Comment Summary

FDA's Advanced Notice of a Proposed Rulemaking on September 1, 2005

Drug Approvals: Circumstances under which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-the-counter Drug Product

Final

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Preface

This document summarizes comments the U.S. Food and Drug Administration (FDA) received in response to its Advanced Notice of a Proposed Rulemaking (ANPRM) published in the *Federal Register* on September 1, 2005 (70: 52050-52051). The ANPRM requested comments in response to seven questions about circumstances under which an active ingredient may be simultaneously marketed in both a prescription drug product and an over-the-counter (OTC) drug product. By the deadline, November 1, 2005, FDA received approximately 47,000 comments, including 17 different form letters. The focus of this report is on comments responsive to the ANPRM questions. Nearly all of the comments addressed miscellaneous issues outside the scope of the ANPRM questions (e.g., included comments regarding approval of a specific drug product). Comments regarding these miscellaneous issues are summarized in sections 1, 2, 10, and 11, albeit in less detail.

In short, ICF's approach to develop this summary involved the following steps:

(1) Review of the comments or representative form letters to identify those comments responsive to the ANPRM questions.

(2) Tracking of the comments' positions on each question and the issues or categories of arguments presented, using CommentWorks[SM] software.

(3) Extract responsive and substantive arguments' excerpts and assign them to issues in the CommentWorks[SM] databases.

(4) Sort the comment excerpts by issue to prepare this summary.

ANPRM Question	Section in Summary and Issue Outline
1.A Should FDA initiate a rulemaking to codify its interpretation of section 503(b) of the Act regarding when an active ingredient can be simultaneously marketed in both a prescription drug product and an OTC drug product?	3
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Appendix A of this report contains a table that shows the total counts of comments that addressed each issue. The counts are based on issue coding of 18,000 comments in the CommentWorks[SM] database, to which were added the quantity of associated "bundled" form letters. Appendix B of this report is a list of studies or technical publications that were cited in the comments.

1. Comments Unrelated to Specific Questions in the ANPRM—Drug Approval

Many of the comments discussed issues unrelated to the specific questions in the ANPRM and commented on the controversy surrounding approval of Plan B (0.75 mg levonorgestrel tablets).

1.1 General Comments on Drug Approval Process

Thirty-five comments presented general comments on FDA's drug approval process, FDA's responsibilities to the public, or how the drug approval process should be scientific, not politically influenced.

1.2 Specific Comments on Drug Approval for Plan B

Roughly 47,000 comments (approximately 18,000 without all form letters included) contained specific statements on the drug approval process for Plan B. Positions included:

- Approve Plan B for OTC sales for all (i.e., available OTC for all age groups) [16,470 comments];
- Approve simultaneous marketing approach proposed by the Plan B sponsor (i.e., marketed both OTC and by prescription to women 17 and younger) [158 comments];
- Continue Plan B's prescription-only status [620 comments (roughly 590 without all form letters included]; or
- Not allowing the drug product in any form (i.e., oppose drug product in any form) [147 comments].

Additionally, approximately, 1,337 comments presented statements on Plan B's approval process, but it was unclear which approval method was preferred. One comment contained a request that FDA publish or email a list of the scientific studies that were used to support the approval of Plan B as an OTC product. [EC788-9]

1.3 Specific Comments about Other Drug Product(s)

Nine comments [EC21; EC59; EC106; EC127; EC150; EC762; EC793; EC5174; EC16655] contained specific statements about another drug product (e.g., 5% testosterone, Vioxx, Celebrex).

2. Comments Unrelated to Specific Questions in the ANPRM—FDA's General Rulemaking Process

2.1 Comments on Time, Manner, and Nature of Rulemaking Process

The majority of the comments that addressed FDA's general rulemaking process specifically addressed the time, manner, and nature of the rulemaking process [34,086 comments

(approximately 5,999 without all form letters included)]. Typically these comments presented the view that the rulemaking regarding Plan B is a delay tactic.

2.2 Support ANPRM Request for Comments

Approximately 12 comments expressed support for the ANPRM request for comments, welcoming the opportunity to comment on this important health policy issue.

2.3 Oppose ANPRM Request for Comments

Roughly 473 comments expressed opposition to the ANPRM request for comments.

3. Should FDA Initiate a Rulemaking Regarding its Interpretation of Section 503(b)? [ANPRM Question 1.A.]

3.1 Yes

One-hundred and ninety-nine comments supported initiation of a rulemaking.

3.2 No

Five-hundred and twenty-one comments (249 without all form letters included) opposed a rulemaking.

3.3 Federal Food, Drug, and Cosmetic Act (FD&C Act) and Amendments

Among the comments which presented supporting arguments for answers to the ANPRM question regarding a rulemaking, there was discussion concerning whether the FD&C Act requires rulemaking. Three comments pointed out that although the FD&C Act defines prescription drugs, it does not expressly define OTC drugs. [EMC355; EMC368; EMC373-2,3] Another comment stated that FDA's unwritten interpretation is consistent with the law. [EC15931-2] The comments expressed the need for FDA to begin a rulemaking process to clarify when a substance may be marketed both OTC and by prescription. Several other comments expressed support for FDA's action to allow simultaneous dual marketing after appropriate review. [EC16; EC32; EC98; EC146; EC364-2]

Similarly, other comments stated that the statute clearly defines prescription drugs, but a rulemaking is unnecessary. The comments show a disagreement, however, about whether the statute should be interpreted as supporting or opposing simultaneous dual marketing. Several comments, including those submitted by a professional society, advocacy groups, and a number of individuals, suggested that a drug could either require a prescription or be marketed OTC (if found to be safe), but not both. These comments suggested that FDA must ensure that an OTC drug is safe enough to be used in approved circumstances without the supervision of a physician, in which case the drug should be removed from regulation as a prescription drug. Conversely, a product determined to be unsafe should require a prescription. [C403-2; C414-1,2,4,5,11; EC21-

2; EC56-3; EC59-2; EC83; EC106; EC213; EC216-11; EC447; EC527-2; EC609-4; EC610-4,16; EC623-10; EC 668; EC680-11; EC1080-1,2; EC14598; EC15687-1,2,3]

A drug company's comment also noted that the definition of prescription drugs is clear and that no rulemaking is needed, but FDA has the authority to remove mandatory prescription requirements. The comment stated that simultaneous marketing might occur when there are multiple formulations with different safety profiles. [C407-1,2,3,4,6] Some advocacy groups' comments expressed the belief that the broad statutory language for a prescription drug in FD&C Act §503(b), which refers to "its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use," means that a drug product should not be marketed as OTC based solely on the age of a subpopulation. [C414-2] The American Society for Reproductive Medicine's comment, however, presented the argument that the broad language would still allow FDA to determine that a drug product has a "potentiality for harmful effect" if used by a woman under a certain age or that "collateral measures" necessary for its safe use by such women include the availability of a licensed practitioner to supervise its use. Age as a relevant factor in applying FD&C Act §503(b) is a reasonable interpretation of the statute. [C350-2,5]

Two comments pointed out that under FD&C Act §503(b) of the statute, a prescription drug product is limited by an approved application under FD&C Act §505, and that FDA could approve the same drug as OTC and prescription, depending on different circumstances or conditions of the product's proper use, such as limitations on the appropriate patient population. [EC281-2; C350-9] The Consumer Healthcare Products Association's comment expressed agreement that the statute allows FDA to draw fine distinctions among dosage forms, methods of administration, indications, or uses to regulate an ingredient differently in different settings. There are instances where an active ingredient is seen as an OTC drug in one dosage form and strength for a specified indication and also has uses or additional labeling under consultation with a health professional. [C412-1,2] The National Research Center for Women's comment pointed out that an age restriction could be a condition of use of the product because there would be a difference in comprehension levels (i.e., younger users need a physician's assistance). The comment presented the belief that the statute allows simultaneous dual marketing without the need for a rulemaking. [EC2314-2,3]

Another comment expressed support for the idea that intended uses of a drug in different subpopulations constitute different uses of the drug, and thus create different drugs, within the meaning of the statute. [C415-12]

3.4 Change to Interpretation Without Rulemaking Violates Administrative Procedure Act (APA)

Four comments presented views on how the APA relates to the rulemaking. The APA requires notice and comment prior to promulgation of a rule, and one advocacy group stated that FDA must initiate full rulemaking proceedings in order to institute simultaneous dual marketing of the same drug product. [C414-25,29] Another organization's comment expressed agreement that public input is needed on the important issue of simultaneous dual marketing, and stated that

FDA must address objections raised to age-based classification for prescription and OTC drug sales. [EC15690-1,9]

3.5 Supplemental New Drug Application (SNDA) and New Drug Application (NDA) Regulations

Three comments provided statements related to the SNDA and NDA regulations. One organization's comment presented the belief that the regulatory framework is clear and should lead to swift decisions on NDAs. The comment stated that FDA must consider whether clear and understandable labeling can be written when making decisions. [C350-1,6] Two comments noted that FDA must consider safety and effectiveness and the benefit-to-risk ratio when making decisions on NDAs. [C350-1,6 and C414-4] An advocacy group's comment pointed out that an application seeking an exemption from prescription status for a drug should be evaluated based on whether the drug is safe and effective for use in self-medication. A decision should not be based on political factors. [C61-4] Another organization's comment emphasized that FDA has the authority to approve an application or to change a drug's status without a rulemaking. [EMC446-4]

3.6 Court Opinion Legal Arguments

Three comments provided court case arguments either in support of or in opposition to a possible FDA rulemaking. One comment presented the argument that a general statement of policy, such as a statement concerning simultaneous dual marketing, which has a binding effect on the public requires FDA to use notice and comment procedures. See Pacific Gas and Electric v. FERC, 506 F.2d 33 (D.C. Cir. 1974). It was pointed out in the comment that interpretative rules that merely clarify or explain existing law do not require notice and comment [Malone v. BIA, 38 F3rd 433 (9th Cir. 1994)]. However, the comment presented the belief that simultaneous dual marketing presents a new and about-face interpretation of the FD&C Act. In this kind of situation, court cases support a notice and comment rulemaking. See NRDC v. SEC, 389 F. Supp. 689 (D.D.C. 1974); D&W Food v. Block, 786 F.2d 751 (6th Cir. 1986); NRTA v. USPS, 430 F. Supp. 141 (D.D.C. 1977), affirmed 593 F.2d 1360; Benton v. Kessler, 799 F. Supp. 281 (E.D.N.Y. 1992). [C414-26]

Another comment stated that under settled legal principles, FDA may "fill the gaps" in the statute through reasonable interpretation. See U.S. v. Mead Corp., 533 U.S. 218,234 (2001); Chevron, USA, Inc. v. Natural Resources Defense Council., 467 U.S. 837 (1984). [C350-5]

A third comment expressed opposition to a rulemaking that would allow the marketing of a drug product as OTC based solely on the age of a subpopulation and noted that courts have historically noted safety risks particular to oral contraceptive prescription drug products. See Turner v. Edwards, 1969-1974 FDLI Jud. Rec. 471,471 (D.D.C. 1970). [C414-2]

3.7 Other Legal Arguments

Several comments presented other legal arguments supporting or opposing a rulemaking. One comment contained a question about whether the information in the labeling for prescription

drugs, which is required under 21 CFR §201, can be simplified for OTC drug product labeling. Requirements for safe and effective use of contraceptives in 21 CFR §310 call for comprehensive labeling, which would suggest a need for physician interpretation and prescription-only sale. [C414-27,28]

