action is contained in the Rules Docket. A copy of it may be obtained by contacting the Rules Docket at the location provided under the caption **ADDRESSES.**

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

The Proposed Amendment

Accordingly, pursuant to the authority delegated to me by the Administrator, the Federal Aviation Administration proposes to amend part 39 of the Federal Aviation Regulations (14 CFR part 39) as follows:

PART 39—AIRWORTHINESS DIRECTIVES

1. The authority citation for part 39 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701.

§ 39.13 [Amended]

2. Section 39.13 is amended by adding the following new airworthiness directive:

Fokker Services B.V.: Docket 2000–NM–293–AD.

Applicability: All Model F.28 Mark 1000, 2000, 3000, and 4000 series airplanes, certificated in any category.

Note 1: This AD applies to each airplane identified in the preceding applicability provision, regardless of whether it has been modified, altered, or repaired in the area subject to the requirements of this AD. For airplanes that have been modified, altered, or repaired so that the performance of the requirements of this AD is affected, the owner/operator must request approval for an alternative method of compliance in accordance with paragraph (b) of this AD. The request should include an assessment of the effect of the modification, alteration, or repair on the unsafe condition addressed by this AD; and, if the unsafe condition has not been eliminated, the request should include specific proposed actions to address it.

Compliance: Required as indicated, unless accomplished previously.

To detect and correct improper rigging of the liftdumper micro switches, which could result in inadvertent extension of the liftdumpers during takeoff roll, accomplish the following:

Inspection and Functional Check

(a) Within 2 months after the effective date of this AD: Perform a one-time general visual inspection for proper rigging of the liftdumper micro switches installed in the left-and right-hand sides of the pedestal; and a functional check of the micro switches; as specified in Fokker Service Bulletin F28/27–186, including Manual Change Notification MCNM F28–020, dated May 8, 2000. Perform the inspection and the check in accordance with the Accomplishment Instructions of the service bulletin. If the micro switches are not rigged within the specifications provided in the service bulletin, prior to further flight, re-rig the cam in accordance with the service bulletin.

Note 2: For the purposes of this AD, a general visual inspection is defined as: ''A visual examination of an interior or exterior area, installation, or assembly to detect obvious damage, failure, or irregularity. This level of inspection is made under normally available lighting conditions such as daylight, hangar lighting, flashlight, or droplight, and may require removal or opening of access panels or doors. Stands, ladders, or platforms may be required to gain proximity to the area being checked.''

Alternative Methods of Compliance

(b) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM–116, FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM–116.

Note 3: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM–116.

Special Flight Permits

(c) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 4: The subject of this AD is addressed in Dutch airworthiness directive 2000–073, dated May 31, 2000.

Issued in Renton, Washington, on September 13, 2000.

Donald L. Riggin,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 00–24000 Filed 9–18–00; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 00N–1463]

RIN 0910–AB78

Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require that all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use contain additional labeling information about the emergence of drug-resistant bacterial strains. The proposal reflects a growing concern in FDA and the medical community that overprescription and inappropriate use of systemic antibacterials has contributed to a dramatic increase in recent years in the prevalence of drug-resistant bacterial infections. The proposal is intended to encourage physicians to prescribe systemic antibacterials more judiciously and only when clinically necessary. The proposal is also intended to encourage physicians to counsel their patients about the proper use of such drugs and the importance of taking them exactly as directed.

DATES: Submit written comments by December 4, 2000. See section III of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Gary K. Chikami, Center for Drug Evaluation and Research (HFD–520), Food and Drug Administration, 9201 Corporate Blvd., Rockville, MD 20852, 301–827–2120.

SUPPLEMENTARY INFORMATION:

I. Background

Antimicrobial resistance among disease-causing bacteria represents a serious and growing public health problem in the United States and worldwide. Many bacterial species, including the species that cause pneumonia and other respiratory tract infections, meningitis, and sexually transmitted diseases, are becoming increasingly resistant to the antimicrobial drugs used to treat them. Several bacterial species have developed strains that are resistant to every approved antimicrobial drug, thus severely limiting the therapeutic options available for adequate treatment.

