drug Facts label. FDA invites specific comment on which warnings included in this category, if any, should be kept on the outside package and how FDA should address the importance of future warnings required under this section.

6. Section 201.66(c)(5)(ix): This section requires the pregnancy/breast-feeding warning set forth in § 201.63(a) and the third trimester warning set forth in § 201.63(e) or in certain approved drug applications. Lil’ acknowledged that this information should continue to appear on the external package labeling. FDA concurs that this information is needed at the point of purchase and must appear in the outer package labeling.

7. Section 201.66(c)(5)(x): This section requires the warning to “Keep out of reach of children” and the accidental overdose/ingestion warnings set forth in § 330.1(g). Lil’ provided a number of reasons why this information could appear inside the package. Lil’ stated that convenience-size OTC products are

usually not purchased, taken home, and stored. Instead, said Lil', they are usually consumed shortly after purchase to satisfy a consumer's immediate need. Lil' added that it is not industry practice to sell OTC drug products to children, which reduces the likelihood of a child possessing a convenience-size package. Finally, Lil' asserted an overdose is extremely unlikely given the dosing limitations in a "convenience-size" package.

FDA agrees. Under § 330.1(g), FDA has authority to grant an exemption from these warnings where appropriate upon petition. FDA is not inclined to use this authority to exempt convenience-size products from these warnings altogether. However, we are proposing to allow these warnings to appear inside OTC convenience-size packages on either an insert or inner-package labeling.

8. Section 201.66(c)(6): This section requires the Drug Facts labeling to include the directions for use described in an applicable OTC drug monograph or approved drug application. The regulations in 21 CFR 201.5 describe adequate directions for use for drugs as "directions under which the layman can use a drug safely and for the purposes for which it is intended." Directions can include: Uses of the drug; quantity of the dose (based on age); frequency, duration, time, and route or method of administration; preparation for use (i.e., shaking, dilution).

Lil' stated that, for one- or two-dose products, having the directions for use at the point of purchase is less important because of the following:

- The package will not contain enough product for continued dosing and overdose, and
- The consumer's likely intent is to take the product immediately.

FDA believes that for all OTC drugs, including convenience-size packages, it is preferable for all of the directions information to appear in one location

to best inform consumers how to use the product. Because the directions may be lengthy, FDA is proposing that this information appear in full on the inside package labeling for OTC convenience-size drug products. However, FDA believes that it is important to inform consumers that the directions are inside the package. In addition, FDA believes that it is also important to inform consumers at the point of purchase that the product is not intended for use in certain age groups. Therefore, FDA is proposing that the following information appear in the outer package labeling in 7-point bold type size under the heading Directions: “See inside for directions. This product is not for children under [insert appropriate age] without asking a doctor.” FDA believes this approach strikes a balance between package size and the need for information about age limitations at the point of purchase. This will also enable consumers to make appropriate purchase decisions at the point of purchase and use OTC convenience-size packages safely for their intended purposes.

9. Section 201.66(c)(7): This section requires, under the heading “Other information,” additional information that is not included under § 201.66(c)(2) through (c)(9), but which is required by or is made optional under an applicable OTC drug monograph, other OTC drug regulation, or is included in the labeling of an approved drug application. Examples include: (1) Required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(c)), (2) phenylalanine/aspartame content required by § 201.21(b), if applicable, and (3) additional information authorized to appear under this heading, such as the storage temperature and tamper evident statement. Lil’ suggested that any reference to sodium, aspartame, or other special ingredients still appear on the outer labeling, while all other statements

in this section appear on the inside package labeling. Lil' noted that the contents of convenience-size packages are customarily consumed upon purchase, lessening the need for storage and temperature warnings.

FDA agrees with Lil', except for the location of the tamper evident statement. The regulations in 21 CFR 211.132(c) require the tamper-evident statement to be prominently placed on the package in such a manner that it will be unaffected if the tamper-evident feature of the package is breached or missing. To meet this requirement, FDA has determined that the tamper-evident statement must appear on the outer package labeling. However, the tamper-evident statement is not required to appear within the Drug Facts portion of the labeling and may appear elsewhere on the outer packaging.