Another comment suggested that if Congress requires interpretations to be justified, then a rulemaking would be appropriate. [EC505] Another comment expressed the belief that a rulemaking is unnecessary because FDA could simply warn of health risks for younger patients on the packaging of the drug. The comment noted that in the past, FDA has not required special sales practices to regulate who buys drugs that are not supposed to be given to children below a certain age. [EC23-2] A different comment also presented opposition to a rulemaking and presented the argument that FDA is attempting to make an artificial distinction by suggesting that the age of the consumer changes the nature of the product. [EC323]

3.8 Policy Arguments

Many comments presented policy arguments. Of these comments, 27 stated that a rulemaking would improve future FDA decisions. Most of these comments stated that a rule would provide clarity for decisions about future products. [EC12-1,2; EC15; EC27-2; EC54; EC85; EC107; EC399-14; EC495-2; EC535-2; EC626; EC1041-1,2; EC13851-2; EC16675-4,5; EMC355-2; EMC383] Some comments mentioned the importance of consistency and accountability and the need to reduce subjectivity, particularly given the expected increases in future applications. [EC27-1; EC165; EC281-1; EC495-2; EC921-2; EC13845-4; EC13851-2; EC16675-5; EMC397; EMC368-4,] A few comments pointed out that a rule would simplify the process and help FDA maximize its efficiency and effectiveness. [EC281-1; EC365; EC13845-1,7] Another comment said rules should advance with technology and society; this comment supported rules to allow multiple applications of the same molecule. [EC224-6]

Thirteen comments written in response to the ANPRM question mentioned that the current prescription and OTC system is not sufficient and that a third class of "behind-the-counter" or pharmacist-distributed drugs is needed. [e.g., C403; C489-2; EC33-2; EC38-4; EC98-6; EC109-2,5,9; EC155-7; EC162; EC408-1,8; EC14491-5; EC16675-3] Some of these comments stated that pharmacists would function as safeguards as more drugs are available OTC. [C489-2; EC98-6; EC109-9; EC14491-5; EC16675-3] Three comments pointed out that some states and other nations already have more than two classes of drugs. [EC109-9; EC155-7, C415] Another comment cited the skills, knowledge, and distribution mechanisms of pharmacists; the benefits for consumers; and the ability of pharmacists to refer patients to physicians when indicated as benefits to a "behind-the-counter" system. [EC408-1,8]

Twenty-six other comments presented miscellaneous arguments in support of initiating a rulemaking and made suggestions concerning the content of the rule. Some of the benefits of initiating a rulemaking include: improving current rules, allowing public input, and helping consumers understand how FDA makes decisions, and clarifying criteria for which a drug may be used and marketed both OTC and by prescription. [e.g., EC623; EC827-2; EMC355-2; EMC374-5; EC12-2; EC52-3; EC610-19] In addition, a rulemaking can encourage accessible and affordable drugs and take into account the availability of a drug in other countries. [EC516-

4; EMC373-4,9,10; EMC383-3,5] The rule can clarify how simultaneous dual marketing would work, address emergency contraception, and specify stipulations, such as the involvement of a medical professional. [EC297; EC399-2,12; EC811-2; EC940; EC14388-2] In addition, the rule can specify an individual's responsibility for making health decisions and can set standards for drug companies. [EC99-2; EMC397-1] If an active ingredient is safe and effective, but approval is held up by bureaucracy or ideology, then a rulemaking is needed to clarify FDA's policy. [EC6; EC527; EC895]

On the other hand, 25 comments stated that a rulemaking is unnecessary because FDA's interpretation of the statute is clear in its present form, although sometimes these comments were in disagreement about what that interpretation is. Some of these comments pointed out that FDA has permitted simultaneous dual marketing on a number of occasions, so ample precedents already exist. [C412-1,13; C415-9; EC81; EC98; EC 212; EC15931] Other comments presented the argument that FDA's distinction between prescription and OTC drugs is clear and it is apparent that a product should not be available both OTC and by prescription. [C307-3,4,6; EC213; EC399-4; EC610-2; EC671-1,8; EC839-1,3] One comment stated that it is not FDA's role to protect the public from physically harmless drugs or to monitor social use of drugs. [EC325] A few comments simply stated that FDA's current interpretation is straightforward and clear. [EC58-2; EC323-3; EC951-2]

Approximately 17 comments presented the argument that circumstances for OTC safety are case-specific, so the evaluations should be done on a case-by-case basis. A few of these comments suggested that these differences among OTC products mean that an FDA rulemaking would be inappropriate, because a rulemaking could not address all situations. [C403-1,2; EC212-2,3; EC569-9; EC16675-1] Other comments, on the other hand, expressed the belief that a rulemaking is needed to clearly distinguish between prescription and OTC drugs and to allow for exceptions for individual drugs with unique circumstances. [EC311; EMC374] Still other comments pointed out that case-by-case decisions are needed, but did not associate this observation with the question of whether a rulemaking is needed. [EC76-1,7; EC224-3]

Two comments strongly expressed the belief that a formal rulemaking is unnecessary but that written guidance on FDA's interpretation of FD&C Act §503(b) would be useful. In particular, the comments stated that amendments to FDA's 1999 "Draft Guidance for Industry: Applications covered by §505(b)(2)" are needed. [C403-1,3; C453-2,5]

Eight comments raised cost-benefit concerns regarding a rulemaking. Of these nine comments, seven stated that a rulemaking on FDA's interpretation would be a waste of money and have little or no benefit. [e.g., C307-2; C407-6; EC54-4,7; EC80-4; EC211-7; EC566-8]

Further policy arguments in opposition to a rulemaking were presented by 26 comments. For the most part, these arguments were critical of the idea of simultaneous marketing. They cited the confusion it causes, the need for re-evaluation of many drugs, and the public health risks of allowing OTC access to prescription drugs. [e.g., C71-6; EC43-2; EC56-2; EC80-7; EC157; EC319; EC569-5,6; EC671-2,8; EC680-2; EC710; EC839-2; EC882-2; EC1032; EC1080; EMC166] A comment pointed out that rulemakings have not been needed for previous examples of simultaneous marketing. [EC4] Other comments presented the argument that going

3.9 Examples of Previous FDA Actions Allowing Simultaneous Marketing of Prescription and OTC Products

Forty-six comments presented examples of previous FDA actions allowing simultaneous marketing. The majority of the examples these comments provided were of previous drug approvals, some of which (such as meclizine, nicotine products, ibuprofen, and H2 blockers) were already listed in the ANPRM. [e.g., C350-8; EC15-2; EC24; EC95-3; EC98; EC323-2; EC2107-2; EC11670; EC13845-2; EC15687-1; EC16427; EMC368] Other comments indicated there were many medications and drugs that are being simultaneously marketed, but did not give specific examples. [EC6; EC240; EC687-2; EC779; EC951-4; EC2314-3; EC14388-4; EC14491-3] While, other comments provided the following drugs as examples: Claritin, naproxen (Aleve), omeprazole (Prilosec), folic acid tablets, Prevacid, and hydrocortisone. [C307-5; C412-3; EC13-2; EC81; EC93; EC148; EC155-2; EC206; EC216-8; EC418; EC762; EC951-17] The Consumer Healthcare Products Association provided numerous examples of instances where a particular ingredient is seen as an OTC drug in one or more settings, but is a prescription drug or includes prescription labeling, professional labeling, or professional information in others. [C412-3,4,5,6,7]

Duramed Research, Inc. and Duramed Pharmaceuticals, Inc. (Duramed) cited FDA's Manual of Policies and Procedures of the Center for Drug Evaluation and Research as expressly contemplating that a prescription and an OTC version of a drug product may differ only in the population for which they are indicated. [C415-10,11]

The comment cited further support for simultaneous marketing provided by FDA policy with respect to veterinary drugs. With respect to the prescription legend, veterinary drugs are subject to provisions very similar to § 503(b)(4). Compare FDCA § 503(b)(4), 21 U.S.C. § 353(b)(4) with FDCA § 503(f)(4), 21 U.S.C. § 353(f)(4). The CVM Program Policy & Procedures Manual Guide 1240.2220 § 3.d (Mar. 9, 2000) states:

> In the past, the same products used in varying routes of administration, dosage forms, and in varying species of animals may have been labeled prescription in one instance and non-prescription for other uses. The primary question is whether adequate directions for use can be written to assure safe and effective use. If an average food animal producer can safely and effectively administer a product, but a companion animal owner, regardless of label directions, cannot administer it safely and effectively, then the prescription status of the product must be different relative to these intended uses. If directions can be written for use for a particular route of administration (intravenous, intraperitoneal, etc.) for one animal species but not for another, it is not inconsistent to grant OTC status for the one use and require the Rx legend for the other.

Duramed presented the argument that the passage plainly contemplates that identical versions of a veterinary drug may be labeled in one instance (for one population) by prescription and in another instance (for another population) OTC. The comment stated that no further policy development is needed. [C415-15]

Sanofi-aventis suggested that the Agency's October 1999 Draft Guidance for Industry regarding "Applications Covered by §505(b)(2)" could lead to a simultaneous marketing situation. An application under §505(b)(2) is one for which investigations of safety and effectiveness on which the applicant relies for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use . . ." [FD&C Act §505(b)(2), 21 U.S.C. §355(b)(2)] In its 1999 Draft Guidance, FDA advanced for the first time its unsupported interpretation §505(b)(2) as permitting reliance on proprietary data contained in another manufacturer's application. Sanofi-aventis also argued that FDA asserted in the Draft Guidance that a §505(b)(2) application could be used to obtain a switch in product indication from prescription only to OTC. [C453-3]

Sanofi-aventis presented the argument that, insofar as FDA's Draft Guidance suggested that a §505(b)(2) application is a suitable vehicle for obtaining approval of a switch from a prescription indication to an OTC indication for another applicant holder's product, it does not account for the potential for Durham-Humphrey misbranding issues. Under the Draft Guidance, the Agency could theoretically approve an OTC product in reliance on a pioneer's data for an approved prescription product. That prescription product would continue to be covered by the pioneer's NDA. The pioneer with an approved NDA for its product is entitled to and indeed must sell that product in conformity with the terms of its NDA, including selling it only as a prescription product. Through its Draft Guidance, the Agency opened the door to the same active ingredient being simultaneously marketed as both a prescription and an OTC drug product for the same condition of use, thereby creating an unworkable tension with §503(b) of the FD&C Act. [C453-3]

3.10 Examples of FDA Actions Disallowing Simultaneous Marketing

Approximately three comments presented examples of previous FDA actions disallowing simultaneous marketing. One of these comments stated that FDA has never permitted the same active ingredient to be marketed simultaneously as both a prescription and OTC product for identical conditions of use. [C453] Another comment presented 5% testosterone as an example of a prescription drug that could be marketed to elderly men who need hormone replacement therapy, but is currently not available OTC. [EC793-2]

3.11 Miscellaneous Arguments/Discussions

Two of comments expressed the belief that clinical trials and independent studies should form the basis of any OTC branding in order to ensure safety. [EC495-2; EC610-5] Another comment pointed out that the circumstances in which a product is used may cause the product's harmful effects. [EC52-9] One comment argued that FDA has the legal authority to consider moral and social issues when considering the approval of drugs for OTC sale, specifically Plan B. This legal authority is provided by FDA's jurisdiction over the safety and efficacy of drugs. The comment noted previous cases in which FDA considered social issues when determining a drug's distribution (e.g., phenacetin, hexachlorophene). [C414-41]

4. Is There Significant Confusion Regarding Interpretation of Section 503(b) of the Act?

4.1 Yes

One-hundred and eighty-one comments said there is significant confusion regarding FDA's interpretation of FD&C Act §503(b).