Antimicrobial resistance in bacteria is not a new problem. For as long as antimicrobial drugs have been widely available—over 50 years now—bacteria have demonstrated an ability to develop resistance by a number of mechanisms, such as antibiotic-degrading enzymes. Over the past several years, however, the incidence of resistance in both hospital- and community-acquired

infections has increased dramatically, making many common illnesses more difficult to treat than they were only 5 or 10 years ago.

The rise of resistance in the bacterium *Streptococcus pneumoniae* provides a good example. *S. pneumoniae* is a common cause of middle-ear and sinus infections, as well as several life-threatening illnesses, including pneumonia, bacteremia, and meningitis. Strains of *S. pneumoniae* that are resistant to penicillin were observed as early as the 1960's. Over the following two or three decades, however, the frequency of drug-resistant *S. pneumoniae* strains remained relatively low. Even at the beginning of the 1990's, only about 5 percent of isolates showed decreased susceptibility to penicillin (Ref. 1). But in the past few years, that number has risen dramatically. In fact, in some parts of the country, up to 40 percent of all *S. pneumoniae* isolates are now intermediately or highly penicillin resistant (Ref. 2).

In the hospital setting, antimicrobial resistance is a particularly important problem. Each year in the United States, about 2 million patients acquire an infection while receiving treatment in a health care setting (Ref. 3). According to the Centers for Disease Control and Prevention (CDC), approximately 70 percent of those infections that are bacterial in nature are resistant to at least one of the antimicrobial drugs that have traditionally been used to treat them (Ref. 4).

A. Factors Contributing to the Emergence of Resistance

Several factors contribute to the increasing prevalence of antimicrobial resistance. One of the most important is the overuse or inappropriate use of antimicrobial drugs. The amount of overuse is difficult to establish with accuracy; however, several studies have provided estimates that provide a picture of substantial overuse of these products. Office-based physicians in the United States write more than 100 million antibiotic prescriptions each year. According to the CDC, however, as many as half of those prescriptions—a total of 50 million—are inappropriate, being prescribed for the common cold and other viral infections, including influenza, against which antibiotics are not active (Ref. 5). A recent study of paid Medicaid claims for treatment of respiratory tract infections in Kentucky found that 60 percent of adults received antibiotics to treat the common cold (Ref. 6). A survey of the prescribing patterns of office-based physicians in the United States in 1992 found that approximately 12 million antibiotic prescriptions, or 21 percent of all antibiotic prescriptions to adults, were written to treat colds, upper respiratory tract infections, and bronchitis, even though over 90 percent of these diseases are caused by viruses on which antibacterial drugs would have no effect (Ref. 7).

A 1995 congressional report estimated that 25 to 35 percent of hospital patients receive antibiotics either to prevent infections associated with surgery or to treat disease (Ref. 8). Another study found that from 1980 to 1992, per capita consumption of antibacterial drugs remained relatively constant, but the total volume increased from 86 million to 110 million prescriptions (Ref. 9). Moreover, the pattern of drug use changed over this period, with increased use of broad-spectrum antimicrobial drugs such as cephalosporins and decreased use of narrow-spectrum drugs such as penicillins.

Inappropriate antibiotic prescriptions can have serious consequences. Antimicrobial use increases the selective pressure on bacteria to develop and spread resistant strains. Thus, the more an antimicrobial is used, the more likely it is that bacteria will develop resistance to it.

Incomplete treatment with antibiotics also leads to more rapid selection of resistant organisms (Ref. 10). Even when physicians properly prescribe antibiotics, antibiotic resistance is promoted when patients skip doses or do not complete the entire course of therapy. This is because suboptimal therapy may allow more resistant organisms to survive and spread in the community. Therefore, educating patients about how to take antibiotics is a necessary step in reducing antibiotic resistance (Ref. 11). Patients also need to be educated that antibiotics should not be used to treat viral illnesses.

B. Responding to the Resistance Problem

Bacterial resistance can be reduced by decreasing the use of antibacterial drugs. For example, in response to increased erythromycin resistance of Group A streptococci, Finland implemented a nationwide campaign in 1992 to reduce the use of macrolide antibiotics (the class of which erythromycin is a member). Finnish consumption of this class of drug declined by about 43 percent in the first year and it has remained at a reduced level. By 1996, erythromycin-resistant Group A streptococci had declined in Finland by almost 48 percent (Ref. 12).