10. Section 201.66(c)(9): This section requires the heading "Questions or Comments," followed by the telephone number of a source to answer questions on the product. Lil' stated that, presumably, this section is related to questions and comments about continued consumption of a product. Given the one- and two-dose limitation and the consumer's usual intent for immediate consumption of the product, Lil' contended that this section may be adequately presented inside the package. FDA agrees that this information may appear on the inside labeling of the package.

D. Package Inserts and Inner-Labeling

FDA is also considering different ways to present the Drug Facts labeling inside the package. Currently, FDA favors the following options: (1) A package insert that contains complete Drug Facts labeling in accord with § 201.66(d)(1) through (d)(9), including all the information exempted from the outside labeling under proposed § 201.66(b)(5) and (d)(11); or (2) permitting the Drug Facts labeling that is not required to appear on the outside container or

wrapper to be printed on the inside of the outer container or wrapper in the required Drug Facts order. FDA believes the package insert containing the complete Drug Facts labeling is the preferred approach because it will be complete and less confusing to consumers. However, FDA is aware that information can be printed on the inside of cardboard and other containers, and Lil' mentioned inner-package printing as a possible approach. FDA's major concern about labeling appearing on the inside of the outer container or wrapper is whether consumers can (or will) open the package without tearing the part that contains the labeling, and the ease with which the information can be read once the outer container or wrapper is opened. FDA believes if this second option is allowed, it should be conditioned upon the package having an easy way to be opened (e.g., a pull tab), so that when the package is opened, the inside labeling information is readily exposed and can be easily read. FDA invites specific comment on the comparative costs of these methods of providing labeling inside the outer container, and whether there are packaging techniques readily available that would allow for these convenience-size packages to be easily opened without tearing the part of the package that contains labeling information. FDA also invites comment on other ways that Drug Facts labeling information could be presented inside a convenience-size package and comparative costs with the two methods discussed above.

E. Information Available on the Outside Container or Wrapper

FDA discusses in section II of this document its basis for proposing to modify labeling for convenience-size OTC drug packages, FDA believes that convenience-size OTC drug packages, as defined by limited dose and container size in section III of this document, can adequately meet public health needs without presenting on the outer package all of the information required by the

Drug Facts Rule. FDA does not believe that such modifications can be justified for larger packages, which contain enough medication for repetitive dosing and/or have sufficient available labeling space to bear all of the information required under the Drug Facts Rule. FDA is seeking feedback about whether the information proposed for the outer package, and available at the time of purchase, is adequate to support safe and effective use of the dose of medication to be allowed in a convenience-size OTC drug package. FDA is seeking comment on whether there should be an additional requirement that provides for full product information to be available at the point of purchase (e.g., a shelf-talker or extender, or a tear-off Drug Facts information sheet) if some of the Drug Facts information is not available on the outer package.

F. Summary of Optional Alternative Labeling for Convenience-Size Packages

In summary, based on the previous discussion, it is FDA's view that as much of the Drug Facts labeling as possible should appear on the outside container or wrapper of convenience-size packages and be available to consumers at the point of purchase. FDA recommends that, when possible, manufacturers of convenience-size OTC drug packages as described in proposed § 201.66(b)(5) try to fit all of the Drug Facts labeling on the outer container or wrapper using the modified format currently available in § 201.66(d)(10). However, given the unique status of convenience-size OTC drug products--including the reduced risks associated with their limited contents, the "size sensitive" retail setting in which they are sold, and the fact that many are purchased for immediate consumption--FDA is proposing to allow certain Drug Facts information to appear inside a convenience-size OTC drug package. Accordingly, FDA is proposing a new § 201.66(d)(11) (existing § 201.66(d)(11) is being redesignated as § 201.66(d)(12)) to state that OTC drug

