annual PDR costs would increase by $1.2 million ($19,500 x 60), equaling a present value of approximately $8.2 million or $10.0 million over 10 years with a 7 or 3-percent discount rate, respectively (table 13).

TABLE 13.—COSTS TO INCLUDE FDA-APPROVED PATIENT LABELING WITH LABELING OF EXISTING PRESCRIPTION PRODUCTS[1, 2]

Year	One-Time Labeling Revision Costs ($ million)	Annual Incremental Printing Costs ($ million)	Annual PDR Costs ($ million)	Total Costs ($ million)
1	0.2	0.8	1.2	2.2
2	0.0	0.8	1.2	1.9
3	0.0	0.8	1.2	1.9
4	0.0	0.4	1.2	1.5
5	0.0	0.4	1.2	1.5
6	0.0	0.4	1.2	1.5
7	0.0	0.4	1.2	1.5
8	0.0	0.4	1.2	1.5
9	0.0	0.4	1.2	1.5
10	0.0	0.4	1.2	1.5
Total Cost	0.2	4.8	11.7	16.7
Present Value of Total Discounted at 3 percent	0.2	4.2	10.0	14.4
Present Value of Total Discounted at 7 percent	0.2	3.6	8.2	12.0

[1] Numbers may not sum due to rounding.
[2] This estimate assumes that products with Medication Guides already conform to this requirement of the final rule.

2. Labeling Changes for New and Recently Approved Prescription Drug Products

a. *Affected products.* The final rule would require that prescription drug labeling conform to format and content requirements for three categories of products: (1) All NDAs, BLAs, and efficacy supplements submitted to FDA on or after the effective date, (2) NDAs, BLAs, and efficacy supplements approved over the 5 years preceding the effective date or pending on the effective date of the final rule, and (3) any ANDA that references a listed drug with labeling conforming to the requirements of the final rule. For the first category of products, the prescription drug labeling requirements would apply when a sponsor files an NDA, BLA or efficacy supplement. Products in the second category must file supplemental applications within 3 to 7 years of the

issuance of the rule, according to the implementation plan described in the preamble (see Table 5). For ANDA products (generic products), the implementation schedule for the affected reference listed drug applies. This rule does not cover labeling for OTC products (including those approved under an NDA).

Estimates of the number of new applications that would be affected by the rule are updated and based on application approvals since 1997. During this period, an average of 97 NDAs and 10 BLAs were approved each year. FDA assumes that this average rate will continue. The number of affected products approved within 5 years before the effective date are estimated as the number of NDAs approved during the 5-year period from 1997 through 2001 without subsequent efficacy supplements.

Most efficacy supplements are filed and approved within 5 years of the approval date of their original application. Over time, prescription drug labeling of most products affected by the final rule will already conform to the requirements of the final rule when an efficacy supplement is submitted. Beginning in year 3, therefore, the number of labeling revisions as a result of an efficacy supplement will decline over time.

The initial analysis of impacts did not include estimates of the number of generic products that would be affected because the period of exclusivity for most innovator products covered by the rule would extend beyond the 10-year horizon. However, a subsequent analysis of data from "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) found that some older innovator products with generic equivalents have recent approvals of efficacy supplements or NDAs for new dosage strengths that could trigger revision of the labeling of some reference listed drugs. Although the

overall number of older innovator products affected by the final rule is anticipated to be small, normally there are multiple generic products for each reference listed drug. Therefore, beginning in year 3, the final rule is estimated to affect an average of 42 generic products annually. Table 14 shows the number of products projected to be affected by the final rule during the 10-year period following the effective date.

TABLE 14.—ESTIMATED NUMBER OF AFFECTED PRODUCTS BY APPLICATION TYPE

Year	New NDAs and BLAs	Efficacy Supplements	Approvals 5 Years Prior to Effective Date	ANDAs	Total
1	107	69	0	0	176
2	107	69	0	0	176
3	107	52	69	42	270
4	107	39	69	42	257
5	107	29	68	42	246
6	107	22	69	42	240
7	107	16	69	42	234
8	107	12	0	42	161
9	107	9	0	42	158
10	107	7	0	42	156
Total	1,070	324	344	336	2,074

b. *Prescription drug labeling design costs.* The cost of designing prescription drug labeling that conforms to the final format and content requirements will depend heavily on when, during a product's life cycle, labeling design occurs. Costs will be highest for products already marketed with approved prescription drug labeling that otherwise would not be changed. Conversely, design costs will be lowest for products that are closely related to a prior product application that has already had its prescription drug labeling changed to the new format or for generic drug labeling. Costs for currently marketed products that would be undergoing relabeling for other reasons (e.g., related to an efficacy supplement) will be in between these extremes.

FDA has previously estimated that it takes about 2 months of full-time effort to design a novel patient information guide (for the first prescription drug in a therapeutic class), but less than 1 week to redesign a guide following a previously approved prototype (i.e., innovator drugs in the same therapeutic class for which patient information was already developed) (60 FR 44232). The final rule requires reordering of the detailed information in the prescription drug labeling and addition of Highlights and Contents. Although FDA designates the new order, detailed discussion and drug-specific decisions (e.g., regarding exactly what should be listed in Highlights) may be necessary. Because negotiation of labeling is a routine part of the review process, including Highlights and Contents does not increase this time burden on manufacturers or the agency. Therefore, the time required to revise labeling conforming to the requirements of the final rule will fall between the time required to design a novel patient information guide and time required to redesign a guide. Although sponsors of new applications and efficacy supplements would incur many of the same design costs as sponsors of existing innovator products, they would experience no additional testing, preparation, and application costs. For the initial analysis, it was anticipated that manufacturers would incur one-time costs up to $5,000 for each new product and $7,500 for each existing product to conform to the format and content provisions of the rule (65 FR 81082 at 81106 through 81107). These one-time per product costs are updated to $6,190 and $8,700, respectively. Modifying prescription drug labeling for ANDAs is anticipated to cost generic drug manufacturers about $1,300 per product, including $830 in labor costs and $470 in material costs for artwork and scrap (68 FR 6062 at 6074).

Once product labeling contains Highlights, any substantive revisions of key sections of the labeling must be listed in the recent major changes section along with the month and year the revision was incorporated. However, the final rule also requires that after 1 year, the information about recent major changes must be removed the next time the labeling is reprinted. Manufacturers voluntarily change drug product labeling frequently during the first 5 years a product is marketed. During this period, the agency anticipates that manufacturers would remove recent major changes from Highlights at the same time they voluntarily change labeling and, thus, would incur no additional costs. After 5 years on the market, however, some manufacturers would incur additional costs to remove recent major changes in the timeframe specified by the final rule. The earliest this might occur is in year 7 after the initial redesign of the labeling.[15] Based on the agency's experience with products that have been on the market for more than 5 years, up to 10 percent of the products affected by the final rule might be required to remove recent major changes in year 7 or later, at a per product cost of approximately $1,600. Over 10 years, the present value of these costs could equal about $0.1 million with either a 7 percent or 3 percent discount rate.

As shown in table 15, the total first-year costs would amount to $1.1 million. Costs increase to a high of $1.6 million in years 3 and 4. After the seventh year, when all products approved within 5 years prior to the rule's effective date or pending on the effective date have redesigned prescription drug labeling, the costs decline to about $0.8 million per year. As a result, the estimated total present value of the costs of redesigning prescription drug

[15] Recent major changes must remain in the Highlights for at least 1 year. Any major change after year 5 would therefore remain on the labeling through year 6 or later.

labeling over 10 years is about $8.8 million and $10.5 million with a 7 and 3 percent discount rate, respectively.