4.2 No

One-hundred and thirty-five comments stated there is not significant confusion regarding FDA's interpretation of FD&C Act §503(b).

4.3 Arguments Supporting Significant Confusion Regarding FDA's Interpretation

The American Pharmacists Association (APA) argued that confusion was demonstrated by the various reactions and differing opinions in response to FDA's decision to seek public comment on simultaneous marketing. APA's comment pointed out that, after the FDA's announcement, members of the private sector made conflicting pronouncements on whether the FDA has the authority to approve a product for both prescription and OTC sales; how FDA has handled similar approvals in the past; and what restrictions, if any, the Agency can place on such approvals. [EC16675-8] Another comment presented a similar argument and suggested that there must be confusion, since a drug company is requesting an action that was supposedly illegal. [EC27-3]

Several of the comments presented the argument that there is confusion because the FD&C Act does not explicitly define OTC drugs and the language used is vague and open to interpretation. [EC408-2; EC610-6; EMC397-2] Another comment pointed out that there is confusion in the terminology used for the ingredient (the raw drug) versus the medicine (the compound drug). The comment suggested clarification in terminology is needed. [EC1080-3] Two comments pointed out that the FD&C Act does not discuss or define age limits or enforcement, which also results in confusion. [EMC368-1; EMC397-2]

A few of the comments that suggested there is significant confusion, pointed out that FDA has acknowledged that its interpretation of FD&C Act §503(b) has not been explicitly set forth in any regulations that discuss the process by which FDA classifies drugs as OTC or prescription. Another comment cited confusion due to the lack of a documented "decision tree" for the process of FDA approval of a product for OTC sale. Without an official interpretation of the Act or implementation of regulations; manufacturers, health care professionals, state regulatory bodies, and even FDA officials, may not have a clear understanding of FDA's process for classifying, or in some cases, reclassifying drugs as prescription or OTC products. [EC365-3; EC495-4; EC15687-1; EC16675-7]

Other comments noted that FDA's interpretation was difficult to understand because it was written in legal jargon that is not easily understood by the general public or a well informed layman. [EC623-2; EC827-3]

Some of the comments stated that confusion about FDA's interpretation is a result of political and religious disagreement and pressures surrounding Plan B. The comments stated that the Agency has generated confusion by various actions, including departure from its precedents and its delayed decision on Plan B in response to political influence on both sides of the issue. One comment cited how an allergy medication was switched to OTC status without controversy, unlike the current situation. [EC96-3; EC135-2; EC171-3; EC195-2; EC206-3; EC325-2, EC364-3; EC516-3; EC2009-6]

4.4 Arguments Indicating That Little or No Confusion Exists

Several comments presented the argument that FDA's interpretation is clear and neither the private nor public sector is confused by it. Consumer Healthcare Products Association argued that there are adequate historical cases with similar drugs, so there should not be any confusion. The comment stated that there is a range of precedents for using both broad and narrow distinctions for marketing and labeling a range of ingredients in more than one way. GlaxoSmithKline argued that their FDA submission experience led them to conclude that there is no confusion and FDA's interpretation is very clear. Another comment said that this clarity is shared by the American consumer, who understands that some medications are reasonably safe for self-medication in lower doses, but require physician monitoring for higher doses and certain uses. One comment pointed out that this issue would have come up earlier if there was significant confusion. [C307-2; C412-8; EC16543-2]

Duramed's comment indicated that they found no history of confusion regarding FDA's interpretation of §503(b)(1i) of the FD&C Act as permitting simultaneous prescription and OTC marketing when some meaningful difference exists that makes the drug safe and effective for one patient population only under the supervision of a licensed practitioner, but safe and effective for another patient population without such supervision. Although FDA has repeatedly found conditions under which an active ingredient may be marketed simultaneously both by prescription and OTC, and has presumably on occasion refused to find that such conditions exist, Duramed stated that they were unable to locate any challenges to the interpretation of §503(b) that FDA utilizes to make such determinations. Its review of case law revealed no published opinion addressing purported confusion regarding FDA's interpretation. Similarly, its review of the academic literature, including a review of journals specific to issues relating to FDA and food and drug law, revealed that there has been no scholarly work identifying, or seeking to resolve, any confusion as to FDA's interpretation. [C415-16].

Other comments indicating that little or no confusion exists stated that FDA's interpretation is straightforward, simple, science-based, or is in keeping with the intent of the law. Similarly, other comments presented the argument that the interpretation is clear; however confusion is being claimed due to personal politics, those unfamiliar with the law, media attention, and/or proposals for age limitations. [EC213-2; EC297-2; EC311-2; EC323-3; EC626-2; EC1129-2; EC2009-7; EC15931-2; EMC368-1; EC96-3; EC325-2]

5. Would Rulemaking for Clarification Dispel Confusion? [ANPRM Question 1.C.]

5.1 Yes

One-hundred and four comments stated that a rulemaking would dispel confusion.

5.2 No

One-hundred and forty-one comments responded in the negative—that a rulemaking would not dispel confusion.

5.3 Arguments That Support Concept That a Rulemaking Would Provide Clarification

Approximately 22 comments provided arguments that support the concept that codifying FDA's interpretation and clarifying what actions are to be taken would make progress in alleviating confusion. These comments stated that a rulemaking's clear, concise language would provide clarification. In addition, improving the confusing language of §503(b) will allow easier interpretation of what constitutes a prescription drug or an OTC drug. In addition, a more formal, dated document would serve as a source of legitimate and educational information for other stakeholders. It would establish clear guidelines for drug vendors and manufacturers for when they introduce a new product and identify the decision makers. [e.g., EC15-4; EC109-4; EC827-4; EC13851-5; EC14388-3; EC16675-9,22; EMC355-2; EMC397-3; EC146-3]

5.4 Arguments That a Rulemaking Would Not Provide Clarification

Some of the comments argued that FDA's interpretation is clear, there is no confusion, and therefore, this question is moot. [C61-1; C307-2; C415-1; EC61; EC2314-8]

Other comments presented the argument that a rulemaking would just add to the confusion and make the issue of OTC status more complex. The comments stated that requiring subpopulation factors and other bureaucratic requirements would further cloud the issue when it is conveyed to the public. The rulemaking will not change the politics involved. [EC33-4; EC43-5; EC206-4; EC680; EC762; EC1129-3] Another comment presented the argument that although confusion would not be dispelled, the regulation would serve citizens in other ways. [EC147]

5.5 Arguments That a Rulemaking Would Not Provide Clarification

Several comments did not clearly support or oppose a rulemaking to provide clarification. Comments were supportive of a rulemaking if it met certain conditions. For example, comments favored the rulemaking if it favored the population rather than industry [EC1032-4], would not change the intent of the law [EC1041-4], or was based on legitimate concerns about the safety and efficacy of drugs [EC895-3].

6. If FDA Limited Sale of OTC Product to Sub-population, Would FDA be Able to Enforce Limitation as a Matter of Law? [ANPRM Question 2.A.]

6.1 Yes

Of the comments that were written in response to this question, 174 stated that FDA would be able to enforce the limitation.

6.2 No

One-hundred and ninety-three comments expressed the belief that FDA would not be able to enforce the limitation. However, many of the comments that stated that FDA would not be able to enforce the limitation expressed concern about enforcement as a practical matter (see section 7).

6.3 Legal/Policy Arguments that Support/Detail FDA's Authority to Enforce Limitation on Availability of OTC Products by Sub-population

One comment presented the assertion that a drug intended for one patient population is a different new drug from the identical drug for a different patient population, and that FDA has the legal authority to enforce a prescription limitation as to a sub-population. If FDA requires a prescription for sale of a drug to a sub-population, then selling to someone in that sub-population without a prescription would constitute a prohibited act under §301(k) of the statute. [C415-13,19] Similarly, another comment stated that FDA could restrict an unapproved new drug, which can include a drug intended for use by a consumer outside the approved sub-population. [C350-11] A drug company's comment stated that the statute gives FDA authority to determine the approvability of a drug product as described by a sponsor. [C307-8] Another drug company pointed out that FDA may determine that a drug can be used safely on a "prescription-only" basis or a manufacturer may confine distribution to prescription status, so simultaneous or dual-marketing can occur. In addition, FDA is authorized to ensure that OTC labeling permits a drug product to be used safely. [C407-5,7] Another comment stated that FDA's Office of General Counsel has already determined that age restrictions for an OTC product are legal, and there is no indication that counsel was concerned about enforceability. [EC2314-9]

One comment stated that no statutory provision prevents FDA from imposing an age limitation on the prescription drug status of a new drug. [C350-5] Another comment stated that the FD&C Act would not prevent FDA from instituting this policy. [EC58-4] A third comment expressed agreement that there was no reason why a single molecule cannot be sold in two different formats. [EC224]

FDA has approved simultaneous dual marketing where some "meaningful difference" exists that makes the prescription product safe only under a practitioner's supervision. Several comments presented the argument that age limitations are in line with other "meaningful differences." Age is similar to other differences in condition of use or "indication." [C350-8,9; C415-18; EC2314-2; EC14388-4; EC14491-3,4]

Some comments mentioned other agencies and products that have limits on sub-populations. Age restrictions can be enforced as a matter of law and are practical as well. [EC107-3; EC176-5; EC495-7; EC11670-5; EMC374-3] Two comments warned that FDA must ensure that the sub-population is not being discriminated against and that the limitation was in place for demonstrable scientific and safety reasons. [EC311-4; EC364-5] One comment noted that FDA uses label comprehension, self-selection, and actual use studies when considering switches from prescription to OTC use. [C412-10] Another comment presented the belief that although FDA should be able to legally enforce the limitation, the agency might be swamped with enforcement issues in the future. [EC281-5]

6.4 Examples/Precedents That Support/Detail FDA's Authority to Enforce Limitation by Sub-Population

Several comments mentioned the example of nicotine replacement therapy. In 1996, FDA approved the OTC sale of Nicorette, a smoking-cessation product, for consumers 18 years of age or older. A pre-approval requirement was that the age limitation was understood at both a label and a practical level. [C307-7; C350-2,10; EC7-2; EC2314-9; EC11670-2,5; EC16675-11,12]

6.5 Legal/Policy Arguments That FDA Does Not Have Authority to Enforce the Limitation

Many comments [approximately 344 (94 without all form letters included)] presented the argument that FDA's authority is limited to drug safety, effectiveness, and labeling. Some of these comments presented the argument that the Agency cannot control the behavior of consumers or the practice of pharmacies, and it does not have the authority to draw distinctions between sub-populations based on age. [C407-8; C412-9; C414-11; EC32-3; EC49-2; EC146-4,6; EC323-2; EC626-5; EC921; EC2107-10; EC15687-3; EC15690-2,3] One comment noted that parental notification and consent for the medical treatment of minors are areas of state regulation. [EC15690-4] One comment presented the belief that the statute's broad definition of "prescription drug" means that an OTC exception should not be carved out for a currently approved prescription product. In addition, the comment stated that there was no legal support for considering a difference in a sub-population related to age to be a "meaningful difference," which would support dual marketing. FDA lacks the authority to enforce the age limitation or to create a "behind-the-counter" class of drugs. [C414-3,12,13,21] Another comment expressed agreement that simultaneous dual marketing by sub-population is not supported. [EC14261-2,3]