Important steps in decreasing the prevalence of antibacterial resistance and slowing its future development and spread are to educate physicians and the public about the problem of antibiotic resistance and to encourage more judicious use of antimicrobial drugs. FDA believes that professional labeling can be used to accomplish these objectives. Therefore, FDA is proposing to require that the labeling for systemic antibacterial drug products include certain statements about the inappropriate use of antimicrobials and the link between inappropriate use and the emergence of drug-resistant bacterial strains. Under the proposal, the labeling would include the following reminders for physicians:

- Antibacterial drugs should only be used in situations where a bacterial infection is either proven or strongly suspected.
- The type of bacteria involved in an illness and its antimicrobial susceptibility pattern should generally be identified before an antibacterial is chosen.
- The antibacterial chosen should be targeted for the specific organism to be eradicated rather than opting for a more broad-spectrum drug.
- Antimicrobial therapy should be modified once microbiologic results (both pathogen involved and susceptibility patterns) are available.
- Patients should be counseled about the proper use of antibacterials and the importance of taking them only as directed.

C. Scope of the Proposal

The focus of this proposed rule is systemic antibacterial drug products. Bacteria, however, are not the only microorganisms that can develop resistance to the drugs designed to treat them. Viruses, fungi, and parasites have the same ability. Treatment of these infections raise some different and unique scientific and regulatory issues and the agency would like to receive comments on approaches for dealing with resistance problems that may exist for dealing with these situations. Similarly, the treatment of mycobacterial infections (e.g., tuberculosis or leprosy) raises unique issues and the drugs that are intended to treat these infections are not covered by this rule. The agency would also like to receive comments on approaches to dealing with these drugs as well. Finally, topical antibacterials and topical antiseptics are not covered by this proposal.

II. Description of the Proposed Rule

The proposed rule would amend part 201 (21 CFR part 201) by adding new § 201.24 requiring special labeling for all systemic drug products indicated to treat a bacterial infection, except a mycobacterial infection.

Proposed § 201.24(a) would require that at the beginning of the label, under the product name, the labeling must state that inappropriate use may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of the drug product and related antimicrobial agents, and that the drug product should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. Proposed § 201.24(b) would require that the ''Clinical Pharmacology'' section state that appropriate use of the drug product includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile.

Proposed § 201.24(c) would require that the ''Indications and Usage'' section state that local epidemiology and susceptibility patterns of the listed microorganisms should direct initial selection of the drug product for the treatment of the listed indications and that because of changing susceptibility patterns, definitive therapy should be guided by the results of susceptibility testing of the isolated pathogens.

Proposed § 201.24(d) would require that the ''Precautions'' subsection entitled ''General'' state that inappropriate use may increase the prevalence of drug resistant microorganisms and may decrease the future effectiveness of the drug product and related antimicrobial agents. This subsection would also include a statement that the drug product should only be used to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.

Proposed § 201.24(e) would require that the ''Precautions'' subsection entitled ''Information for Patients'' state that patients should be counseled that the drug product should be used only to treat bacterial infections and that it does not treat viral infections. The subsection would also advise physicians to counsel patients that the medication should be taken exactly as directed.

III. Effective Date and Proposed Implementation Plan

FDA proposes that any final rule based on this proposed rule become effective 1 year after the date of its publication in the **Federal Register**. After that date, new drug applications (NDA's) submitted under 21 CFR 314.50 and abbreviated new drug applications (ANDA's) submitted under 21 CFR 314.94 for systemic antibiotic drug products intended for human use (except those intended to treat mycobacterial infections) would have to comply with the labeling requirements under proposed § 201.24. Holders of approved NDA's or ANDA's would be encouraged to make the labeling changes prior to the effective date of the final rule and would submit supplements that do not require preapproval under 21 CFR 314.70(c) or 21 CFR 314.97. Holders of pending applications would submit amendments under 21 CFR 314.60 or 21 CFR 314.96. To streamline the agency's review, these supplements and amendments would include only the labeling changes proposed in this rulemaking.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation).