TABLE 15.—ESTIMATED PRESCRIPTION DRUG LABELING DESIGN COSTS[1]

Year	Current Value ($ million)					Present Value ($ million)	
	NDAs and BLAs	Efficacy Supplements	Approvals 5 Years Prior to Effective Date	ANDAs	Total	Total Discounted at 3 percent	Total Discounted at 7 percent
1	0.7	0.4	0.0	0 0	1.1	1 1	1.0
2	0.7	0.4	0 0	0.0	1.1	1.0	1.0
3	0.7	0 3	0.6	0.1	1.6	1.5	1.3
4	0.7	0.2	0.6	0.1	1.6	1.4	1.2
5	0.7	0.2	0.6	0.1	1.5	1.3	1.1
6	0.7	0.1	0.6	0.1	1.5	1.2	1.0
7	0.7	0.1	0.6	0.1	1.5	1.2	0.9
8	0.7	0.1	0.0	0.1	0.8	0.7	0.5
9	0.7	0.1	0.0	0.1	0.8	0.6	0.4
10	0.7	0.0	0.0	0.1	0.8	0.6	0.4
Total	6.7	2.0	3.0	0.4	12.2	10.5	8.8

[1] Numbers may not sum due to rounding.

c. *Costs associated with producing longer labeling accompanying drug products and drug samples (trade labeling).* The proposed rule would have required that trade labeling be printed in 8-point minimum type size, almost doubling the current average length for the labeling. Several comments from pharmaceutical manufacturers stated that the agency had underestimated the retooling and packaging line costs that would be incurred to include this longer trade labeling (see comment 124). A few large firms estimated that new equipment would cost between $135,000 and $700,000 per packaging line and could total up to $40 million for a large firm if trade labeling of all products were affected. As discussed in section XI.F of this document ("Alternatives Considered"), the agency recognized that including all products in the final rule would substantially increase costs to industry and, therefore, limited the final rule to new and recently approved products (see section XI.F.3 of this document). Furthermore, approximately half of the affected products shown

in table 14 will be new approvals that have not yet established packaging. Nevertheless, based on the potential economic impact the larger type size might have on pharmaceutical manufacturers, for the final rule the agency reduced the minimum size requirement for trade labeling to 6 points, a size generally reported as acceptable in comments from manufacturers (see comment 102). Thus, the new format and content requirements of the final rule will lengthen trade labeling by approximately 20 square inches when printed on two sides. Longer prescription drug labeling increases the cost of paper, ink, and other ongoing incremental printing costs. As discussed below, even in 6 points, a small number of products are still expected to incur some equipment costs (e.g., different insert-folding machinery).

i. *Incremental printing costs for trade labeling.* U.S. retail pharmacies dispense about 3.3 billion prescriptions per year, of which an estimated 790 million are for unit-of-use products that include prescription drug labeling within the package (65 FR 81082 at 81107, updated using IMS data at *http://www.ims-health.com*). If the non-unit-of-use prescriptions average one piece of labeling per 3.3 prescriptions, the total number of labelings accompanying retail products equals roughly 1.5 billion. Further, adding hospital pharmaceutical volume, estimated at approximately 54 percent of retail volume, yields an annual total of 2.4 billion pieces of trade labeling accompanying prescribed products. Allowing 10 percent for wastage indicates that manufacturers distribute roughly 2.6 billion pieces of labeling with prescribed products each year. Since 60 percent of all prescriptions are for branded products, about 1.6 billion pieces of labeling are currently included with about 2,440 branded products and about 1.0 billion pieces are included

with 2,900 generic products.[16] Using 650,000 pieces per innovator product and 370,000 pieces per generic product, at a cost of $0.18 and $0.19 per 100 pieces, respectively, yields annual per product cost estimates of $1,165 and $700, respectively. Table 16 shows the estimated number of revised labelings and annual incremental printing costs over 10 years.

Trade labeling must also accompany drug product samples. However, the number of samples distributed for a specific product depends on a manufacturer's marketing strategy and may vary from year to year. Although IMS Health (IMS) reported that the volume of samples distributed in the United States between 1997 and 2000 ranged from 860 million to 920 million (Ref. 36), sales representatives normally leave one piece of labeling for every 10 samples they distribute. Even though new products are sampled more often than older products, some manufacturers continue to distribute samples throughout the life cycle of their product. While the actual number of samples including reformatted trade labeling is uncertain, we anticipate that manufacturers may spend up to $0.2 million annually to print longer trade labeling to accompany drug samples (table 16).

[16] Derived from "Approved Drug Products with Therapeutic Equivalence Evaluations," CDER, FDA, 2001. The estimate is a count of all branded products marketed under an NDA and differentiated by active ingredient, therapeutic equivalence, dosage form, or manufacturer, not including multiple dosage strengths. Although not counted, adding biologicals would not significantly alter results.

Table 16.--Incremental Annual Printing Costs for Longer Trade Labeling in 6-Point Minimum Type Size[1]

Year	Number by Type (million)			Current Value ($ mil)				Present Value ($ mil)	
	NDA, BLA, and ES	ANDA	Samples	NDA, BLA, and ES	ANDA	Samples	Total	Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	110	0	90	0.2	0.0	0.2	0.4	0.4	0.3
2	230	0	90	0.4	0.0	0.2	0.6	0.5	0.5
3	380	16	90	0.7	0.0	0.2	0.9	0.8	0.7
4	520	31	90	0.9	0.1	0.2	1.1	1.0	0.9
5	650	47	90	1.2	0.1	0.2	1.4	1.2	1.0
6	780	62	90	1.4	0.1	0.2	1.7	1.4	1.1
7	900	78	90	1.6	0.1	0.2	1.9	1.6	1.2
8	980	93	90	1.8	0.2	0.2	2.1	1.7	1.2
9	1,100	110	90	1.9	0.2	0.2	2.3	1.7	1.2
10	1,100	120	90	2.0	0.2	0.2	2.4	1.8	1.2
Total	6,750	560	900	12.1	1.1	1.6	14.7	12.1	9.4

[1] Numbers may not sum due to rounding.

ii. *Equipment costs.* The original analysis estimated that 1 percent of affected existing products would be required to adjust packaging equipment with trade labeling printed in 8 points. According to several comments, trade labeling is currently printed in type sizes of 4.5 points and larger (see comment 102). Thus, it is unlikely that the minimum type size requirement of the final rule (i.e., 6 points for trade labeling) will require firms to purchase new packaging equipment. However, in a few cases where existing labeling is printed in type sizes between 4.5 points and 6 points, firms may need to adjust packaging lines for longer labeling. Since the labeling of many ophthalmic drug products is printed in type sizes smaller than 6 points, the proportion of recent approvals for ophthalmic products was used as a proxy for the proportion of affected products that will incur some equipment costs. For the final analysis, 5 percent of existing products affected by the rule (i.e., products with new efficacy supplements, products approved in the 5 years prior to the effective date of the rule, and affected ANDAs) will incur costs of $200,000 each product. As shown in table 17, the estimated present value of equipment changes totals $7.2 million and $8.7 million over 10 years discounted at 7 and 3 percent respectively.

TABLE 17.—COST OF ADJUSTMENTS TO PACKAGING LINES TO ACCOMMODATE LONGER TRADE LABELING[1, 2]

Year	Estimated Number of Affected Products	Total Cost ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	3	0.7	0.7	0.6
2	3	0.7	0.7	0.6
3	8	1.6	1.5	1.3
4	8	1.5	1.3	1.1
5	7	1.4	1.2	1.0
6	7	1.3	1.1	0.9
7	6	1.3	1.0	0.8
8	3	0.5	0.4	0.3
9	3	0 5	0.4	0.3
10	2	0.5	0.4	0.2

TABLE 17.—COST OF ADJUSTMENTS TO PACKAGING LINES TO ACCOMMODATE LONGER TRADE LABELING[1, 2]—Continued

Year	Estimated Number of Affected Products	Total Cost ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
Total	50	10.0	8.7	7.2

[1] Numbers may not sum due to rounding.
[2] For products with labeling printed in type sizes smaller than 6 points, the final rule may require that some packaging lines be retooled. Based on NDA, ANDA or efficacy supplements approvals for ophthalmic drug products between 1997 and 2001, an estimated 5 percent of the existing products affected by the rule will require some change to packaging equipment at an average cost of $200,000 per product.

d. *Layout and design costs for prescription drug labeling not accompanying drug products.* The final rule specifies a minimum type size of 6 points for trade labeling and 8 points for all other prescription drug labeling distributed by a manufacturer (e.g., labeling required to be distributed with promotional materials or in promotional settings). Firms choosing to print all prescription drug labeling for a product in the same type size (8 points or larger) will incur no additional design costs. However, if trade labeling is printed in a type size smaller than 8 points, a firm will incur additional costs of $810 per product to change and proof read the layout, and to prepare artwork for the labeling not accompanying the drug product. It is uncertain how many firms will print labeling in different type sizes. However, if all new and recently approved innovator products are affected, the total present value of the additional design costs is approximately $1.0 million or $1.2 million over 10 years discounted at 7 or 3 percent respectively (table 18).