Regarding court cases, a comment cited APhA v. Weinberger, 377 F. Supp 824 (D.D.C. 1974), which held that FDA lacked statutory authority to impose certain post-approval controls on methadone. [C414-14] Another comment suggested that restrictions on OTC products would raise the question of right-to-privacy, as determined in Griswold v. Connecticut. [EC1041-5] Other comments presented the belief that the question has been addressed in court cases about parental notification. [EC211-4; EC677-3] One comment alluded to a case in Maryland related to pharmacists' refusal to dispense emergency contraception due to religious beliefs. [EC839-9]

Several comments contained opposition to the idea that younger consumers would not have OTC access to a product if that product has been found to be safe. The comments suggested that this would be discriminatory. [EC9; EC16-3; EC38-2; EC43-11; EC81-4; EC93-4; EC213-3; EC505-2; EC762-7; EC921-5; EC11670-7; EC15931-3] One of these comments favored risk warnings, but not limited access. [EC213-3] Other comments expressed the belief, however, that parents of minors should be included on major medical decisions, and parental consent should be obtained before sales to minors. [C71-7; EC535-6; EC2107-11] Some comments predicted confusion, controversy, and litigation if FDA pursues this policy. [EC6-13; EC15-6; EC34-4; EC80-4; EC82; EC106-4; EC566-5,7; EC569-7; EC609-1; EC680-6; EC716-5] One of these comments contained the question of why aspirin, which is not safe for young people, is still marketed OTC to all age groups. [EC6-13] Other comments observed that enforcement would fall on the sellers of the product, not on FDA. [EC325-4; EC609-5]

6.6 Authority of Other Entities to Enforce the Limitation

Approximately 36 comments mentioned the authority of State agencies to enforce point-of-sale requirements. One comment noted that some states offer emergency contraception behind the counter but other states are unable or unwilling to expend the resources needed to enforce the restrictions. [C414-16,17,18] Additionally, the comment stated that attempts to restrict consumer access to nonprescription controlled substances have failed. In addition, pharmacist-only distribution has not succeeded because pharmacists did not want to assume liability risks and take on additional burdens. Another comment raised additional objections to FDA's suggestion for an age-based classification. The comment stated that FDA would be intruding into an area of traditional state regulation. States, however, do not have regulatory schemes to deal with illegal distribution of OTC drugs to minors. Many states require parental notification for major medical decisions, but making a drug available OTC would render parental consent impossible. [EC15690-3,4,5,7] A few comments mentioned that in some states the sale of OTC cold medicines is restricted to those over 18 and requires showing a photo ID. [EC24-4; EC951-13; EC1086-4] Other comments stated that state and federal bodies have powers to make distinctions between ages and to enforce the requirements. [EC155-6; EC216-5; EC951-10] One comment noted that state law should be able to require products to be marketed only by licensed pharmacists, who could determine if the requirements for OTC sale were met. [EC297-4]

Approximately 454 (204 without all form letters included) comments expressed the belief that enforcement of an age restriction could easily be handled in the same way as alcohol and tobacco enforcement. [e.g., EC6-3,5,7; EC7-2,4; EC24-2,4; EC32-5; EC47; EC61-6,7; EC96-5; EC98-7; EC146-8; EC160-3,4; EC165-2; EC176-5; EC206-6,11; EC213-4; EC216-6; EC217-2; EC224-2,7; EC240-5; EC311-5; EC323-5; EC325-3,6; EC365-5; EC418-8; EC516-6; EC535-5,7; EC623-4; EC626-4; EC779-2; EC860-6; EC951-9; EC1565-2; EC2107-4; EC13851-7; EC14388-6; EC14491-4; EMC397-4] Several comments, however, presented possible difficulties with such enforcement. [EC4-4; EC38-3; EC56-6; EC399-8; EC610-8; EC668-5; EC677-5; EC678-6; EC813-3; EC1080-5; EMC166-2]

6.7 Miscellaneous Arguments/Discussions

Some comments expressed uncertainty about whether limitations to a sub-population could be enforced, but a few comments stated that FDA should proceed regardless. [EC4-3; EC12-3; EC95-6; EC147-5; EC2107-5] One comment presented the belief that the answer depends on whether science dictates an age cutoff. [EC11670-4] Another comment emphasized the need for having a means to verify the end-user of the product. [EC73-4] One comment stated that there should be a limitation for drugs that are to be taken intermittently [EC399-5], and another comment stated that there should be a limitation only if the product is harmful after a certain number of doses. [EC99-5] A comment stated that allowing OTC marketing would create a problem with healthcare prescription plans. [EC165-5] One comment presented the belief that the only sub-populations that FDA can regulate differently are minors versus adults. [EC522-4]

7. Would FDA be Able to Enforce Limitation to Sub-population as a Practical Matter? [ANPRM Question 2.B.]

7.1 Yes

One-hundred and forty-nine comments thought that FDA would be able to enforce a sub-population limitation as a practical matter.

7.2 No

One-hundred and ninety-two comments suggested that the FDA would not be able to practically enforce the limitation.

7.3 Actions FDA Could Take in Order to Enforce Limitation of an OTC Product to a Sub-population

7.3.1 Regulate Product Sponsor

Several industry comments and the American Pharmacists Association (APA) comment argued that FDA can enforce a sales limitation through regulation of the product sponsor. Certain restrictions and limitations may be implemented as a condition of approval. If the Agency, in conjunction with the product sponsor, determines that a sales limitation is appropriate, the FDA can require the sales restriction through the approved labeling as part of the conditions of approval. This process would mirror the conditions of approval for Nicorette although the particular sales restriction (i.e., age, sex, etc.) could vary. [EC16675-14; C307-7; C415; C350]

A comment said that §503(b) states that a prescription drug is limited by approved application under §505. The comment presented the argument that “prescription drug” status is defined by the limitations that must be spelled out in the approval of a drug application. The

statute does not state that the FDA is limited in its approval and must define an approved drug as only OTC or prescription. Therefore the statute could allow the FDA via its official approval to designate the same drug as OTC and prescription dependent on different circumstances, in this proposal's case, age. [EC281-2]

Ultimately the product sponsor and retailer, not the FDA, would be responsible for ensuring that the product is supplied according to its approved labeling. As with any other OTC product, the FDA would not be responsible for policing any off-label use of the product. If the sponsor's efforts proved unsuccessful, a practical, regulatory consequence is withdrawal of NDA approval. [EC16675-14; C307-7; C415; C350; EC146-5] In its application, the sponsor would have to demonstrate that the age limitation was understood at both a label and practical level and prepare clear instructions and warnings.

Other comments suggested that the Agency could use its authority under Subpart H to require a risk management program if the Agency has concluded that the drug may only be safely used in a particular subpopulation as a prescription product. APA said that Subpart H of the Act gives the Agency the authority to approve a product with restrictions to assure safe use "if the FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted" (21 CFR 314.520). The restrictions can include distribution restricted to certain facilities or physicians with special training or experience; distribution conditioned on the performance of specified medical procedures; or limitations imposed that are commensurate with the specific safety concerns presented. [EC6675-18]

Several comments suggested that a risk management program for a dual-status drug could include the following limitations:

- Educational programs for retailers, pharmacists, consumers, and physicians that clearly set forth the prescription age restriction; [C415-28; EC16675-11,14; EC779-3]

- Readily accessible patient information regarding use of the drug (e.g., toll-free phone number on labeling, supplementary patient leaflet); [C350-13; C415-28]

- Training to encourage age verification, including training to ensure proper identification and discretion; [C307-7]

- Marketing plan that limits sales to clinics, retailers with licensed pharmacies, or other dispensing environment; [C415-28; EC162-2; EC224-2; EC870-4; EC16675-23]

- Marketing plan that excludes convenience stores or vending machines for sales; [C350-13; EC16675-11; C307-7]

- Post-market surveillance/monitoring programs to restrict off label use by those that do not meet the age restriction for OTC use, including a program of retailer re-training to correct deficiencies and help ensure ongoing compliance; [C307-7; C415-28; C350-12]

- Avoidance of direct-to-consumer advertising (see March 16, 2005 Letter from Robert J. Meyer, CDER, FDA to Amylin Pharmaceuticals regarding approval of Symlin (pramlintide acetate) and PhRMA's July 2005 *Guiding Principles: Direct to Consumer Advertisements About Prescription Medicines*); [C350-12]

- Incentives to retailers to shelve age-restricted drugs close to the pharmacy or with other OTC drugs; [C350-13]

- Limitations on "trial size" or "sample" packs; [C350-13]

- Use of child- resistant packaging. [C350-13]

7.3.2 Other FDA Enforcement Practices that it has the Legal Authority to Put in Place

Duramed's comment suggested that FDA employ many enforcement mechanisms to curb prescription abuse and referred to Robert J. Meyer's September 13, 2005, testimony before the Committee on Government Reform. Duramed argued that FDA could use these mechanisms to enforce a prescription requirement to a sub-population. [C415-21]

Duramed's comment and another comment noted that FDA has the inherent authority to publicize the importance of strict adherence to prescription requirements, and could undertake a public education campaign to ensure that women under the age of 16 are aware of their need to obtain a prescription to buy Plan B. (See also FD&C Act § 705, 21 U.S.C. § 375.) For example, as Dr. Meyers testified, FDA recently partnered in launching a "prescription drug abuse prevention education effort, with the primary goal of preventing and reducing the abuse of prescription drugs . . . by teens and young adults." The comments suggested that FDA could launch a similar educational campaign. [C415-28; C4125-25]

Finally, Duramed's comment suggested that FDA can monitor its enforcement success by making annual reports to the Department of Health and Human Services concerning the methods and effectiveness of enforcement efforts. For one example, the Substance Abuse and Mental Health Services Administration (SAMHSA), division of HHS, conducts an annual National Survey of Drug Use and Health of a random sample of U.S. households. This survey seeks to determine the prevalence of non-medical use of prescription drugs. The comment stated that FDA should work with SAMHSA to randomly sample, as part of its annual survey, the number of individuals who violate the age restrictions, report its findings, and thereby monitor the effectiveness of its enforcement efforts over time.

7.4 Other Point-of-sale Enforcement Suggestions

Most of the comments written in response to this question identified down-stream enforcement actions, but did not address whether FDA has the authority to implement these actions. These comments are summarized here.