The agency believes this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in the two statutes cited above. The proposed rule would amend the content of the professional labeling for human prescription antibacterial drugs. Based on the analysis below, as summarized in table 1, FDA projects the annualized costs of complying with the proposed changes to be approximately $0.5 million. The agency also finds that if the proposed rule reduced the excess medical and productivity costs associated with antibacterial resistance by just 1 percent, the annual benefits would exceed $4 million. While FDA has determined that the proposed rule is a ''significant regulatory action'' as defined in section 3(f)(4) of Executive Order 12866, the proposed rule is not an economically significant rule as described in the Executive Order, because the annual impacts on the economy are substantially below $100 million. With respect to the Regulatory Flexibility Act, the agency certifies that this proposed rule will not have a significant effect on a substantial number of small entities. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation-adjusted statutory threshold is $110 million.

TABLE 1.—SUMMARY OF QUANTIFIABLE BENEFITS AND COSTS ($ MILLION)

Benefits and Costs	One-Time	Annual	Total Annualized
Benefits[1]			
Avoided cost of hospital infections		3.75	3.75
Indirect cost of longer hospital stays		0.43	0.43
Total Benefits		4.18	4.18
Costs			
One-time labeling revision	1.95		0.28

TABLE 1.—SUMMARY OF QUANTIFIABLE BENEFITS AND COSTS ($ MILLION)—Continued

Benefits and Costs	One-Time	Annual	Total Annualized
Annual incremental printing cost		0.03	0.03
Annual PDR costs		0.15	0.15
Total Costs	1.95	0.18	0.46

[1] Assumes medical and productivity costs now attribute to antibacterial resistance are reduced by 1 percent.

A. Benefits

Bacterial resistance to antibacterial drugs directly affects health care costs by requiring the use of newer and more expensive drugs and by requiring longer treatment and hospitalization periods for patients infected by resistant bacteria. Moreover, many disease-producing bacteria adapt to environmental changes and develop resistance to new drugs within a few years of widespread use thereby reducing the effectiveness of new drug therapies (Ref. 13). The societal costs of the infections from these resistant bacteria include both the direct costs for additional drugs and medical care and the indirect costs of lost productivity for patients with extended illness and increased mortality.

1. Direct Costs of Bacterial-Resistant Infections

Most studies on the cost of hospital infections in the United States have not separated infections caused by resistant bacteria from those caused by susceptible bacteria. Researchers from the CDC, examining summary reports of outbreak investigations for 1971 through 1980, as well as published and unpublished reports of infections caused by bacteria with known antibacterial resistance, found that infections from resistant bacteria were typically associated with substantially longer hospital stays. The examined studies, however, had too few subjects to allow statistical analysis (Ref. 14).

Two studies of urban hospitals in the northeastern United States have directly compared the costs of infections caused by resistant and susceptible bacteria. In the first study, using hospital discharge data from hospitals in New York City, researchers modeled differences between infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and those caused by methicillin-sensitive *Staphylococcus aureus* (MSSA). They estimated that each MRSA infection costs an additional $2,500 in direct medical costs and longer hospital stays (Ref. 15). The death rate attributable to the MRSA infection was more than double that of MSSA infections (i.e., 21 percent versus 8 percent).

In the second study, conducted at a Boston hospital, researchers examined the economic impact of antibiotic resistance in Pseudomonas aeruginosa (Ref. 16). This study compared the mortality rate, length of stay, and costs for three groups: (1) Patients with susceptible bacteria, (2) patients with some baseline resistant bacteria, and (3) patients with resistance that emerged while hospitalized. Daily hospital charges of $2,059 were the same for all three groups. Furthermore, length of stay and mortality rate were similar for patients infected with susceptible bacteria and those with baseline resistant bacteria. However, patients in which resistant bacteria emerged during hospitalization incurred additional costs of $7,340 for 3.5 extra days and had a 250 percent higher mortality rate (27 percent versus 7.7 percent).