TABLE 18.—ESTIMATED ONE-TIME LAYOUT AND DESIGN COSTS FOR LABELING NOT ACCOMPANYING DRUG PRODUCTS[1,2]

Year	Number of Affected Products	Total Costs ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	176	0.1	0.1	0.1
2	176	0.1	0.1	0.1
3	228	0.2	0.2	0.2
4	215	0.2	0.2	0.1
5	204	0.2	0.1	0.1
6	198	0.2	0.1	0.1
7	192	0.2	0.1	0.1
8	119	0.1	0.1	0.1
9	116	0.1	0.1	0.1
10	114	0.1	0 1	0.0

TABLE 18.—ESTIMATED ONE-TIME LAYOUT AND DESIGN COSTS FOR LABELING NOT ACCOMPANYING DRUG PRODUCTS[1,2]—Continued

Year	Number of Affected Products	Total Costs ($ million)	Present Value ($ million)	
			Total Discounted at 3 Percent	Total Discounted at 7 Percent
Total	1,738	1.4	1.2	1.0

[1] Firms are expected to only print this type of labeling for 3 years after the launch of a new innovator drug product.
[2] Numbers may not sum due to rounding.

e. *Costs associated with producing longer prescription drug labeling not accompanying drug products.* In contrast to trade labeling, with the new content and format requirements the length of current labeling will increase an average of about 93 percent when printed in 8-point type size. At this length, the incremental printing costs will increase by $0.85 per 100 pieces. To calculate the annual cost to print prescription drug labeling not accompanying drug products, FDA estimated that pharmaceutical representatives detailing drug products would distribute approximately 50 million pieces of prescription drug labeling annually. Because most detailing involves relatively new products, the products most affected by this rule, FDA assumed that manufacturers would incur additional printing costs for all of this labeling, amounting to about $0.4 million annually.

Finally, FDA estimated that about 730,000 pieces of prescription drug labeling per approval would be distributed each year by mail or at conferences to physicians, other health care practitioners, consumers, retail pharmacy outlets, and hospital pharmacies for 3 years following approval of a new drug.[17] As shown in table 19, annual total costs peak at $4.4 million in year 5. Over 10 years with a 7 or 3 percent discount rate, the present value of the incremental printing costs for longer prescription drug labeling not

[17] For each approval, it was assumed that all physicians involved in primary care and 25 percent of physicians practicing a medical specialty would receive two mailings per year, or an estimated 646,150 pieces (i.e., (222,400 x 2) + (0.25 x 402,700 x 2)), for 3 years following product launch. An additional 10 percent or 64,615 pieces are estimated to be distributed annually for 3 years to other health care practitioners or consumers. Furthermore, FDA assumes that 55,581 retail pharmacy outlets and 8,020 hospital pharmacies would receive 1 mailing to announce the launch of a new innovator product in the year of approval (65 FR 81082 at 81108, updated).

accompanying drug products would be about $24 million or $29 million, respectively.

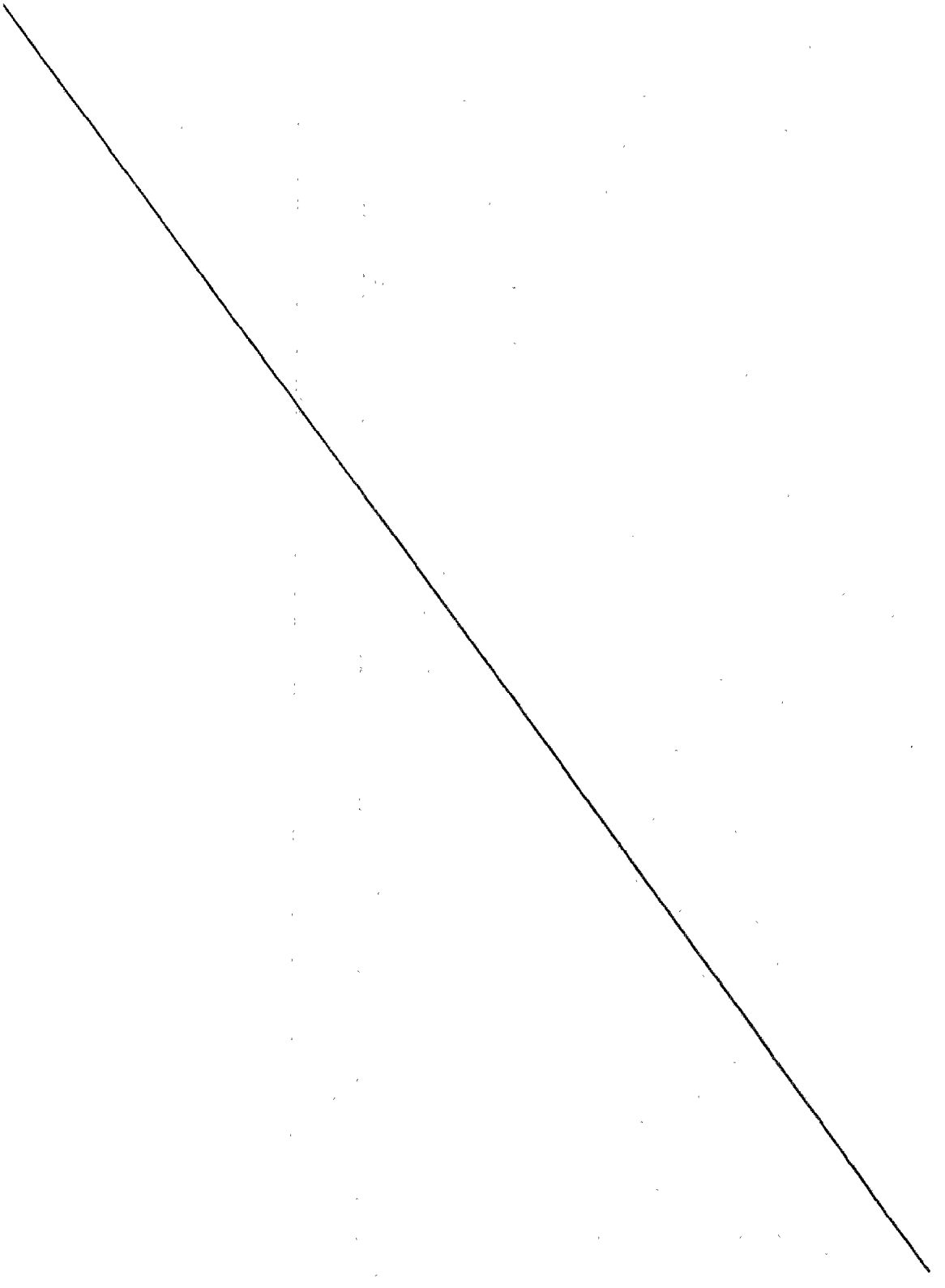

Table 19.--Annual Incremental Printing Costs for Longer Prescription Drug Labeling Not Accompanying Drug Products Printed in 8-Point Minimum Type Size[1]

Year	Number of Affected Innovator Products	Number of Pieces and Type of Delivery (million)		Current Value of Costs ($ mil)			Present Value ($ mil)	
		In-Person	Mailed	In-Person	Mailed	Total Cost	Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	176	50	140	0.4	1.2	1.6	1.5	1.5
2	176	50	260	0.4	2.2	2.6	2.5	2.3
3	228	50	430	0.4	3.6	4.0	3.7	3.3
4	215	50	450	0.4	3.8	4.3	3.8	3.3
5	204	50	470	0.4	4.0	4.4	3.8	3.2
6	198	50	450	0.4	3.8	4.2	3.6	2.8
7	192	50	430	0.4	3.7	4.1	3.3	2.6
8	119	50	370	0.4	3.1	3.6	2.8	2.1
9	116	50	310	0.4	2.6	3.1	2.3	1.7
10	114	50	260	0.4	2.2	2.6	1.9	1.3
Total	1,738	500	3,600	4.0	30.2	34.5	29.3	23.9