7.4.1 Implement "Behind-the-counter" System (Pharmacist Distributed)

Ninety-two comments suggested that enforcement could be accomplished by requiring pharmacies to keep a dual-status drug behind the pharmacy counter and have it dispensed only by pharmacists or some other type of learned intermediary. [e.g., C443-1; EC33; EC109-6; EC146-7; EC408-8; EC489-2; EC12379-3; EC14491-5; EC16675] If FDA adopted a third "behind the counter" or "counseling" class of drugs, registered pharmacists who distribute the drug to a member outside of the subpopulation without physician approval would violate his/her duties as a licensed professional and be subject to discipline. [C443-1; EC33; EC155-7]

Several comments pointed out that many pharmacies have moved some medicines behind the counter [e.g., pseudoephedrine (Sudafed)] to prevent theft, and suggested that dual-status drugs could be treated the same way. [EC81-5; EC201-3; EC14491-5]

One comment stated that FDA allows the involvement of licensed pharmacists to determine if the requirements, if any, for OTC sale were met with Category 4 and 5 controlled drugs, where allowed by individual state law. [EC297-4] Another comment said that the State of California has a pharmacist distribution system for emergency contraception and it works well if there is enough counseling space in the pharmacies. [EC155-7] Legislation was proposed in New York State (A. 116 Paulin/S.3661 Spano) to allow New York State pharmacists and registered nurses to dispense emergency contraception without a prescription, but they would have to follow written procedures and distribute information. [C489-2] Duramed's comment cited eight states that permit pharmacist distribution of Plan B: Massachusetts, Alaska, California, Hawaii, Maine, New Hampshire, New Mexico, and Washington. [C415]

However, a few comments expressed concern about the behind-the-(pharmacy) counter approach because some pharmacists refuse to distribute certain medications due to religious objections. [EC5-5]

Several comments suggested that the person purchasing the drug OTC be required to sign a log or certification acknowledging that they meet the age requirements and that it is illegal to pass the drug to someone else. [EC24-4; EC66-5; EC155-7; EC2107-7; EC14491-5] Other comments suggested the pharmacist prepare an electronic pharmacy record of the transaction (similar to recording an oral prescription from a physician onto paper) and store it with other pharmacy records, the difference being that there would be no prescription required for adults. This information could assist in tracking the number of drugs a person takes. [EC98-4; EC307-3] Another comment contained the suggestion that enforcement might be possible if the OTC product is transacted in the manner that some exempt narcotics were handled in the periods prior to the 1980s, when simple ledgers were kept for limited portions of the sale of exempts for a narrow window of time. [EC58-5]

7.4.2 Involve other Authorities (e.g., States, State Boards of Pharmacies)

The American Society for Reproductive Medicine and the National Association of Boards of Pharmacy suggested that FDA and the drug manufacturer could cooperate with state pharmacy boards and local pharmacies to ensure enforcement of the age limitation at the point of

sale. FDA has entered into memoranda of understanding (MOUs) with state regulatory agencies to supplement investigative abilities. See FDA's *Investigations Operations Manual*, Chapter 3, Federal-State Cooperation. [C350-14; C443-1] If pharmacists are responsible for complying with sales restrictions, then state boards of pharmacies and others with authority to deal with issues of professional responsibility can issue sanctions and/or notify FDA of violations. [EC2314-10]

Duramed argued that FD&C Act §909, 21 U.S.C. §399, authorizes FDA to make grants to states for the purpose of conducting examinations and investigations of potential violations. In addition, FDA can allocate grants to local governments to aid them in their enforcement efforts. Duramed also noted that state drug inspectors, in connection with local law enforcement, are also involved in enforcing prescription requirements. President Bush's 2005 National Drug Control Strategy recognizes that state prescription drug monitoring programs are highly effective in curbing prescription drug abuse. The commenter also suggested undertaking joint investigative efforts with the Drug Enforcement Administration to enforce the limitation to a subpopulation as it has done in other matters. [C415-21]

One commenter pointed out that through the support of families, communities, and public schools access to OTC drugs can be limited. For example, children's access to aspirin is minimal because of these support mechanisms. [EC623-12]

7.4.3 Monitor Compliance and Enforcement/Conduct Random Inspections

Duramed's comment presents the argument that FDA is authorized by FD&C Act § 704, 21 U.S.C. § 374, to conduct inspections of establishments that are subject to the requirements of the FD&C Act, which include pharmacies selling drug products. Anyone who refuses to permit such an inspection is subject to criminal penalties under FD&C Act § 301(f), 21 U.S.C. § 331(f), and § 303(a), 21 U.S.C. § 333(a). Under FD&C Act § 702, 21 U.S.C. § 372, FDA may conduct examinations and investigations, through officers and employees of the Department of Health and Human Services or through any health, food, or drug officer or employee of a state and local government, duly commissioned by the Secretary of Health and Human Services as an officer of the Department. Through use of its own, or state investigators, FDA can conduct random, unannounced inspections of pharmacies or stores, to ensure that they are enforcing the prescription limitation of Plan B for women younger than age 15.

Another comment said that state departments of health will inspect the enforcement process as it does in other inspections. [EC216-5]

7.4.4 Require Identification for Age

Over 150 comments presented the argument that the stores can enforce the limitation to an age-based sub-population by requiring identification—such as a driver's license or government identification card—that proves that the customer meets the age restriction, as is done for nicotine products, tobacco, and alcohol. [e.g., C415-5; EC10 -4; EC1086-5; EC1129-5; EC132-5; EC1565-3; EC165-3; EC216-6] Several of these comments suggested that cash

registers be programmed to automatically require an age to be entered before the sale can be completed. [e.g., EC6-6,9]

However, other comments stated that FDA should not impose requirements that would make retailers confirm age by checking identification or requiring sworn statements verifying age. Some suggested not everyone of age has identification with their age on it. [EC1044-4, EC839-8] Other comments cited privacy concerns, as the pharmacist would learn the identity of the requestor. These comments posed the question of whether there are Health Insurance Portability and Accountability Act (HIPAA) restrictions on pharmacy personnel having access to personal patient information. [EC81-5] Other comments presented concerns about how easy it is to gain access to forged identification. [EC193-2]

7.4.5 Pursue Criminal Actions Against Violators

Twenty-two comments suggested that FDA can enforce requirements by pursuing criminal actions, fines, penalties, or suspension of pharmacy licenses against violators. [e.g., EC47-2; EC860-2; EC2107-5; EC13851-10; EMC373-5] Duramed's comment presented the argument that FDA can use a number of means to pursue such enforcement. Cases can be developed, through FDA's network of field offices, reviewed by FDA headquarters, and then submitted to the Office of Consumer Litigation (OCL) in the Department of Justice. OCL then determines whether to pursue criminal or civil remedies, if any. FDA can also refer cases through the Office-of Criminal Investigations (OCI). OCI can refer cases directly to United States Attorneys' Offices. [C415-23]

7.4.6 Other Actions

Several comments said that the OTC version of the dual status drug could be kept behind the sales or register counter like cigarettes. [EC194-4; EC399-8; EC779-2]

In addition, a few comments suggested conducting periodic undercover attempts to purchase the product and see if product is sold correctly, as is done with tobacco and alcohol. [EC7-4; EC691-5; EC951]

Another comment suggested that the age-limit be set at 18 so that minors' access is restricted to the drug. [EC2107-6]

7.5 FDA will be Unable or it will be Difficult to Enforce as a Practical Matter

7.5.1 FDA Does Not Have Authority to Enforce Limitation, Therefore it Cannot Enforce as a Practical Matter

Concerned Women for America's comment stated that because FDA does not have the statutory authority to enforce an age restriction, enforcement activities would fall to the states, local governments, or pharmacies. FDA has no regulations to instruct third parties in appropriate enforcement activities, nor is there any mechanism for FDA to ensure that enforcement is carried

out. [C414-15] Similarly, other comments stated that there is no mechanism for enforcing an age-related limitation. [EC569-3]

Another comment presented the argument that restricting a product's availability would probably require new case law or re-visitation of existing precedents to determine the legality of restricting such products, as well as the FDA's authority to do so. Given the current erosion of support for broad interpretation of the Commerce Clause, it appears unlikely that the FDA would be able to do so in the current legal environment. [EC1041-6]

7.5.2 Infrastructure for FDA Enforcement (e.g., Resources, Personnel, Training, Monitoring, Third-party Regulations) Not in Place

Eighteen comments, including comments from the Concerned Women for America and the Association of American Physicians and Surgeons, presented the argument that FDA does not have the economic or personnel resources to effectively enforce an age restriction. [e.g., C414-15; EC15690-5]

Concerned Women for American's comment presented the argument that the healthcare system does not have the infrastructure to support a behind-the-counter class of drugs. Pharmacists are expected to provide counseling, report adverse drug events, among other things, but often do not (see *Nonprescription Drugs: Value of a Pharmacist-Controlled Class Has Yet to Be Determined*, Report GAO/PEMD-95-12. Washington, DC.: U.S. General Accounting Office, Program Evaluation and Methodology Division, August 1995 at 57-59,65, 79). Pharmacies would have to grant pharmacists time away from dispensing drugs to meet with patients; the burden of this cost may increase drug costs. [C414-19] Other comments stated that pharmacists should not be required to "police" who is buying what OTC drug and how old they are; these professionals are occupied with other duties to provide the correct prescription medication. [EC195-4; EC210-1]

7.5.3 Actual Compliance will be Difficult/Impossible/Burdensome to Achieve

Many comments [approximately 415 (165 without all form letters included)] stated that compliance with an age limitation will be difficult or impossible to achieve or actual compliance will be overly burdensome to society.

Many comments presented the argument that older friends, relatives, or other adults can purchase the drug and give (or sell) it to a person that does not meet the age restriction. [C71-2; C83-2; EC16770-9; EC677-6] While other comments cited problems with alcohol and cigarette sales to underage customers as evidence that age-based restrictions of drugs would similarly be difficult to enforce. [EC15-5; EC21-3; EC38-3; EC110-3; EC11670-8; EC15391-4]

A few comments presented concern that consumers are likely to violate age restrictions for a dual-status drug because they are ignorant of the risks involved, do not read instructions, and are unaware of side effects. [EC610-4] Another comment stated that teenagers are particularly vulnerable to peer pressure and misinformation. [EC15690-6]

Two comments presented the argument that the costs associated with enforcement would outweigh the benefits. The burden ultimately would be placed on society and tax payers rather than the drug company. [EC65-5; EC80-5] Another comment revealed concern that efforts to enforce age-restrictions would also restrict access by the "legal" population. [EC1009-1]

7.6 Miscellaneous Arguments/Discussions

One comment asked how simultaneous marketing would affect insurance reimbursements. The comment suggested that selling the OTC version at a higher price than the prescription version might discourage misuse of the product. [EC13026-6]

Another comment suggested that enforcement is not needed if the drug is truly safe for OTC marketing. [EC364-6]

Finally, one comment felt the right of pharmacists to refuse to dispense certain drugs would be taken away if such medications were moved to OTC. [EC839-9]

8. Assuming Legal to Market Both, may the Prescription and OTC Products be Legally Sold in the Same Package? [ANPRM Question 3.A.]

8.1 Yes

One-hundred and eighty-three comments stated that it would be legal to sell the prescription and OTC product in the same package.

8.2 No

One-hundred and fifty-two of the comments stated that it would not be legal to sell the prescription and OTC product in the same package.