products that meet the convenience-size package definition in § 201.66(b)(5) may use an optional alternative version of the Drug Facts labeling in which certain information otherwise required to appear on the outside wrapper or container of an OTC drug product under § 201.66(c)(5)(vi), (c)(5)(vii), (c)(5)(viii), (c)(5)(x), (c)(6), (c)(7), and (c)(9) may appear inside the package. FDA further proposes, under § 201.66(d)(11), that the Drug Facts labeling on the outside container or wrapper contain the statement “See information inside before using,” in bold italic type no smaller than 7-point size. This statement would appear either immediately after and on the same line as the “Drug Facts” title, or immediately beneath the “Drug Facts” title and above the horizontal hairline that would otherwise immediately follow the “Drug Facts” title. FDA is also proposing that the following information appear in the outer package labeling in 7-point bold type size under the heading Directions: “See inside for directions. This product is not for children under [insert appropriate age] without asking a doctor.” FDA invites specific comment on this wording and format and other wording or formats that would convey the same message.

FDA is also considering different ways to present the exempted Drug Facts labeling inside the OTC drug package. Currently, FDA favors the following options: (1) A package insert that contains complete Drug Facts labeling in accord with § 201.66(d)(1) through (d)(9), including all the information exempted from the outside labeling under proposed § 201.66(b)(5) and (d)(11); or (2) permitting the Drug Facts labeling that is not required to appear on the outside container or wrapper to be printed on the inside of the outer container or wrapper in the required Drug Facts order.

IV. Legal Authority

This rule, if finalized, would not require OTC drug product labeling to bear new kinds of information. Rather, the rule would modify the format of the current OTC Drug Facts labeling to accommodate the unique circumstances associated with the packaging, marketing, purchase, and use of “convenience size” OTC drug packages.

FDA’s legal authority to modify § 201.66 arises from the same authority under which FDA initially issued the regulation, including 21 CFR parts 201, 301, 502, 505, 507, and 701 of the act. This authority is described in detail in the **Federal Register** of February 27, 1997 (62 FR 9042 through 9043).

V. Analysis of Impacts

The economic impact of the Drug Facts Rule was discussed in the final rule (64 FR 13254 at 13276). That discussion included estimates of the increased costs for small package products that could not fit the new Drug Facts labeling to enlarge the package or to use other labeling techniques (e.g., risers) to fit the information. FDA estimated that 6.4 percent of all shelf-keeping units (SKUs) had labels that either would not fit or were indeterminate (too close to call) and, thus, might require a new packaging configuration to accommodate the new format (64 FR 13254 at 13283). Convenience size packages were included in the estimate, as well as other small package sizes. The Consumer Healthcare Products Association has stated that “convenience-sizes” represent less than 1 percent of the retail market (Ref. 3).

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory

alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, FDA must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

FDA has concluded that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section, FDA has determined that this proposed rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current threshold after adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product.

The purpose of this proposed rule is to define OTC “convenience-size” drug products and to provide Drug Facts labeling alternatives for these

products that would enable manufacturers, repackers, or distributors to provide certain labeling information on the inside of the package, either in a package insert or by internal package printing. This alternative approach would apply only to packages that meet the proposed package size and dose limitations.

The economic impact for relabeling OTC drug products was previously addressed in the final rule. This proposed rule provides an alternative labeling approach to accommodate the Drug Facts labeling requirements.