[1] Numbers may not sum due to rounding.

f. *Physicians' Desk Reference (PDR) Costs.* FDA estimates that the new Highlights, including any boxed warnings, and Contents would add about a half page to the PDR labeling of each affected prescription drug product. Based on conversations with Medical Economics (the publisher of the PDR) on the cost per printed page, FDA estimates that the annual publishing costs of the extra space required for printing the expanded prescription drug labeling would be about $5,550 for each affected product, plus an additional cost if the product was included in one of two annual supplements. FDA assumed that these costs would be incurred by the pharmaceutical industry via publishing fees paid to Medical Economics. The agency assumed that 75 percent of the new drugs and efficacy supplements would be published in the PDR (some smaller firms decline to publish labeling in the PDR). FDA also assumed that 90 percent of the new drugs published would be included in the PDR supplements and 33 percent of the published efficacy supplements would be included in the PDR supplements (about half are actually included, but only two-thirds of these include full prescription drug labeling; the remainder include only the added indication). FDA also assumed that the prescription drug labeling changes made as a result of the 5-year rule (applications approved in the 5 years preceding the effective date of the final rule) would not be included in the PDR supplements. Based on these assumptions, the estimated cost of publishing the extended prescription drug labeling in the PDR would be about $1.2 million for year 1. These costs would continue to increase over time as all drug approvals after the effective date of the rule would have longer PDR listings. The estimated annual and total costs of printing longer PDR listings are shown in table 20.

TABLE 20.—COST TO PRINT LONGER LISTINGS IN THE PDR[1, 2]

Year	Current Value ($ million)			Present Value ($ million)	
	PDR Bound	PDR Supplement	Total Costs	Total Discounted at 3 Percent	Total Discounted at 7 Percent
1	0.7	0.5	1.2	1.2	1.1
2	1.5	0.5	2.0	1 8	1.7
3	2 4	0.5	2.9	2.6	2.4
4	3.3	0.5	3.8	3.3	2.9
5	4.2	0.4	4.6	4.0	3.3
6	5 0	0.4	5.4	4.5	3.6
7	5.8	0.4	6.2	5.0	3.9
8	6.3	0.4	6.7	5 3	3.9
9	6.8	0.4	7.2	5.5	3.9
10	7.2	0.4	7.6	5.7	3.9
Total	43.1	4.5	47.6	39.1	30.5

[1] Numbers may not sum due to rounding.
[2] Printed in 6.5-point type size at an average per page cost of $9,755.

Table 21 summarizes the estimated compliance costs for the three major cost categories over a 10-year period.

TABLE 21.—COMPLIANCE COSTS OVER 10-YEAR PERIOD[1]

Year	Cost Category ($ million)			Total Costs ($ million)
	Design and Producing Trade Labeling; Modify Packaging Equipment	Reformat and Producing Labeling Not Accompanying Drug Products	Printing PDR	
1	3.1	1.7	2.4	7.3
2	3.1	2.8	3.1	9.0
3	4.9	4.2	4.1	13 2
4	4.6	4.4	4.9	13.9
5	4.6	4.6	5.8	15.0
6	4.8	4.4	6.6	15.8
7	5.0	4.3	7.4	16.6
8	3.8	3.6	7.9	15.3
9	4.0	3.1	8.3	15.5
10	4.0	2.7	8.8	15.5
Total Current Value	42.0	35.9	59.3	137.2
Total Present Value Discounted at 3 Percent	35.7	30.5	49.0	115.3
Total Present Value Discounted at 7 Percent	29.2	24.9	38.8	92.9

[1] Numbers may not sum due to rounding.

E. Impacts on Small Entities

1. The Need for and the Objective of the Rule

Developments in recent years have contributed to an increase in the length and complexity of prescription drug labeling, making it more difficult for

health care practitioners to quickly find specific information about a drug. Therefore, practitioners expend time that could be spent with patients and may miss critical information about the safe and effective use of prescription drug products. The objective of the requirements is to improve prescription drug labeling by making it easier for health care practitioners to access, read, and use labeling information about prescription drug products. The agency believes that having better access to critical information will improve the use of prescription drugs and lead to a decrease in the number of preventable adverse reactions that occur in the United States each year.

2. Description and Estimate of the Number of Small Entities Affected

This final rule would affect all small entities required to design their prescription drug labeling to comply with this rule. The Small Business Administration (SBA) considers Pharmaceutical Preparation Manufacturing firms (NAICS 325412) and Biological Product Manufacturing firms (NAICS 325414) with fewer than 750 and 500 employees, respectively, to be small. U.S. Census reports in 1999 there were 265 biological product manufacturing firms (Ref. 37) and 749 pharmaceutical preparation manufacturing firms (Ref. 38). However, employment size classes for pharmaceutical preparation manufacturing do not correspond to SBA size categories. Nevertheless, 1999 Census data suggest that approximately 94 percent of biological product manufacturing firms and at least 87 percent of the pharmaceutical preparation manufacturing firms could be considered small. Despite the large number of small manufacturers, large companies manufacture most prescription drug products. Although the agency cannot predict the number of new approvals granted to small entities, the following estimates are based on 5 years of recent submissions (65 FR 81082 at 81110, updated for 1997–2001). On average, 17

small entities will receive product approvals each year. In addition, about 64 small entities will be affected during years 3 to 7 of the rule, when applicants with products approved 5 years prior to the effective date of the final rule must submit reformatted prescription drug labeling for approval. Only six firms will have more than two existing products affected by the rule. Of these six, four firms will have two products affected in the same year and one firm will have three products affected in a single year.

The compliance requirements for small entities under this final rule are the same as those described above for other affected entities. Compliance primarily involves: (1) designing prescription drug labeling that conforms to the content and format requirements, and (2) once the labeling is approved by FDA, ensuring that all future printed prescription drug labeling is in the new format with the required minimum type size. Because manufacturers already submit labeling with NDAs, BLAs and efficacy supplements to FDA, no additional skills will be required to comply with the final rule.

The group of small entities likely to bear the highest total costs under this final rule are those firms that have: (1) Existing products with prescription drug labeling that must be revised in the first year or (2) more than one affected high-volume product per year, such as a small firm with two or three recently approved, high-volume products that must undergo prescription drug labeling reformatting simultaneously in the same year. However, the high-cost small entities are also the small firms with the highest sales of affected product; thus, their incremental cost per unit sold is likely to be relatively low. In contrast, small firms with a single, low-volume product would have lower costs of compliance, but the incremental cost per unit sold would be higher.

Although the agency solicited comment on the initial regulatory flexibility analysis from small entities, the only comments submitted specifically about the impact on small entities were from large firms (see comment 122). The following examples illustrate possible impacts on small entities with different production volumes. Prescription drug labeling costs are estimated for a small firm with a single carton-enclosed product (marketed under an NDA) that must: (1) Have its labeling reformatted in year 3 of the rule and (2) add patient information in year 1. Table 22 outlines the projected per-unit and total costs to the firm with 3 different levels of production: 1,000, 10,000, and 100,000 units produced per year.

In addition to the costs identified in table 22, a very small number of small firms might incur equipment costs to include longer prescription drug labeling in carton-enclosed products. It is likely, however, that this one-time capital cost (estimated at $200,000) will affect a total of no more than two or three small firms in the 10 years following implementation of the rule. Based on this analysis, FDA believes that the final rule would not have a significant impact on most small entities in this industry, but it is possible that a few small firms may be significantly affected by the final rule.

TABLE 22.—ESTIMATED COSTS FOR HYPOTHETICAL SMALL FIRM WITH A SINGLE PRODUCT, UNDER THREE ALTERNATIVE LEVELS OF PRODUCTION[1]

Cost Category	Number of Units Produced and Sold Each Year		
	100,000	10,000	1,000
Example 1—Revise labeling of product approved less than 1 year prior to effective date:			
Prescription drug labeling redesign/application	$8,700	$8,700	$8,700
Printing trade labeling[2]	$200	$20	$2
Printing prescription drug labeling not accompanying drug products[3]	$1,050	$105	$10
Total	$9,950	$8,825	$8,712
Additional cost per unit sold	$0.10	$0.88	$8.71
Example 2—Add printed patient information to existing labeling for a product:			
Prescription drug labeling redesign	$2,850	$2,850	$2,850
Printing trade labeling[4]	$750	$75	$8
Printing longer PDR[5]	$19,500	$19,500	N/A
Total	$23,100	$22,425	$2,858
Additional cost per unit sold	$0.23	$2.24	$2.86

[1] Numbers may not sum due to rounding.
[2] Number of pieces of trade labeling printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $0.001791 per labeling.