8.3 Legal Arguments Supporting One Package Label for Prescription and OTC Sales

Some of the comments that addressed this question presented the argument that a single package label could be created for the prescription and OTC product that fulfills both the prescription and OTC statutory requirements. [EC13-2; EC14491-2] GlaxoSmithKline's comment presented a labeling approach that addresses and satisfies both the prescription and OTC statutory labeling requirements [i.e., FD&C Act § 503(b)(2), 21U.S.C. § 353(b)(2) and FD&C Act § 353(b)(4)(A)] by accompanying or adhering prescription labeling to the OTC pack at point of dispensing and including specific prescription healthcare professional labeling. GlaxoSmithKline's comment explained that labeling approaches to address both prescription and OTC requirements, like this one, could be approved under prescription or OTC NDAs. [C307-9]

Duramed's comment presented another labeling approach to fulfill both the prescription and OTC labeling requirements. The comment contained the suggestion that the single package

label include the following: (1) adequate information and directions to ensure safe, effective, and appropriate OTC use; (2) a statement of any "prescription only" restrictions in the legend (e.g., prescription only for women under age 17); and (3) appropriate space on the label for the pharmacist to affix the traditional prescription label when the product is obtained via prescription. Duramed's comment stated that in July 2004 they submitted proposed labeling and outer packaging to the Reproductive Health and OTC Divisions of FDA's CDER; which addressed the labeling issues associated with the specific case of Plan B. [C415-29]

Some of the comments emphasized the need for the single package label for the prescription and OTC product to include a statement explaining any age restrictions or age specific issues and any relevant warnings. [EC77-6; EC81-6; EC98-5; EC281-7; EC323-7; EC779-5; EC860-3; EC903-4; EC14491-2] One comment noted that many current OTC products contain similar statements, such as "if under age 2, consult a doctor." [EC903-6] Another comment presented the suggestion that if FDA creates a single package label for the sale of prescription and OTC products, FDA should carefully select the wording for the package. For example, FDA should use the phrase side effects, not adverse events and specific situations in which drug should not be used, not contraindications for the package labeling. [EC212-6]

One comment stated it would be a violation of FD&C Act § 502(a) if there were different labels for a drug that works in the exact same way for every user, but is available via prescription and OTC sales. Different packaging would suggest that the product is different in some way, which constitutes misbranding under FD&C Act § 502(a). [EC2314-11]

Duramed's comment disputed arguments that different package labels are necessary because there is a need for separate National Drug Code (NDC) numbers for prescription and OTC sales. The comment presented the argument that a single NDC number will fulfill all of the purposes of the NDC system, so one package label is legal. [C415-35] The National Research Center for Women's comment presented the argument that creating a single package label to fulfill prescription and OTC labeling requirements is possible and provided the current Plan B packaging as an example. The comment presented the explanation that the current Plan B packaging consists of a lengthy insert and a label that has the intended uses, directions, and warnings written in a clear and consumer friendly way. [EC2314-13]

8.4 Policy Arguments Supporting One Package Label for Prescription and OTC Sales

Many of the 28 comments that provided policy arguments in support of a single package label, presented the argument that there should be one package label for the prescription and OTC product, since having two different packages for the exact same product is unnecessary, confusing, and misleading. The comments emphasized that restrictions on the distribution of the prescription product does not make the prescription product any different than the OTC product. However, having different package labels for the prescription and OTC product gives the impression that there is a meaningful difference between the products and may even lead consumers to believe that the OTC drug is safer than the prescription drug. Therefore, this unnecessary packaging distinction leads to consumer confusion and stress. [C71-5; EC126-6;

EC141-6; EC167-6; EC201-4; EC240-6; EC281-7; EC323-7; EC951-18; EC1086-6; EC14261-4; EC1565-4; EC16675-19; EMC355-5]

Other comments stated that having one package label for marketing the prescription and OTC product would reduce the cost and burden for multiple parties involved. Two comments noted that dispensing pharmacies' inventory would be simplified if one package label is used, thus reducing their burden. Conversely, if different packages are used a pharmacy may have inventory issues if they run out of one type of product (prescription or OTC), since they will not be able to sell the other type of product (prescription or OTC) in its place even though it is the same drug. [EC91-4; EC281-7] Another two comments stated that one package label would ease the burden on the manufacturer of the product. [EC11670-11; EC12379-4] The majority of comments discussed how a single package label would reduce the cost and burden for consumers. Several comments stated that the financial cost and burden to the consumer would be reduced with a single package label since the cost and burden for manufactures to create a single package label is less than creating different labels. These comments emphasized the necessity of having a product that is sold via prescription and OTC cost exactly the same amount, since the product and the packaging are the same and the only difference is the method of distribution. [EC4-5; EC96-7; EC522-6; EC762-11; EC11670-12; EMC355-5]

In addition, some comments noted that FDA should have a single label for the product sold by prescription or OTC, since having different labels will not aid in enforcement of distribution. These comments emphasized that the main issue is not the packaging, but controlling the distribution of the product. [EC7-5; EC24-5; EC53-7; EC76-11; EC281-7; EC680-9; EC951-16]

Another comment stated that by making the product available via prescription and OTC, the subpopulation required to obtain the prescription would incur higher costs, since they would have to pay for a physician's visit. [EC1032-6]

8.5 Legal Arguments Opposing One Package for Prescription and OTC Sales

Pfizer, Inc.'s comment and other comments cited the legal differences between the statutory requirements for the distinct labeling of prescription and OTC products. Any drug required by FDA or by manufacturer direction to be marketed by prescription must have certain items on its label. For example, drugs required by FDA to be marketed by prescription must have "prescription only" on the label. In addition, all prescription drugs must contain adequate information for medical practitioners to prescribe the drug safely and for the purposes intended, but do not have to have adequate directions for consumer use; since prescription drugs are exempt from Section 502. Conversely, OTC drugs must not have the "prescription only" mark on the label and must have adequate instructions for consumer use [21 U.S.C. § 353(b)(2) and § 353(b)(4)(A)]. In addition, Kirkpatrick & Lockhart Nicholson Graham's comment on behalf of Concerned Women for America, et al. stated that, historically, courts have noted that if birth control pills were widely disseminated outside the prescription drug product channels, different labeling standards may apply (e.g., Turner v. Edwards, 1969-1974 FDLI Jud. Rec. 493, 494 (D.D.C. 1971)). Another example Kirkpatrick & Lockhard Nicholson Graham cited as demonstrating the regulatory distinction between prescription and OTC labeling is the regulatory

requirements for the interstate label, which requires prescription products to bear a caution statement, but prohibits OTC products from bearing this same statement. Additionally, the regulatory provisions governing oral contraceptives require package inserts that are extensive in reach and exhaustive in content (921 C.F.R. § 310.501). [C414-5] Many comments stated that these and other distinct regulatory requirements for prescription and OTC sales cannot be met by a single package label for both prescription and OTC products. [C407-2; C414-5,8,9,10,27; EC117-4; EC1080-7; EC15687-5].

Many of the comments that addressed this question stated that FDA should not use one package label for prescription and OTC sales, since different package labels for prescription and OTC sales would make enforcement of the distribution regulations and tracking of violations easier. [EC54-6; EC91-4; EC97-8; EC132-6,7; EC171-6,7; EC535-10; EC610-12; EC677-7; EC716-2; EC788-6; EC896-3] Two comments presented the explanation that having different packaging and thus different NDC numbers for prescription and OTC products would allow pharmacies to program their automated point of sale systems to help with tracking and enforcement. [EC12-6; EC827-8] Additionally, a comment stated that to further aid in enforcement of distribution regulations, the pills for prescription and OTC sales should look different in addition to being distributed in different packaging. [EC90-5] Other comments said that the products should be in different packages to facilitate enforcement and limit customer and vendor confusion. [EC132-7; EC171-6,7]

The Academy of Managed Care Pharmacy's comment stated that separate packaging is also necessary because the products must have distinct National Drug Code (NDC) numbers for managed care organizations, other third-party payers, and drug information database providers to differentiate the prescription and OTC products for claims adjudication. [EC15687-6] A comment expressed agreement that it may be necessary to use different packaging for prescription and OTC sales, since using the same package could affect insurance coverage and reimbursement. [EC85-5]

Two comments discussed how using the same package labeling for prescription and OTC sale will affect issues of liability. One comment raised the question of who would be liable if an OTC product was sold to someone in a restricted subpopulation who then sustained an injury. [EC111-5] Another comment contained the suggestion that using the same packaging may make the pharmaceutical companies vulnerable to lawsuits. [EC813-4]

8.6 Policy Arguments Opposing One Package for Prescription and OTC Sales

Approximately 26 comments stated that having one package label for the same product sold by prescription and OTC would result in medication errors and other potential threats to patient safety. One comment revealed concern that having the same drug sold by prescription and OTC in the same packaging will lead to self medication and abuse of the drug by consumers. [EC13197-4] Many comments pointed out that having one package label would cause confusion and thus errors by personnel responsible for distributing the product (e.g., pharmacists and physicians). [C403-5; EC52-7; EC85-5; EC97-8; EC132-6,7; EC147-6; EC160-7; EC171-6,7; EC307-4; EC555-6; EC940-5,6; EC1121-5] Two comments noted that patient safety may

decline if one package label is used, since those who do not have to obtain the prescription will not be seen by a physician. [EC65-2; EC87-9]

Other comments said that having a single package label would cause consumer confusion, which may result in risks to patient safety. [EC33-8; EC34-6; EC65-2,7; EC85-5; EC93-5; EC132-6,7; EC165-4; EC171-6,7; EC426-5; EC518-8; EC609-7; EC678-8; EC813-1] In addition, two comments stated that different labels are necessary because that the general public does not have the training to understand the contraindications, side effects, and warnings on a standard drug label. [C83-5; EC121-4] To ease consumer confusion, some comments suggested that the labels are different and include an explanation of any restrictions on the dispersal of the product (e.g., age related restrictions) and include warnings that are simple and easy to understand. [C83-5; EC121-4; EC216-9; EC2107-9; EMC397-6] Another comment presented the suggestion that having different packaging would also help reduce misuse because psychologically the prescription labeling looks "more serious." [EC311-6]

In addition to having different packaging for the same active ingredient sold by prescription and OTC, one comment stated that the two products should have different brand names to make marketing easier. [EC405-5]

Arnall Golden Gregory LLP's comment stated that marketing the same active ingredient in the same packaging for sale by prescription and OTC product is contrary to the meaningful difference standard. Therefore, separate packaging is needed to make it clear that the products are not the same. [C403-5]

One comment noted that having one package label would cause a breakdown of the prescription system, since consumers could obtain an OTC product instead of obtaining the product by prescription. [EC34-6; EC626-6] Five comments stated that having the same packaging for prescription and OTC sales permits trading/swapping, as well as buying and redistributing of the product; which is contrary to the purpose of dual dispensed products. [EC58-7; EC99-7; EC827-9; EC1121-5; EC1927-4]

8.7 Examples of Prescription and OTC Labeling that is Similar, but with One or Two Differences (e.g., Dosage/Age Distinction)

Several comments provided examples of prescription and OTC labeling that is similar, but with one or two differences (e.g., dosage/age distinction). One comment noted that Prilosec (Omeprazole) is currently sold via prescription and OTC. The only distinction between the prescription and OTC Prilosec is the type of salt used, however this has no biological significance. [EC13-2] Another comment stated that the active ingredient in Ibuprofen is sold by prescription and OTC, but the packaging is different. [EC522-7; EC940] Zantac was also given as an example of a drug that has the same active ingredient that is available by prescription and OTC. [EC85-5] In addition, the Consumer Healthcare Products Association noted that there are many examples where distinctions in indications, dosage forms, or strengths have led to the creations of separate packages for products in both the simultaneous marketing realm and the OTC realm. For example, the following products have separate packaging: antifungals (dosage form, indication, and/or strength distinctions); an ingredient which can be used as an

antihistamine or as a sleep aid (indication and strength distinctions); minoxidil (gender and strength distinctions); and analgesics (strength and/or indication distinctions). [C412-12]. The American Pharmacists Association provided the example, Meclizine, which is prescription for vertigo and OTC for nausea caused by motion sickness. [EC16675-20]