In the final rule (64 FR 13254 at 13283), FDA estimated 4.5 percent of all OTC drug SKUs may require increased package sizes to accommodate the new Drug Facts format. The one-time cost to industry was about \$38.1 million and the annually recurring costs were estimated to be \$11.5 million for the added package and label materials (64 FR 13254 at 13284). The cost analysis included a number of alternative package configurations, including adding an outer carton, a fifth panel (a back panel), enlarging the package, and adding a peel-back or two-ply label using existing or retooled packaging lines. Package inserts or double-sided printing were not considered in that analysis. In some circumstances these two alternatives could be less costly than the others included in the analysis. This proposed rule allows manufacturers additional flexibility to choose the least costly packaging alternative to meet their marketing requirements but would probably have little effect on the overall cost of relabeling. In the original analysis FDA did not identify which of the small package sizes that could not accommodate the Drug Facts format would be considered convenience sized packages. As such, we cannot breakout the estimated costs from the Drug Facts Rule (64 FR 13254 at 13276 to 13285) that applied to convenience-sized packaged products.

Because this proposed rule does not mandate changes to packaging, but increases manufacturers choice of package configurations FDA certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the proposed labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a “collection of information” under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling requirements are a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) 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.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized as proposed, would have a pre-emptive effect on State law. Section 4(a) of the Executive Order requires agencies to “construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” Section 751 of the act (21 U.S.C. 379r) is an express pre-emption provision.

Section 751(a) of the act provides that: “* * * no State or political subdivision of a State may establish or continue in effect any requirement— * * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*). * * *”

Currently, this provision operates to pre-empt States from imposing requirements related to the regulation of nonprescription drug products. (See section 751(b), (c), (d), and (e) of the act for the scope of the express pre-emption provision, the exemption procedures, and the exceptions to the provision.) This proposed rule, if finalized as proposed, would amend the format and content requirements for the labeling for OTC convenience size drug packages. Although any final rule would have a pre-emptive effect, in that it would preclude States from issuing requirements related to the labeling of OTC convenience size drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. FDA also notes that even where the express pre-emption provision is not applicable, implied preemption may arise (See *Geier v. American Honda Co.*, 529 US 861 (2000)).

FDA believes that the pre-emptive effect of the proposed rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that “when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all

affected State and local officials notice and an opportunity for appropriate participation in the proceedings.” FDA is providing an opportunity for State and local officials to comment on this rulemaking.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document and FDA’s economic impact determination. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

X. Proposed Effective Date

FDA is proposing that any final rule that may issue based on this proposal for OTC convenience-size drug products become effective 18 months after its date of publication in the **Federal Register**. FDA is proposing that the compliance date for OTC convenience-size drug products with annual sales less than \$25,000 would be 24 months after the date of publication in the **Federal Register**. The compliance date for all other OTC convenience-size drug products would be 18 months after the date of publication in the **Federal Register**.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP1, Docket Number 2001P-0207.

2. Letter from S. Galson, FDA, to J. M. Nikrant, Lil' Drug Store Products, Inc., coded LET 1, Docket Number 2001P-0207.

3. Letter from R. W. Soller, CHPA, to C. Ganley, FDA, dated October 3, 2000, Docket Number 1998N-0337.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 201 be amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.66 is amended by redesignating paragraphs (b)(5) through (b)(12) as paragraphs (b)(7) through (b)(14), respectively, and by redesignating paragraph (d)(11) as paragraph (d)(12), and by adding new paragraphs (b)(5), (b)(6), and (d)(11) to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

* * * * *

(b) * * *

(5) Convenience-size package means a package containing no more than two doses, as defined in paragraph (b)(6) of this section, of an OTC drug product that, because of its limited available labeling space, both qualifies for the modified labeling set forth in paragraph (d)(10) of this section and would

require more than 60 percent of its total surface area available to bear labeling to meet the labeling requirements set forth in paragraph (d)(10). This definition does not include OTC drug packages that contain ipecac syrup or activated charcoal.

(6) Dose means a maximum single-serving for an adult (or child for products marketed only for children) as specified in the product's directions for use. For products marketed with directions for use for both adults and children, dose means a maximum single serving for a child as specified in the product's direction for use.

* * * * *

(d) * * *

(11) *Convenience-size packages.* The labeling of products that meet the convenience-size package definition in paragraph (b)(5) of this section shall appear in accord with either paragraph (d)(10) or paragraph (d)(11)(i) of this section.