[3] To calculate the cost for printing labeling not accompanying drug products, the number of units is adjusted by the ratio of the average number of pieces printed for mailings to the average number printed as trade labeling (i.e., 1.126), and multiplied by the incremental printing cost of $0.0085 per piece.
[4] Number of pieces of trade labeling printed is calculated as units produced/year plus 10 percent wastage factor, at an incremental printing cost of $0.006837 per labeling.
[5] Assume that prescription drug labeling is already being printed in the PDR. Most low-volume products (i.e., less than 10,000 units per year) will not have labeling in the PDR.

F. Alternatives Considered

1. Do Nothing

The agency considered and rejected this option. The current prescription drug labeling is complex, requiring health care practitioners to spend unnecessary time seeking information they need for the safe and effective use of drug products by their patients. Preventable adverse reactions have many causes and are a serious public health issue. Changing prescription drug labeling to meet the needs of health care practitioners that use it is one of many public health initiatives aimed at reducing these adverse reactions and improving health care.

2. Formatting Alternatives

FDA has considered numerous alternative formats, including a longer Highlights. Highlights is limited to one-half page in 8 points to respond to health care practitioners' concerns about length as well as to reduce the incremental printing costs to manufacturers.

The agency also considered requiring larger minimum type sizes. A 10-point minimum size requirement would increase the amount of paper needed to print the average reformatted labeling by about 200-square inches at an incremental cost of $18,000 per million pieces. Over 10 years, the total present value of producing longer trade labeling in 10 points compared to 6 points would equal $95 million or $120 million with a 7- or 3-percent discount rate, respectively. In addition to higher incremental printing costs, requiring 10-point minimum type size would make labeling so large that many

manufacturers would be forced to modify or replace packaging equipment. The agency therefore rejected this option because the potential benefits of the larger type size did not outweigh the costs.

The agency also considered and rejected a 10-point minimum size requirement for labeling not accompanying drug products. Compared to the minimum requirement of 8 points in the final rule, this larger type size would have taken about 100-square inches more paper at an incremental cost of $9,000 per million pieces.

Finally, the agency proposed a minimum size requirement of 8 points for trade labeling instead of the 6-point requirement in the final rule. At 6 points, the average revised labeling will increase by about 20-square inches. Requiring the larger minimum size would take another 70-square inches of paper and cost industry about $6,000 per million pieces of trade labeling. Because this requirement would be burdensome on industry, the agency rejected the 8-point minimum type size.

3. Alternative Categories of Affected Products

Three alternative categories of products to be covered by the rule were considered: (1) All drugs, (2) a set of innovator and generic drugs on a "top 200 most prescribed" list, and (3) the "top 100" or "top 200" drugs with the most adverse reactions. The agency believes including only labeling of new and more recently approved drug products is the best option for implementing the new format requirements (see comment 113). Even this limited set of products will require substantial resources from both industry and the agency for a period of several years. The agency's proposed implementation plan, which is being finalized in this rule as proposed, is intended to make the best use of these resources. Because there is a lack of standardized data on

prescription volume and volumes can fluctuate considerably over time, the agency does not believe that categories based on volume would be prudent or feasible. As discussed in the preamble to the proposed rule (65 FR 81082 at 81098), the plan targets newer products because practitioners are more likely to refer to the labeling for newer products. Internal agency analysis finds that fully 40 percent of adverse reaction reports submitted to the FDA are for drugs approved within the last 3 years. Therefore, the agency rejected these three alternative categories in order to focus efforts on recently approved drug products whose labeling is more likely to be consulted by physicians.

4. Alternative Implementation Schedule

FDA considered a shorter implementation schedule of 3 years after the effective date for all applications and efficacy supplements approved 5 years prior to the effective date. The agency selected the more gradual implementation schedule of up to 7 years to reduce the cost impact of the rule, especially on small entities.

XII. Civil Justice Reform

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988.

XIII. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. Miller, G. A., "The Magical Number Seven, Plus or Minus Two: Some Limits on Our Capacity for Processing Information," *Psychological Review*, 101(2):343–352, 1994.

2. Shiffrin, R. M., and R. M. Nosofsky, "Seven Plus or Minus Two: A Commentary On Capacity Limitations," *Psychological Review*, 101(2):357–361, 1994.

3. Allen, P. A., and L. C. Crozier, "Age and Ideal Chunk Size," *Journal of Gerontology: Psychological Sciences*, 47(1):47–51, 1992.

4. Food and Drug Administration, "Consumer Comprehension and Preference for Variations in the Proposed Over-the-Counter Drug Labeling Format," in OTC vol. 28, Docket No. 96N–0420, Division of Dockets Management.

5. National Surveys of Prescription Medicine Information Received by Consumers, *http://www.fda.gov/cder/ddmac/y2ktable.htm.*

http://www.fda.gov/cder/ddmac/y2kTITLE.htm.

6. Kripalani, S., "The Write Stuff: Simple Guidelines Can Help You Write and Design Effective Patient Education Materials," *Texas Medicine*, 91:40–45, 1995.

7. Backinger, C. L., and P. A. Kingsley, "Write It Right: Recommendations for Developing User Instructions for Medical Devices Used in Home Health Care," Department of Health and Human Services, Publication No. FDA 93–4258, 1993.

8. Mettger, W., and J. Mara, "Clear & Simple: Developing Effective Print Materials for Low-Literate Readers," Bethesda, MD, National Cancer Institute, Publication No. NIH 95–3594, 1994, *http://oc.nci.nih.gov/services/Clear_and_Simple/HOME.htm.*

9. Silver, N. C., and C. C. Braun, "Perceived Readability of Warning Labels with Varied Font Sizes and Styles," *Safety Science*, 16:615–625, 1993.

10. Wilkins, A. G., and M. I. Nimmo-Smith, "The Clarity and Comfort of Printed Text," *Ergonomics*, 30:1705–1720, 1987.

11. Transcript of public meeting on prescription drug labeling, Docket No. 95N–0314, October 30, 1995.

12. Eastern Research Group, Inc., "Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Rule," appendix A, March 5, 1999.

13. Connelly, D. P. et al., "Knowledge Resource Preferences of Family Physicians," *Journal of Family Practice*, 31(2):121–122, 1990.

14. Ely, J. W. et al., "What Clinical Information Resources Are Available in Family Physicians' Offices?" *Journal of Family Practice*, 48(2):135–139, 1999.

15. Ely, J. W. et al., "The Information Needs of Family Physicians: Case-Specific Clinical Questions," *Journal of Family Practice*, 35(3):265–269, 1992.

16. Gorman, P., "Information Needs in Primary Care: A Survey of Rural and Nonrural Primary Care Physicians," *Medinfo*, 10 (Pt. 1):338–342, 2001.

17. National Association of Chain Drug Stores, "Industry Facts-at-a-Glance—Rx Sales 2001," *http://www.nacds.org/wmspage.cfm?parm1=507#rx* (last viewed 8/27/02).

18. U.S. Department of Labor, Bureau of Labor Statistics, "2000 National Occupational Employment and Wage Estimates—29–1051 Pharmacists," *http://www.bls.gov/oes/2000/oes291051.htm* (last viewed 8/27/02).

19. U.S. Department of Labor, Bureau of Labor Statistics, *Occupational Outlook Handbook, 2002–03*, Pharmacists (occupation code 29–1051), 2002, *http://www.bls.gov/oco/ocos079.htm* (last viewed 9/13/02).

20. Jousimaa, J. et al., "Physicians' Patterns of Using a Computerized Collection of Guidelines for Primary Care," *International Journal of Technology Assessment in Health Care*, 14(3):484–493, 1998.

21. U.S. Census Bureau, "Table 153, Physicians by Selected Activity: 1980 to 1999," *Statistical Abstract of the United States: 2001*, p. 106.