8.8 Examples of Similar Labeling of Prescription and OTC Products that are the Same Drug and Dose, in the Market Place or Previously Marketed

Other comments provided examples of similar labeling of prescription and OTC products that are the same drug and dose, in the marketplace currently or previously marketed. One comment stated that it is currently possible to buy Claritin (loratadine) 10 mg either via prescription or OTC. [EC148-1] Two other comments presented Claritin as an example of a drug that is available in the same packaging via prescription and OTC. [EC206-8 and EC951-17] Another comment said Meclizine 25 mg is currently available via prescription or OTC. [EC73-6] C-V cough medicines are available with the same packaging by prescription only in some states and OTC after signing for them in other states. [EC155-13] One comment noted that pseudophedrine has been moved to behind-the-counter status, but the packaging has not changed. [EC216-3] The Consumer Healthcare Products Association's comment also noted that Clotrimazol/H2s was deemed similar enough by the manufacturer and FDA to require separate packaging. However, the comment noted that typically explicit dosage instructions based on the age of a child do not result in separate packaging. [C412-11]

8.9 Miscellaneous Arguments/Discussions

Some of the comments presented the concern that questions about the packaging in the ANPRM are merely a diversion and are not the best way for FDA to spend its time. [EC194-6; EC196-7; EC213-6; EC323-7]

One comment noted that this ANPRM question is not a legal question, as much as it is a marketing question. The comment stated that OTC drugs are often packaged for daily dosage and include incentive labeling (e.g., labeling that says 50% more free), while prescription drugs are often just allocated from a large container into a small vial for dispensing. The comment contained the suggestion that OTC style of labeling is used for an active ingredient sold in both prescription and OTC form. [EC364-7]

Two comments emphasized that if the same packaging is used for the prescription and OTC products, then the price for the prescription and OTC products should be the same. The comments presented the explanation that making the price for the products different if the same package is used would be unfair and unethical. [EC96-8; EMC355-5] In addition, several comments noted that if the same package is used for the OTC and prescription products then the more stringent labeling requirements should be used (i.e., if the current prescription product labeling requirements are more stringent than the OTC labeling requirements, the prescription labeling requirements should be used to create the package) to ensure that the consumer has the most complete data. [EC13-3; EC61-9; EC1129-6]

One comment noted that as long as the product's side effects are not severe enough to meet the criteria for an adverse event and the proposed dosing instructions in the package are clearly written, such that counseling by a licensed practitioner is not necessary, the product can be sold OTC. [EC212-8]

On comment presented the suggestion that if FDA creates a single package label for prescription and OTC product sales, FDA should carefully select the wording for the OTC and prescription package. For example, FDA should write side effects, not adverse events and specific situations in which drug should not be used, not contraindications. [EC212-6]

Within the comments, there was some confusion concerning the wording of this ANPRM question, "Assuming it is legal to market the same active ingredient in both a prescription and OTC product, may the different products be legally sold in the same package?" and the subsequent question, "If the two products may be lawfully sold in a single package, under what circumstances would it be inappropriate to do so?" Some comments written in response to these questions revealed that the phrase in these questions, "in the same package," was misinterpreted to mean that the prescription and OTC products may be physically contained in the same package, instead of the meaning FDA seems to have intended, that the packaging/labeling may be the same for the prescription and OTC products. These comments addressed the problems and issues that would result from physically packaging the two products together. [EC212-6; EC654-6; EC677-7; EC1032-7; EC13197-3; EMC368-3]

Other comments discussed the confusion that resulted from the wording of the questions. These comments pointed out that referring to the prescription and OTC products as "two products" is misleading, since the products are exactly the same, but with sales restrictions. [C403-5; EC16-5; EC323-8; EC680-10]

In addition, there were a few other responses to these ANPRM questions that reveal general confusion about the issues. For example, one comment said that it is inappropriate to distribute the products in the same package without a parent's approval. [EC716-8] Another comment stated that using the same package is inappropriate for people from other countries if they buy the product in the United States, since obtaining the product without a prescription or without separate and distinct packaging may be illegal in their country. [EC85-6]

9. If They Can be Legally Sold in Same Package, Under What Circumstances Would it be Inappropriate to do so? [ANPRM Question 3.B.]

9.1 Circumstances in which it is Inappropriate to Distribute Products in a Single Package

Of the comments that responded to Question 3.B of the ANPRM, 66 provided specific circumstances in which it is inappropriate to distribute prescription and OTC products in the same package. Some of the specific circumstances include instances where there are differences between the prescription and OTC products, such as differences in the:

- Products' strength [C412-12; C415-36; EC66-7,8; EC16675-20; EMC397-6],

- Dosage [e.g., C412-12; C415-36; EC66-8; EC167-6 EC201-5; EC364-8],
- Indication [C412-12; EC399-11; EC47-3; EC16675-20; EMC397-6],
- Side effects [EMC397-6],
- Formulation [e.g., EC5-8; EC160-8; EC167-6; EC951-16; EC1041-7, EC1129-7],
- Route of administration [EC16675-20],
- Associated risk [EC6-11; EC121-5], and/or
- Directions for use [e.g., C415-36; EC109-8; EC172-3,4; EC364-8; EC903-5].

Some comments stated that OTC and prescription products that could potentially cause severe reactions, permanent harm, or fatalities in the population, should not be sold in the same packaging. [EC168-7; EC416-7; EC678-9; EC860-4; EC15931-6,7] In addition, some comments stated that it is not appropriate to distribute the prescription and OTC products in the same package if the following circumstances exist:

- The prescription and OTC products are manufactured by different companies [EC201-5];
- The prescription and OTC product sales need to be tracked separately [EC12-6; EC94-7];
- The prescription product does not contain the typical identifying information about the intended recipient of the product (e.g., name, doctor, etc.) [EC311-7];
- The package for the prescription and OTC product does not specify the age restrictions [EC6-11];
- FDA determines that the data do not support both the prescription and OTC requirements of section 503(b) [C307-10]; or
- It is necessary to present information about the product or medical condition differently to different populations [EC81-7; EC408-7; EC691-7].

Several comments noted that if access to the prescription only product is not enforceable then it is inappropriate to use the same package. [EC7-5; EC58-8; EC146-9; EC426-6; EC15931-6]

Several comments emphasized that the circumstances in which it is inappropriate to sell prescription and OTC products in the same package are case specific. One comment presented the argument that decisions about whether to use the same package should be made on a case by case basis, since there will be exceptions. [EC212-7] When making case specific decisions about prescription and OTC packaging, one comment presented the suggestion that FDA consider the following factors: reduction of consumer confusion, data exclusivity rights, and ease of use. [C412-12] Another comment emphasized that there may be cases in which a doctor feels a different dosage of the drug is required, so using the same packaging would be inappropriate. [EMC374-4] One comment presented Plan B as a specific circumstance in which it is inappropriate to distribute the prescription and OTC product in the same package. [EC896]

Of the comments that were written in response to this question, 73 stated that is always inappropriate to sell prescription and OTC products in the same package [e.g., EC27-8; EC33-8; EC52-8; EC99-8; EC117-5; EC160-7; EC278-5; EC518-9; EC610-13; EC671-7; EC717-5; EC788-7; EC940-6] Two of these comments stated that it is always inappropriate to sell prescription and OTC products in the same package because doing so causes people to believe the OTC product is not as dangerous and does not have the serious side effects of the

prescription product. [EC52-8; EC518-9] Another comment stated that by not having the prescription and OTC products in one package there are fewer problems. [EC99-8]

9.2 Circumstances in which it is Appropriate to Distribute Products in a Single Package

Thirteen comments presented specific circumstances in which it is appropriate to distribute the prescription and OTC products in the same package as long as there are not any differences in between the prescription and OTC products for the following characteristics: formulation [EC1129-6; EC2314-12], amount of active ingredient [EC516-8; EC1129-6], warnings [EC1129-6], indications [EC47-4], potency [EMC355-5], or directions for use [EC172-3]. The National Research Center for Women stated that using the same package is appropriate as long as the drug has an identical method of action for each user of the product. [EC2314-12] One comment stated that assuming the OTC product is prohibited for a subpopulation, if the drug companies market the OTC product in areas that reach the subpopulation then the packaging for the OTC product should be the same as the prescription product. [EC53-8] One comment stated that is appropriate to use the same package if the enforcement of restrictions occurs at the point of sale. [EC32-6] Another comment presented Plan B as a specific circumstance in which it is appropriate to distribute the prescription and OTC product in the same package. [EC12379-5]

Of the comments that answered this last question in the ANPRM, approximately 472 (222 without all form letters included) suggested that it is always appropriate to use the same package for prescription and OTC products. [e.g., EC4-6; EC22-7; EC24-6; EC32-6; EC76-12; EC80-6; EC96-8; EC107-6; EC148-2; EC155-14; EC167-4; EC172-3; EC176-7; EC195-6; EC181-8; EC194-7; EC199-8; EC206-9; EC213-7; EC224-10; EC240-7; EC365-8; EC418-6; EC555-7; EC626-7; EC762-12; EC1086-7; EC11670-13; EC15931-6] Two of these comments elaborated by stating that making the prescription package different from the OTC package would be an act of discrimination. [EC213-7; EC15931-6]

9.3 Miscellaneous Arguments/Discussions

One comment presented the argument that the packaging for the prescription and OTC products is irrelevant. [EC535-9] Another comment suggested that this issue of using the same packaging for the prescription and OTC products should be explored by FDA, since this issue is within FDA's expertise. [EC141] One comment stated that the FDA is not contemplating different product packaging to ensure safety, as it has done in the past, but is instead accommodating a particular product marketing consideration, which is unacceptable. [EC623-8] A rule making discussion would resolve this issue, pointed out one comment. [EC654-7]

10. Studies/Data Provided in Comment

There were 22 comments that cited studies or technical publications. The studies/data from these comments are listed in Appendix B.