The total number of annual infections caused by resistant bacteria is uncertain. Although diagnosis codes exist for infections with drug-resistant microorganisms, they are intended only to supplement other codes for infectious conditions and may not always be included in patient data. As a result, these hospital patient records may provide only an estimate of the minimum number of cases of drug-resistant infections in a given year. The U.S. National Center for Health Statistics publishes annual estimates of the number of diagnoses (by diagnosis code) in nonFederal short-stay hospitals from the National Hospital Discharge Survey (NHDS). For 1995 and 1997, respectively, NHDS estimates suggest about 18,000 and 43,000 cases of infections by resistant microorganisms (Refs. 19 and 20). Data from a larger national sample of hospital patients by the Healthcare Cost and Utilization Project estimate 84,000 diagnoses of resistant infections in community hospitals for 1997 (Ref. 21). Moreover, CDC hospital surveillance data of 5 known strains of resistant bacteria for 1995 suggest a much higher figure, projecting approximately 279,000 cases (Ref. 17). For this analysis, FDA has assumed the average of the 1995 data, or that 150,000 hospital acquired infections per year are attributable to resistant bacteria. Thus, assuming that patients incur additional hospital charges of $2,500 per resistant infection, the total hospital cost attributable to antibacterial resistance is estimated at $375 million annually.

2. Indirect Costs of Bacterial-Resistant Infections

In addition to direct medical costs, patients also incur indirect costs from lost productivity due to resistant bacterial infections. FDA does not know how long a typical hospital stay is extended due to antibacterial resistance. However, if just 1 extra day were needed for relatively simple cases, at an average hourly wage of $16 including benefits, each case would cost about $128 in lost productivity. For cases where few alternatives are effective against the disease-causing bacteria, as with*Pseudomonas*, patients might need an additional 3.5 days in the hospital, with lost productivity cost of about $448 per patient. Assuming the mean of these two estimates, 150,000 cases of resistant bacterial infections would cost the economy about $43 million per year in lost productivity.

3. Reduced Direct and Indirect Costs

In 1997, about 110 million antibacterial prescriptions were written by office-based physicians in the United States (Ref. 18), of which as many as half may have been inappropriate according to the CDC. The proposed rule would alter the professional labeling of these drugs to add concise information relating to the public health risks associated with their inappropriate use. The revised labeling would notify and remind physicians of these risks and prompt physicians to dissuade patients from using antibacterial drugs for diseases not caused by bacteria. These changes are expected to decrease the unnecessary consumption of antibacterial drugs and, in turn, to diminish the growth of antibacterial resistant bacteria. Although FDA cannot quantify the likely magnitude of these effects, if the proposed changes serve to avoid even 1 percent of the above estimated costs of antibacterial resistance, the potential hospital cost savings would amount to $3,750,000 per year in direct costs and $430,000

annually in indirect costs, for a total that exceeds $4 million annually. Moreover, the societal benefits of this rulemaking would be much higher than the economic cost savings because these figures do not include the value of reduced mortality or the benefits of decreasing the rate of development of resistant organisms over time.

B. Costs of Regulation

The proposed rule would require that labeling of systemic antibacterial drug products include information about the inappropriate use of antimicrobial drugs and the link between inappropriate use and the emergence of drug-resistant bacterial strains. The proposed implementation plan would require that labeling for affected prescription drug products comply with the proposed requirements within 1 year after the effective date of the final rule.

1. Affected Products

The proposed rule would affect all systemic antibacterial drug products except those primarily indicated to treat a mycobacterial infection. Antifungal, antiviral, antiparasitic, and topical antimicrobial products would not be subject to the labeling requirements of this proposed rule. Of the approximately 5,300 marketed prescription drug products in the United States, FDA estimates that 737 are antibiotic products, of which 89 are topical products excluded from these requirements.[1] The agency estimates that an additional 113 systemic antibacterial drug products would be required to conform to the labeling requirements.[2] Thus, a total of 761 drug products may be affected by the proposed rule (table 2).

TABLE 2.—NUMBER OF AFFECTED PRODUCTS

Type of Antibacterial Drug Product[1]	Number of Products
Antibiotics with 50,000 or 60,000 series NDA numbers	
Aminoglycosides	83
Cephalosporins	112
Miscellaneous Beta-Lactam Antibiotics	16
Chloramphenicol	17
Macrolides	56
Penicillins	148
Tetracyclines	75
Miscellaneous Antibiotics[2]/Combination Drugs[3]	141
Other antibacterial drug products	
Quinolones	24
Sulfonamides/Sulfones	38
Urinary Anti-Infective Drugs	18
Miscellaneous Anti-Infectives	33
Total number of affected drug products	761

[1] Excludes antifungal drug products, topical drug products, and antibacterial drug products intended to treat a mycobacterial infection.
[2] Includes 42 drug products with active ingredient(s) not on the AHFS list of antibiotics.
[3] Combination drugs contain more than one antibacterial active ingredient.