22. U.S. Census Bureau, "Table 157, Medical Practice Characteristics by Selected Specialty: 1985 to 1998," *Statistical Abstract of the United States: 2001*, p. 108.

23. American Medical Association, "Medical Education FAQs," *http://www.ama-assn.org/ama/pub/category/3627.html* (last viewed 9/13/02).

24. Woosley, R. L., "Drug Labeling Revisions—Guaranteed to Fail?" *Journal of the American Medical Association*, 284(23):3047–3049, 2000.

25. Friedman, M. A. et al., "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?" *Journal of the American Medical Association*, 281(18):1728–1734, 1999.

26. U.S. General Accounting Office, "Adverse Drug Events: The Magnitude of Health Risk Is Uncertain Because of Limited Incidence Data," GAO/HEHS–00–21, January, 2000.

27. Bates, D. W. et al., "Incidence of Adverse Drug Events and Potential Adverse Drug Events," *Journal of the American Medical Association*, 274(1):29–34, 1995.

28. Classen, D. C. et al., "Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality," *Journal of the American Medical Association*, 277(4):301–306, 1997.

29. Senst, B. L. et al., "Practical Approach to Determining Costs and Frequency of Adverse Drug Events in a Health Care Network," *American Journal of Health-Systems Pharmacy*, 58:1126–1132, 2001.

30. 2000 hospital discharges data from the Agency for Health Care Policy and Research (AHCPR), June 25, 1998, *http://www.ahrq.gov/HCUPnet.htm* (last viewed 8/13/02).

31. Bates, D. W. et al., "The Costs of Adverse Drug Events in Hospitalized Patients," *Journal of the American Medical Association*, 277(4):307–311, 1997.

32. Medical Group Management Association, AHRQ, CMS and Partnership for Patient Safety, "Ambulatory Patient Safety: What Do We Know?" *An Agenda for Research in Ambulatory Patient Safety—Synthesis of a Multidisciplinary Conference*, 2000, *http://www.ahcpr.gov/about/cpcr/ptsafety/ambpts2.htm* (last viewed 10/10/02).

33. Thomas, E. J. et al., "Costs of Medical Injuries in Utah and Colorado," *Inquiry*, 36:255–264, 1999.

34. Johnson, J. A., and J. L. Bootman, "Drug-Related Morbidity and Mortality: A Cost-of-Illness Model," *Archives of Internal Medicine*, 155:1949–1956, 1995.

35. Ernst, F. R., and A. J. Grizzle, "Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model," *Journal of the American Pharmaceutical Association*, 41(2):192–199, 2001.

36. IMS Health, "Product Sampling Continues to Spike in U.S.," 2001, *http://www.imshealth.com/public/structure/dispcontent/1,2779,1362–1362–143626,00.html* (last viewed 9/23/02).

37. U.S. Census Bureau, "Statistics of U.S. Businesses; 1999; Pharmaceutical preparation mfg, United States," *http://www.census.gov/epcd/susb/1999/us/US325412.htm* (last viewed 9/12/02).

38. U.S. Census Bureau, "Statistics of U.S. Businesses; 1999; Biological product (except diagnostic) mfg, United States," *http://www.census.gov/epcd/susb/1999/us/US325414.htm* (last viewed 9/12/02).

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procdure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR 601

Adminstrative practice and procedure, Biologics, Confidential business information.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 201, 314, and 601 are amended as follows:

PART 201—LABELING

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

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

■ 2. Section 201.56 is revised to read as follows:

§ 201.56 Requirements on content and format of labeling for human prescription drug and biological products.

(a) *General requirements.* Prescription drug labeling described in § 201.100(d) must meet the following general requirements:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness. Conclusions based on animal data but necessary for safe and effective use of the drug in humans must be identified as such and included with human data in the appropriate section of the labeling.

(b) *Categories of prescription drugs subject to the labeling content and format requirements in §§ 201.56(d) and 201.57.* (1) The following categories of prescription drug products are subject to the labeling requirements in

paragraph (d) of this section and § 201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biologics license application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and § 201.80.

(c) *Schedule for implementing the labeling content and format requirements in §§ 201.56(d) and 201.57.* For products described in paragraph (b)(1) of this section, labeling conforming to the requirements in paragraph (d) of this section and § 201.57 must be submitted according to the following schedule:

(1) For products for which an NDA, BLA, or efficacy supplement is submitted for approval on or after June 30, 2006, proposed conforming labeling must be submitted as part of the application.

(2) For products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006, or that has been approved any time from June 30, 2005, up to and including June 30, 2006, a supplement with proposed conforming labeling must be submitted no later than June 30, 2009.

(3) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2004, up to and including June 29, 2005, a

supplement with proposed conforming labeling must be submitted no later than June 30, 2010.

(4) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2003, up to and including June 29, 2004, a supplement with proposed conforming labeling must be submitted no later than June 30, 2011.

(5) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2002, up to and including June 29, 2003, a supplement with proposed conforming labeling must be submitted no later than June 30, 2012.

(6) For products for which an NDA, BLA, or efficacy supplement has been approved anytime from June 30, 2001, up to and including June 29, 2002, a supplement with proposed conforming labeling must be submitted no later than June 30, 2013.

(d) *Labeling requirements for new and more recently approved prescription drug products.* This paragraph applies only to prescription drug products described in paragraph (b)(1) of this section and must be implemented according to the schedule specified in paragraph (c) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.57(a), (b), and (c) under the following headings and subheadings and in the following order:

Highlights of Prescribing Information

Product Names, Other Required Information

Boxed Warning

Recent Major Changes

Indications and Usage

Dosage and Administration

Dosage Forms and Strengths

Contraindications

Warnings and Precautions

Adverse Reactions

Drug Interactions

Use in Specific Populations

Full Prescribing Information: Contents

Full Prescribing Information

Boxed Warning

1 Indications and Usage

2 Dosage and Administration

3 Dosage Forms and Strengths

4 Contraindications

5 Warnings and Precautions

6 Adverse Reactions

7 Drug Interactions

8 Use in Specific Populations

8.1 Pregnancy

8.2 Labor and delivery

8.3 Nursing mothers

8.4 Pediatric use

8.5 Geriatric use

9 Drug Abuse and Dependence

9.1 Controlled substance

9.2 Abuse

9.3 Dependence

10 Overdosage

11 Description

12 Clinical Pharmacology

12.1 Mechanism of action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 Nonclinical Toxicology

13.1 Carcinogenesis, mutagenesis, impairment of fertility

13.2 Animal toxicology and/or pharmacology

14 Clinical Studies

15 References

16 How Supplied/Storage and Handling

17 Patient Counseling Information

(2) Additional nonstandard subheadings that are used to enhance labeling organization, presentation, or ease of use (e.g., for individual warnings or precautions, or for each drug interaction) must be assigned a decimal number that corresponds to their placement in labeling. The decimal numbers must be consistent with the standardized identifying numbers listed in paragraph (d)(1) of this section (e.g., subheadings added to the "Warnings and Precautions" section must be numbered 5.1, 5.2, and so on).

(3) Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the full prescribing information.

(4) Omit clearly inapplicable sections, subsections, or specific information. If sections or subsections required under paragraph (d)(1) of this section are omitted from the full prescribing information, the heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following

statement must appear at the end of Contents: "* Sections or subsections omitted from the full prescribing information are not listed."

(5) Any risk information that is required under § 201.57(c)(9)(iv) is considered "appropriate pediatric contraindications, warnings, or precautions" within the meaning of section 505A(l)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355A(l)(2)), whether such information appears in the "Contraindications," "Warnings and Precautions," or "Use in Specific Populations" section of labeling.

(e) *Labeling requirements for older prescription drug products.* This paragraph applies only to approved prescription drug products not described in paragraph (b)(1) of this section.

(1) Prescription drug labeling described in § 201.100(d) must contain the specific information required under § 201.80 under the following section headings and in the following order:

Description

Clinical Pharmacology

Indications and Usage

Contraindications

Warnings

Precautions

Adverse Reactions

Drug Abuse and Dependence

Overdosage

Dosage and Administration

How Supplied

(2) The labeling may contain the following additional section headings if appropriate and if in compliance with § 201.80(l) and (m):

Animal Pharmacology and/or Animal Toxicology

Clinical Studies

References

(3) Omit clearly inapplicable sections, subsections, or specific information.