11. Other Miscellaneous Comments Unrelated to Specific Questions Asked in the FR Notice

There was one comment that provided miscellaneous statements unrelated to specific questions in the ANPRM, drug approval, or FDA's rulemaking process. This comment stated that the current economic climate of medical costs increasing ahead of the inflation rate and the average wage is not sustainable. Pharmaceutical companies and the medical providers may have to make adjustments if the economic decline continues. [EC1041-8]

Appendix A: Number of Comments Coded to Each Issue

Issue No.	Total (including each form letter)	Total as listed in CW3	Comment containing form letters (number of form letters in comment)
1. Comments unrelated to specific questions asked in FR notice - Drug approval	1037	1037	
1.1 General comments on drug approval process	35	35	
1.2 Specific comments on drug approval process for Morning-after Pill/Plan B	1337	1337	
1.2.1 Approve for OTC for all	45,722	16,470	EMC1 (1045); EMC42 (9); C8 (61); C31 (22); C72 (26,725); C73 (183); C101 (11); C105 (690); C217 (250); C271 (21); C272 (8); C273 (11); C445 (46); C446 (15); C447 (155)
1.2.2 Approve simultaneous marketing approach (i.e., market both OTC and prescription)	158	158	
1.2.3 Maintain prescription only	620	590	C218 (30)
1.2.4 Oppose drug product in any form	147	147	
1.3 Specific comments about other drug product	9	9	
2. Comments unrelated to specific questions asked in FR notice - FDA's general rulemaking process	2470	2470	
2.1 Comments on time, manner, and nature of rulemaking process	34,086	5999	EMC1 (1045); C72 (26,725); C217 (250); C271 (21); C445 (46);
2.2 Support ANPRM request for comments	12	12	
2.3 Oppose ANPRM request for comments	473	473	
3. Should FDA initiate a rulemaking regarding its interpretation of section 503(b)? [ANPRM Q 1.A.]	0	0	
3.1 Yes	199	199	
3.2 No	521	249	C217 (250); C31 (22)
3.3 Federal Food, Drug, and Cosmetic Act (FD&C Act) Amendments	2	2	
3.3.1 FD&C Act requires rulemaking	1	1	
3.3.2 FD&C Act is clear regarding when a drug should be prescription only	18	18	
3.3.3 Other arguments related to FD&C Act	17	17	

Appendix A: Number of Comments Coded to Each Issue

Issue No.	Total (including each form letter)	Total as listed in CW3	Comment containing form letters (number of form letters in comment)
3.4 Change to interpretation without rulemaking violates Administrative Procedures Act (APA)	4	4	
3.5 Supplemental New Drug Application (SNDA) and New Drug Application (NDA) regulations	0	0	
3.5.1 SNDA/NDA regulatory arguments supporting rulemaking	1	1	
3.5.2 SNDA/NDA regulatory arguments opposing rulemaking	3	3	
3.6 Court opinion legal arguments	0	0	
3.6.1 Court case arguments supporting a rulemaking	1	1	
3.6.2 Court case arguments opposing a rulemaking	2	2	
3.7 Other legal arguments	0	0	
3.7.1 Other legal arguments supporting rulemaking	4	4	
3.7.2 Other legal arguments opposing rulemaking	4	4	
3.8 Policy arguments	0	0	
3.8.1 Rulemaking will improve future FDA decisions (clarity, consistency, efficiency)	27	27	
3.8.2 Two-class system (OTC and prescription) not sufficient – need a third class of "behind-the-counter" drugs (pharmacist distributed)	13	13	
3.8.3 Other policy arguments for initiating a rulemaking	26	26	
3.8.4 Interpretation is clear in present form	25	25	
3.8.5 Circumstances for OTC safety are case-specific	17	17	
3.8.6 Develop/update guidance as alternative for rulemaking	2	2	
3.8.7 Cost-benefit concerns regarding rulemaking	8	8	
3.8.8 Other policy arguments opposing a rulemaking	26	26	
3.9 Examples of previous FDA actions in allowing simultaneous marketing of prescription and OTC products	0	0	
3.9.1 Drug approval examples	46	46	
3.9.2 FDA guidance or other documents (e.g., FDA 1999 Manual of Policy and Procedures (MAPP) statements, testimony, letters to industry, Q&As)	1	1	
3.9.3 Veterinary drug policy	1	1	
3.9.4 Other examples	2	2	
3.10 Examples of FDA actions disallowing simultaneous marketing	3	3	
3.11 Miscellaneous arguments/discussions	9	9	
4. Is there significant confusion regarding interpretation of section 503(b) of the act? [ANPRM Q 1.B.]	0	0	
4.1 Yes	181	181	
4.2 No	135	135	

Appendix A: Number of Comments Coded to Each Issue

Issue No.	Total (including each form letter)	Total as listed in CW3	Comment containing form letters (number of form letters in comment)
4.3 Arguments supporting significant confusion regarding FDA's interpretation	0	0	
4.3.1 FDA's interpretation of FD&C Act 505(b)(2) conflicts with interpretation of 503(b)	1	1	
4.3.2 Diverse industry and public opinion/reaction to ANPRM and statements re: FDA's authority	9	9	
4.3.3 Other legal arguments/conclusions supporting confusion re: FDA's interpretation	6	6	
4.3.4 Other policy arguments/statements supporting confusion re: FDA's interpretation	20	20	
4.4 Arguments indicating that little or no confusion exists	0	0	
4.4.1 Legal arguments that little or no confusion exists	5	5	
4.4.2 Policy arguments that little or no confusion exists	15	15	
4.5 Miscellaneous arguments/discussions	14	14	
5. Would rulemaking for clarification dispel confusion? [ANPRM Q 1.C.]	6	6	
5.1 Yes	104	104	
5.2 No	141	141	
5.3 Arguments that support concept that a rulemaking would provide clarification	0	0	
5.3.1 Legal arguments supporting rulemaking to dispel confusion	4	4	
5.3.2 Policy arguments supporting rulemaking to dispel confusion	17	17	
5.4 Arguments that a rulemaking would not provide clarification	0	0	
5.4.1 Legal arguments that rulemaking would not clarify	2	2	
5.4.2 Policy arguments that rulemaking would not clarify	1	1	
5.4.2.1. Guidance instead of rulemaking	0	0	
5.4.2.2. Other policy arguments	8	8	
5.4.3 There is no confusion, therefore rulemaking unnecessary	10	10	
5.5 Miscellaneous arguments/discussions	17	17	
6. If FDA limited sale of OTC product to sub-population, would FDA be able to enforce limitation as a matter of law? [ANPRM Q 2.A.]	0	0	
6.1 Yes	174	174	
6.2 No	193	193	
6.3 Legal/policy arguments that support/detail FDA's authority to enforce limitation on availability of OTC products by sub-population	0	0	
6.3.1 FD&C Act	6	6	

Appendix A: Number of Comments Coded to Each Issue

Issue No.	Total (including each form letter)	Total as listed in CW3	Comment containing form letters (number of form letters in comment)
6.3.2 No laws prevent the policy	3	3	
6.3.3 Court cases	0	0	
6.3.4 Age limitations are in line with other meaningful differences	10	10	
6.3.5 Other legal arguments	16	16	
6.4 Examples/precedents that support/detail FDA's authority to enforce limitation on availability of OTC products by sub-population	0	0	
6.4.1 Nicotine replacement therapy (e.g., Nicorette)	328	78	C217 (250)
6.4.2 Other examples	1	1	
6.5 Legal/policy arguments that FDA does not have authority to enforce the limitation [or permit dual marketing or implement "behind-the-counter" (pharmacist distribution)] system	0	0	
6.5.1 FDA's authority limited to drug safety, effectiveness/efficacy, and labeling	344	94	C217 (250)
6.5.2 Other FD&C Act arguments	3	3	
6.5.3 Court cases	5	5	
6.5.4 Other argument	35	35	
6.6 Authority of other entities to enforce the limitation	0	0	
6.6.1 State and local agencies have authority to enforce point-of-sale (e.g., recent limitations on cold medicines)	36	36	
6.6.2 Congress	5	5	
6.6.3 Alcohol and tobacco enforcement	454	204	C217 (250)
6.6.4 Other entities	3	3	
6.7 Miscellaneous arguments/discussions	14	14	
7. Would FDA be able to enforce limitation to sub-population as a practical matter? [ANPRM Q 2.B.]	0	0	
7.1 Yes	149	149	
7.2 No	192	192	
7.3 Actions FDA could take in order to enforce limitation of an OTC product to a sub-population	0	0	
7.3.1 Regulate product sponsor	1	1	
7.3.1.1. Require sales restrictions as condition for approval (e.g., restrict sales to entities that are licensed pharmacies)	17	17	
7.3.1.2. Require retailer, pharmacist, and consumer education programs	8	8	
7.3.1.3. Require risk management program	2	2	
7.3.1.4. Other product approval conditions	3	3	
7.3.2 Other FDA enforcement practices that it has the legal authority to put in place	6	6	
7.4 Other point-of-sale enforcement suggestions	1	1	

Appendix A: Number of Comments Coded to Each Issue

Issue No.	Total (including each form letter)	Total as listed in CW3	Comment containing form letters (number of form letters in comment)
7.4.1 Implement "behind-the-counter" system (pharmacist distributed)	92	92	
7.4.2 Involve other authorities (e.g., states, state boards of pharmacies)	7	7	
7.4.3 Monitor compliance and enforcement / conduct random inspections	16	16	
7.4.4 Require identification for age	152	152	
7.4.5 Pursue criminal actions against violators	22	22	
7.4.6 Other actions	31	31	
7.5 FDA will be unable or it will be difficult to enforce as a practical matter	0	0	
7.5.1 FDA does not have authority to enforce limitation, therefore it cannot enforce as a practical matter	6	6	
7.5.2 Infrastructure for FDA enforcement (e.g., resources, personnel, training, monitoring, third-party regulations) not in place	18	18	
7.5.3 Actual compliance will be difficult/impossible/burdensome to achieve	415	165	C217 (250)
7.5.4 Other arguments	13	13	
7.6 Miscellaneous arguments/discussions	10	10	
8. Assuming legal to market both, may the prescription and OTC products be legally sold in the same package? [ANPRM Q 3.A.]	0	0	
8.1 Yes	183	183	
8.2 No	152	152	
8.3 Legal arguments supporting one package label for prescription and OTC sales	0	0	
8.3.1 FD&C Act arguments (e.g., single label could be created that satisfies both sets of statutory requirements)	14	14	
8.3.2 Do not need separate NDC numbers	1	1	
8.3.3 Court cases	0	0	
8.3.4 Other legal arguments supporting one package label for prescription and OTC	6	6	
8.4 Policy arguments supporting one package label for prescription and OTC sales	0	0	
8.4.1 Other policy arguments supporting one package label	28	28	
8.5 Legal arguments opposing one package for prescription and OTC sales	5	5	
8.5.1 FD&C Act - Legal differences between statutory requirements for prescription and OTC	7	7	
8.5.2 Court cases arguments opposing one package	0	0	

Appendix A: Number of Comments Coded to Each Issue

Issue No.	Total (including each form letter)	Total as listed in CW3	Comment containing form letters (number of form letters in comment)
8.5.3 Need separate National Drug Code (NDC) numbers for billing	3	3	
8.5.4 Other legal arguments opposing one package	8	8	
8.6 Policy arguments opposing one package for prescription and OTC sales	3	3	
8.6.1 Single package contrary to meaningful difference standard	2	2	
8.6.2 Risk of medication errors or threats to patient safety	26	26	
8.6.3 Same packaging permits/encourages trading/swapping	7	7	
8.6.4 Other arguments opposing one package	24	24	
8.7 Examples of prescription and OTC labeling that is similar but with one or two differences – e.g., dosage/age distinction	10	10	
8.8 Examples of similar labeling of prescription and OTC products that are the same drug and dose, in the market place or previously marketed	9	9	
8.9 Miscellaneous arguments/discussions	21	21	
9. If they can be legally sold in same package, under what circumstances would it be inappropriate to do so? [ANPRM Q 3.B.]	0	0	
9.1 Circumstances in which it is inappropriate to distribute products in a single package	0	0	
9.1.1 Specific circumstances	66	66	
9.1.2 All circumstances (i.e., it's always inappropriate)	73	73	
9.2 Circumstance in which it is appropriate to distribute in single package	0	0	
9.2.1 Specific circumstances	13	13	
9.2.2 All circumstances (i.e., it's always appropriate, there are no inappropriate circumstances)	472	222	C217 (250)
9.3 Miscellaneous arguments/discussions	12	12	
10. Studies/data provided in comment	22	22	
11. Other miscellaneous comments unrelated to specific questions asked in FR notice	1	1	

Appendix B: Studies/Data Provided in Comments (Issue 10)

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