2. Professional Labeling Design Costs

Industry consultants estimate that, on average, prescription drug manufacturers would incur about $2,000 per product in design and implementation costs for a major revision in the content of professional labeling. Because changes must be made within 1 year of the effective date of the final rule, not all firms will have sufficient time to deplete their inventories of professional labeling. With a 12-month implementation period, consultants estimate per product inventory losses of approximately $570. Thus, including excess inventory losses, the cost to change professional labeling is estimated at $2,600 per product. In the first year, therefore, firms may incur one-time costs of about $2 million.

3. Incremental Printing Costs for Professional Labeling

FDA estimates that an average of 100,000 package inserts may be printed annually for each prescription drug product marketed in the United States.[3] Adding new information about prudent use of antibacterial drug products to professional labeling may increase the size of current package inserts by about 4 percent. With such a small change in the length of professional labeling (i.e., 0.4 inch for the average insert), it is unlikely that many package inserts would actually change size. Nevertheless, industry consultants estimate the cost of printing larger labels to be $0.0086 per 100 square inches. Therefore, if the affected products incurred additional printing costs for longer labeling, an estimated $35 per affected product[4] would imply incremental printing costs of less than $30,000 annually.

4. Physicians' Desk Reference (PDR) Costs

The agency estimates that up to 190 products may need slightly longer PDR listings.[5] According to its publisher, a printed page in the PDR cost $8,000 in 1998. The additional language would add approximately one-tenth of a page to an average PDR listing, costing $800 per product.[6] The annual costs of

[1] Derived from FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, 1998. Products counted had NDA numbers in the 50,000 or 60,000 series (i.e., antibiotics) and a distinct dosage form or manufacturer. This number, however, may overestimate the number of antibiotic products with distinct labeling.

[2] Derived from FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, 1998; and from the 1999 Drug Information, American Hospital Formulary Service (AHFS). Products counted had NDA numbers not in the 50,000 or 60,000 series, active ingredients matching the AHFS list of antibacterial agents, and a distinct manufacturer, active ingredient, or dosage form. Topical dosage forms were excluded.

[3] In 1996, there were approximately 133 million prescriptions for antibacterial drugs written by physicians in office and hospital settings (General Accounting Office (GAO) 1999). An estimated 45.3 million inserts accompanied these 761 drug products, or an average of 59,500 inserts per antibacterial product (45.3 million ÷ 761 products). Moreover, an assumed 40,000 additional inserts per product may be distributed annually by sales representatives as promotional material.

[4] $34.40 = 100,000 inserts/product x $0.000086/square inch x 4 square inches.

[5] 190 products is the rounded up estimate from the following calculation: 761 (drug products affected by proposed rule) x .32 (percentage of those products manufactured by innovators) x .75 (percentage of innovator products listed in PDR) = 182.

[6] $800 per product = $8,000/page x 1/10 page.

printing the larger labels in the PDR, therefore, would increase by $0.15 million.

Over 10 years, the agency estimates that the annualized compliance costs of the proposed rule would be approximately $455,000. These costs are summarized in table 3.

TABLE 3.—COSTS TO REVISE PROFESSIONAL LABELING AND INCREMENTAL PRINTING COSTS

	One-Time Labeling Revision Costs	Annual Incremental Printing Costs	Annual PDR Costs
Per product cost	$2,558	$35	$800
Number of affected products	761	761	190
Total	$1,946,638	$26,178	$152,000
Total annualized costs[1]	$277,162	$26,178	$152,000

[1]One-time costs are annualized over 10 years at 7 percent.