(4) The labeling may contain a "Product Title" section preceding the "Description" section and containing only the information required by § 201.80(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(1)(iv) and § 201.100(e). The information required by § 201.80(a)(1)(i) through (a)(1)(iv) must appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title."

(5) The labeling must contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

(6) The requirement in § 201.80(f)(2) to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling must be implemented no later than June 30, 2007.

■ 3. Section 201.57 is redesignated as § 201.80 and new § 201.57 is added to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) *Highlights of prescribing information.* The following information must appear in all prescription drug labeling:

(1) *Highlights limitation statement.* The verbatim statement "These highlights do not include all the information needed to use (*insert name of drug product*) safely and effectively. See full prescribing information for (insert name of drug product)."

(2) *Drug names, dosage form, route of administration, and controlled substance symbol.* The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04 of this chapter.

(3) *Initial U.S. approval.* The verbatim statement "Initial U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the line immediately beneath the established name or, for biological products, proper name of the product.

(4) *Boxed warning.* A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and bolded. The following verbatim statement must be placed immediately

following the heading of the boxed warning: "See full prescribing information for complete boxed warning."

(5) *Recent major changes.* A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) *Indications and usage.* A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

(7) *Dosage and administration.* A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring

recommendations, and other clinically significant clinical pharmacologic information.

(8) *Dosage forms and strengths.* A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-milligram tablets) and whether the product is scored.

(9) *Contraindications.* A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) *Warnings and precautions.* A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) *Adverse reactions.* (i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

(ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA at (*insert*

current FDA phone number and Web address for voluntary reporting of adverse reactions)."

(iii) For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or VAERS at (*insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions*)."

(iv) For manufacturers with a Web site for voluntary reporting of adverse reactions, the Web address of the direct link to the site.

(12) *Drug interactions.* A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings.

(13) *Use in specific populations.* A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings.

(14) *Patient counseling information statement.* The verbatim statement "See 17 for Patient Counseling Information" or, if the product has FDA-approved patient labeling, the verbatim statement "See 17 for Patient Counseling Information and (insert either FDA-approved patient labeling or Medication Guide)."

(15) *Revision date.* The date of the most recent revision of the labeling, identified as such, placed at the end of Highlights.

(b) *Full prescribing information: Contents.* Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information

preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) *Full prescribing information.* The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) *Boxed warning.* Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) *1 Indications and usage.* This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug

in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) *2 Dosage and administration.* (i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

(iii) Radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it.

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

(4) *3 Dosage forms and strengths.* This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) *4 Contraindications.* This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their

particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state "None."

(6) *5 Warnings and precautions.* (i) *General.* This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) *Other special care precautions.* This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

(iii) *Monitoring: Laboratory tests.* This section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.

(iv) *Interference with laboratory tests.* This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) *6 Adverse reactions.* This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) *Listing of adverse reactions.* This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded

by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) *Categorization of adverse reactions.* Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) *Clinical trials experience.* This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) *Postmarketing experience.* This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

(iii) *Comparisons of adverse reactions between drugs.* For drug products other than biological products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, any such claim must be based on substantial evidence.

(8) *7 Drug interactions.* (i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.

(ii) This section must also contain practical guidance on known interference of the drug with laboratory tests.

(9) *8 Use in specific populations.* This section must contain the following subsections:

(i) *8.1 Pregnancy.* This subsection may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection must contain the following information:

(A) *Teratogenic effects.* Under this subheading, the labeling must identify one of the following categories that applies to the drug, and the labeling must bear the statement required under the category:

(*1*) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: "Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling must also contain a description of the human studies. If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state: "Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug)." The labeling must also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*2*) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled

studies in pregnant women, the labeling must state: "Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state: "Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling must also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*3*) Pregnancy category C. If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling must state:

"Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling must contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling must state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed." The labeling must contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*4*) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling must state: "Pregnancy Category D. See 'Warnings and Precautions' section." Under the "Warnings and Precautions" section, the labeling must state: "(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

(5) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling must state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling must state: "(*Name of drug*) may (*can*) cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) (*Name of drug*) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

(B) *Nonteratogenic effects.* Under this subheading the labeling must contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading must include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(ii) *8.2 Labor and delivery.* If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the Indications and Usage section, this subsection must describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery

or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, it must state that the information is unknown.

(iii) *8.3 Nursing mothers.* (A) If a drug is absorbed systemically, this subsection must contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring must be described.

(B) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection must contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling must state: "Because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, "Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must state: "Caution should be exercised when (*name of drug*) is administered to a nursing woman."

(C) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection must contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling must state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious

adverse reactions in nursing infants from (*name of drug*) (or, "Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling must state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (*name of drug*) is administered to a nursing woman."

(iv) *8.4 Pediatric use.* (A) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(H) of this section, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(B) If there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the "Indications and Usage" section, and appropriate pediatric dosage information must be given under the "Dosage and Administration" section. The "Pediatric use" subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical

Studies" section. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(C) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section. The "Pediatric use" subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information must also be contained in the "Contraindications" and/or "Warnings and Precautions" section(s).

(D)(1) When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling must contain either the following statement or a reasonable alternative:

SL per Diedra Wingate at OFR 1-18-05

The safety and effectiveness of (*drug name*) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (*insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population*).

(2) Data summarized in the preceding prescribed statement in this subsection must be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions must be included in the "Dosage and Administration" section. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients must be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings and Precautions," and "Dosage and Administration" sections.

SR per Diedra Wingate at OFR 1-18-05

(E) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (____) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard must be described in this subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(F) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard must be described in this

subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section and this subsection must refer to it.

(G) If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(H) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the "Contraindications" or "Warnings and Precautions" section.

(v) *8.5 Geriatric use.* (A) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population must be described under the "Indications and Usage" section, and appropriate geriatric dosage must be stated under the "Dosage and Administration" section. The "Geriatric use" subsection must cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection must pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection must be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information must also be

contained in the "Warnings and Precautions" and/or "Contraindications" section(s).

(B) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(*1*) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must include the following statement:

Clinical studies of (*name of drug*) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing

range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

(*2*) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection must contain the following statement:

Of the total number of subjects in clinical studies of (*name of drug*), ____ percent were 65 and over, while ____ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(*3*) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the "Contraindications," "Warnings and Precautions," "Dosage and Administration," or other sections.

(C)(*1*) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they must be described briefly in the "Geriatric use"

subsection and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" and "Drug Interactions" sections ordinarily contain information on drug/disease and drug/drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to use concomitant drugs.

(*2*) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection must include the statement:

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

(D) If use of the drug in the elderly appears to cause a specific hazard, the hazard must be described in the "Geriatric use" subsection, or, if appropriate, the hazard must be stated in the "Contraindications" or "Warnings and Precautions" section, and the "Geriatric use" subsection must refer to those sections.

(E) Labeling under paragraphs (c)(9)(v)(A) through (c)(9)(v)(C) of this section may include statements, if they are necessary for safe and effective use of the drug, and reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (*name of drug*) and observed closely.

(F) If the sponsor believes that none of the requirements described in paragraphs (c)(9)(v)(A) through (c)(9)(v)(E) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons

for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(vi) *Additional subsections.* Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment).

(10) *9 Drug abuse and dependence.* This section must contain the following information, as appropriate:

(i) *9.1 Controlled substance.* If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

(ii) *9.2 Abuse.* This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

(iii) *9.3 Dependence.* This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state and the principles of treating the effects of abrupt withdrawal must be described.

(11) *10 Overdosage.* This section must be based on human data. If human data are unavailable, appropriate animal and in vitro data may be used. The following specific information must be provided:

(i) Signs, symptoms, and laboratory findings associated with an overdosage of the drug;

(ii) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis);

(iii) Concentrations of the drug in biologic fluids associated with toxicity or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses;

(iv) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life threatening;

(v) Whether the drug is dialyzable; and

(vi) Recommended general treatment procedures and specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center). Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs. Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated.