(i) The outside container or wrapper of an OTC convenience-size drug product labeled under this section shall comply in all respects with paragraph (d)(10) of this section, except as modified by paragraphs (d)(11)(i)(A) through (d)(11)(i)(G) and paragraph (d)(11)(ii) of this section.

(A) All information required by paragraph (c)(5)(vi) of this section, including the statement "do not use more than directed," may appear on the inside of the OTC drug package in accord with paragraph (d)(11)(ii) of this section, except any information about potential drowsiness, avoiding alcohol, and using caution when driving a motor vehicle or operating machinery, which shall appear on the outside container or wrapper in accord with paragraph (d)(10) of this section.

(B) All information required by paragraph (c)(5)(vii) of this section may appear on the inside of the OTC drug package in accord with paragraph (d)(11)(ii) of this section, except any information about a potential allergic reaction, which shall appear on the outside container or wrapper in accord with paragraph (d)(10) of this section.

(C) All information required by paragraph (c)(5)(x) of this section, including the statement "Keep out of reach of children" and the accidental overdose/ingestion warnings set forth under § 330.1(g) of this chapter, may appear on the inside of the OTC drug package in accord with paragraph (d)(11)(ii) of this section.

(D) All information required by paragraph (c)(6) of this section may appear on the inside of the OTC drug package in accord with paragraph (d)(11)(ii) of this section. If any such information is placed inside the package, the outside container or wrapper shall state the following in bold italic type no smaller than 7-point under the heading "Directions": "See inside for directions. This product is not for children under [insert appropriate age] without asking a doctor."

(E) All information required by paragraph (c)(7) of this section may appear on the inside of the OTC drug package in accord with paragraph (d)(11)(ii) of this section, except: (1) The tamper evident statement required by § 211.132(c), which must appear on the outside container or wrapper, but need not necessarily appear in the Drug Facts box or similar enclosure; and (2) all information required by paragraphs (c)(7)(i) and (c)(7)(ii) of this section, which shall appear on the outside container or wrapper in accord with paragraph (d)(10) of this section.

per
Brad Brooks, M.D.
12/7/06
AL

(F) All information required by or authorized under paragraph (c)(9) of this section may appear on the inside of the OTC drug package in accord with paragraph (d)(11)(ii) of this section.

(G) In the event that any information is placed inside an OTC drug package under the authority of paragraphs (d)(11)(i)(A) through (d)(11)(i)(G), the outside container or wrapper of that package shall state the following in bold italic type no smaller than 7-point: “See information inside before using.” This statement shall appear either immediately after and on the same line as the “Drug Facts” title or immediately beneath the “Drug Facts” title and above the horizontal hairline that would otherwise immediately follow this title.

(ii) Any and all labeling included inside any OTC drug package or wrapper to comply with any provision of paragraph (d)(11)(i) of this section shall appear in one and only one of the following ways:

(A) In a package insert that contains the complete Drug Facts labeling as defined in paragraph (b)(12) of this section printed in accordance with the specifications in paragraphs (d)(1) through (d)(9) of this section, regardless of whether some of this information also appears on the outside container or wrapper; or

(B) All Drug Facts labeling as defined in paragraph (b)(12) of this section that does not appear on the outside container or wrapper shall be printed on the inside of the outside container or wrapper in the order listed in paragraph (d)(11) of this section and shall appear in accordance with the specifications in paragraphs (d)(1) through (d)(9) or in paragraph (d)(10). The title “Drug Facts (continued)” shall appear at the top of each subsequent panel containing such information. When any Drug Facts labeling is printed on the inside of the outside container or wrapper, the container or wrapper shall have an easy way

to be opened (e.g., a pull tab or something similar) so that the package or wrapper on which the information is printed is unlikely to be torn or destroyed, and the labeling information is readily exposed and can be easily read.

Dated: 11/20/06
November 20, 2006.



Jeffrey Shuren,
Assistant Commissioner for Policy.

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