(12) *11 Description.* (i) This section must contain:

(A) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug or, for biological products, the proper name (as defined in § 600.3 of this chapter) and any appropriate descriptors;

(B) The type of dosage form(s) and the route(s) of administration to which the labeling applies;

(C) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for drug labels or §§ 610.60 and 610.61 of this chapter for biological product labels;

(D) If the product is sterile, a statement of that fact;

(E) The pharmacological or therapeutic class of the drug;

(F) For drug products other than biological products, the chemical name and structural formula of the drug; and

(G) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(ii) If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated.

(13) *12 Clinical pharmacology.* (i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

(A) *12.1 Mechanism of action.* This subsection must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole body). If the mechanism of action is not known, this subsection must contain a statement about the lack of information.

(B) *12.2 Pharmacodynamics.* This subsection must include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect in preventing, diagnosing, mitigating, curing, or treating disease, or those related to adverse effects or toxicity. Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information. Detailed dosing or monitoring recommendations based on pharmacodynamic information that appear in other sections (e.g., "Warnings and Precautions" or "Dosage and Administration") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(C) *12.3 Pharmacokinetics.* This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must

also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

(ii) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section only under the following circumstances:

(A) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(B) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled studies, as defined in § 314.126(b) of this chapter, to be necessary for the safe and effective use may be included in this section only if a waiver is granted under § 201.58 or § 314.126(c) of this chapter.

(14) *13 Nonclinical toxicology.* This section must contain the following subsections as appropriate:

(i) *13.1 Carcinogenesis, mutagenesis, impairment of fertility.* This subsection must state whether long term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If results from reproduction studies or other data in animals raise concern

about mutagenesis or impairment of fertility in either males or females, this must be described. Any precautionary statement on these topics must include practical, relevant advice to the prescriber on the significance of these animal findings. Human data suggesting that the drug may be carcinogenic or mutagenic, or suggesting that it impairs fertility, as described in the "Warnings and Precautions" section, must not be included in this subsection of the labeling.

(ii) *13.2 Animal toxicology and/or pharmacology.* Significant animal data necessary for safe and effective use of the drug in humans that is not incorporated in other sections of labeling must be included in this section (e.g., specifics about studies used to support approval under § 314.600 or § 601.90 of this chapter, the absence of chronic animal toxicity data for a drug that is administered over prolonged periods or is implanted in the body).

(15) *14 Clinical studies.* This section must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program. If a specific important clinical study is mentioned in any section of the labeling required under §§ 201.56 and 201.57 because the study is essential to an understandable presentation of the information in that section of the labeling, any detailed discussion of the study must appear in this section.

(i) For drug products other than biological products, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in

§ 314.126(b) of this chapter and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section. For biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.

(ii) Any discussion of a clinical study that relates to a risk from the use of the drug must also refer to the other sections of the labeling where the risk is identified or discussed.

(16) *15 References.* When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(17) *16 How supplied/storage and handling.* This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information must include, as appropriate:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets) and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation;

(ii) The units in which the dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100);

(iii) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, imprinting, and National Drug Code number; and

(iv) Special handling and storage conditions.

(18) *17 Patient counseling information.* This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling. Any FDA-approved patient labeling printed immediately following this section or accompanying the labeling is subject to the type size requirements in paragraph (d)(6) of this section, except for a Medication Guide to be detached and distributed to patients in compliance with § 208.24 of this chapter. Medication Guides for distribution to patients are subject to the type size requirements set forth in § 208.20 of this chapter.

(d) *Format requirements.* All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2-inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

■ 4. Section 201.58 is revised to read as follows:

§ 201.58 Waiver of labeling requirements.

An applicant may ask the Food and Drug Administration to waive any requirement under §§ 201.56, 201.57, and 201.80. A waiver request must be submitted in writing to the Director (or the Director's designee), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or, if applicable, the Director (or the Director's designee), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200 North, Rockville, MD 20852–1448. The waiver must be granted or denied in writing by the Director or the Director's designee.

§ 201.59 [Removed]

■ 5. Section 201.59 is removed.

■ 6. Newly redesignated § 201.80 is amended by:

a. Revising the section heading;

b. Amending paragraphs (b)(2)(ii), (c)(3)(i), (c)(3)(v), and (g)(4) by removing the phrase "§ 314.126(b)" the second time it appears and by adding in its place the phrase "§ 314.126(c)";

c. Removing the phrase "induced emesis," in paragraph (i)(6);

d. Revising paragraphs (c)(2), (f)(2), and (m)(1); and

e. Adding a new sentence after the first sentence of paragraph (j).

The additions and revisions read as follows:

§ 201.80 Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).

* * * * *

(c) * * *

(2)(i) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

(ii) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

* * * * *

(f) * * *

(2) *Information for patients.* This subsection must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling. The type size requirement for the Medication Guide set forth in § 208.20 of this chapter does not apply to the Medication Guide that is reprinted in or accompanying the prescription drug

labeling unless such Medication Guide is to be detached and distributed to patients in compliance with § 208.24 of this chapter.

* * * * *

(j) *Dosage and administration.* * * * Dosing regimens must not be implied or suggested in other sections of labeling if not included in this section. * * *

* * * * *

(m) * * *

(1)(i) If the clinical study is cited in the labeling in place of a detailed discussion of data and information concerning an indication for use of the drug, the clinical study must constitute an adequate and well-controlled study as described in § 314.126(b) of this chapter, except for biological products, and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section.

(ii) When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

* * * * *

■ 7. Section 201.100 is amended by revising paragraph (d)(3) to read as follows:

§ 201.100 Prescription drugs for human use.

* * * * *

(d) * * *

(3) The information required, and in the format specified, by §§ 201.56, 201.57, and 201.80.

* * * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 8. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 9. Section 314.70 is amended by:

a. Removing from paragraph (b)(2)(v)(B) the phrase "(b)(8)(iv) of this chapter." and adding in its place the phrase "(b)(8)(iv) of this chapter; and";

b. Adding paragraph (b)(2)(v)(C);

c. Revising the introductory text of paragraph (c)(6)(iii); and

d. Revising paragraph (d)(2)(x).

The additions and revisions read as follows:

§ 314.70 Supplements and other changes to an approved application.

* * * * *

(b) * * *

(2) * * *

(v) * * *

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(*1*) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(*2*) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

* * * * *

(c) * * *

(6) * * *

(iii) Changes in the labeling, except for changes to the information required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

* * * * *

(d) * * *

(2) * * *

(x) An editorial or similar minor change in labeling, including a change to the information allowed by paragraphs (b)(2)(v)(C)(*1*) and (*2*) of this section.

* * * * *

PART 601—LICENSING

■ 10. The authority cite for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

■ 11. Section 601.12 is amended by:

a. Adding two sentences after the second sentence and before the third sentence in paragraph (f)(1);

b. Revising the introductory text of paragraph (f)(2)(i);

c. Removing from paragraph (f)(3)(i)(B) the word "and";

d. Removing from paragraph (f)(3)(i)(C) the phrase "Medication Guide." and adding in its place the phrase "Medication Guide; and"; and

e. Adding paragraph (f)(3)(i)(D).

The additions and revisions read as follows:

§ 601.12 Changes to an approved application.

* * * * *

(f) * * *

(1) * * * An applicant cannot use paragraph (f)(2) of this section to make any change to the information required in § 201.57(a) of this chapter. An applicant may report the minor changes to the information specified in paragraph (f)(3)(i)(D) of this section in an annual report. * * *

(2) * * *

(i) An applicant shall submit, at the time such change is made, a supplement for any change in the package insert, package label, or container label, except for changes to the package insert required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (f)(1) of this section), to accomplish any of the following:

* * * * *

(f) * * *

(3) * * *

(i) * * *

(D) A change to the information required in § 201.57(a) of this chapter as follows:

(*1*) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(*2*) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

* * * * *

Dated: 12/7/05
December 7, 2005.

Andrew C. von Eschenbach,
Acting Commissioner of Food and Drugs.

~~[FR Doc. 05-????? Filed ??-??-05; 8:45 am]~~

~~BILLING CODE 4160-01-S~~

275
4
~~273e~~

Dated: DEC - 7 2005
December 7, 2005.

Micheal O. Leavitt,
Secretary of Health and Human Services.

[FR Doc. 05-????? Filed ??-??-05; 8:45am]

BILLING CODE: 4160-01-S