C. Impacts on Small Entities

The proposed rule would affect manufacturers of systemic antibacterial drug products. There are 600 pharmaceutical manufacturers in the United States. The Small Business Administration (SBA) considers firms with fewer than 750 employees to be small. As seen in table 4 below, Census data classify firms in size categories that do not permit a precise determination of the number of pharmaceutical firms that have fewer than 750 employees. However, Census data do show that more than 90 percent of pharmaceutical manufacturers have fewer than 500 employees, and thus are small businesses.[7]

Approximately 125 large and small firms manufacture systemic antibacterial drug products and thus would be affected by the proposed rule. The estimated annualized costs of $600 per product[8] are relatively modest for most manufacturers of antibiotic drugs. Therefore, the impact of the proposed rule would be significant only for those firms that manufacture many affected products. FDA reviewed the list of approved products[9] and identified only four small domestic firms that manufacture more than three antibiotic products.[10] Table 4 compares the estimated costs of compliance to reported average annual sales revenues for pharmaceutical firms of varying sizes. Because almost all manufacturers of antibiotic products in the United States have over 10 employees, the next to the last column of the table shows that these annualized costs are less than one-tenth of one percent of sales revenues. As a result, FDA certifies that this proposed rule would not have a significant adverse effect on a substantial number of small entities.

TABLE 4.—EXAMPLES OF ANNUALIZED AND FIRST-YEAR COSTS TO MODIFY PROFESSIONAL LABELING AS A PERCENTAGE OF AVERAGE ANNUAL SHIPMENT VALUE BY NUMBER OF EMPLOYEES[1]

Number of Employees	Number of Establishments	Value of Shipments (mil$)	Average Annual Per Establishment Shipment Value (mil$)	Annualized Cost to Modify One Product as a Percentage of Shipment Value[2]	Annualized Cost to Modify Two Products as a Percentage of Shipment Value[2]	Annualized Cost to Modify Three Products as a Percentage of Shipment Value[2]	First-Year Costs to Modify Three Products as a Percentage of Shipment Value[3]
Small Businesses By SBA Size Standards (fewer than 750 employees)							
1–4	152	$115.60	$0.76	0.08%	0.16%	0.24%	1.10%
5–9	73	$105.40	$1.44	0.04%	0.08%	0.12%	0.58%
10–19	101	$284.60	$2.82	0.02%	0.04%	0.06%	0.30%
20–49	110	$815.70	$7.42	0.01%	0.02%	0.02%	0.11%
50–99	65	$1,966.80	$30.26	0.00%	0.00%	0.01%	0.03%
100–249	77	$2,912.40	$37.82	0.00%	0.00%	0.01%	0.02%
250–499	56	$11,394.60	$203.48	0.00%	0.00%	0.00%	0.00%
500–999	30	$10,077.70	$335.92	0.00%	0.00%	0.00%	0.00%
Large Businesses by SBA Size Standards (750 or more employees)							
1,000–2,499	21	$14,525.70	$691.70	0.00%	0.00%	0.00%	0.00%
2,500 +	6	$8,219.40	$1,369.90	0.00%	0.00%	0.00%	0.00%

[1]U.S. Department of Commerce, Bureau of the Census,*1992 Census of Manufactures, Industry Series*, Drugs, MC92–1–28C.
[2]Average annualized per product costs = $598
[3]Average first-year per product costs = $2,792

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule does not require information collections subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Public Law 104–13).

[7] U.S. Department of Commerce, Bureau of the Census,*1992 Census of Manufactures*, Industry Series, Drugs, MC92–1–28C.

[8] Total annualized costs per product: $277,162 + $26,178 + $152,000 = $455,336. Average annualized costs: $455,336/761 = $598.34.

[9] FDA's*Approved Drug Products with Therapeutic Equivalence Evaluations*, 1998.

[10] These four small firms manufacture 6, 6, 7, and 13 products respectively.

FDA is proposing to amend its labeling regulations to require that the labeling for systemic antibacterial drug products include certain statements, specified by FDA, about the inappropriate use of antimicrobials and the link between such inappropriate use and the emergence of drug-resistant bacterial strains. These labeling statements are not subject to review by OMB because they are ''originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)) and therefore do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995.

Holders of approved NDA's and ANDA's would be required to submit supplements and holders of pending NDA's and ANDA's would be required to submit amendments to comply with the new labeling requirements. The proposed rule would also require that all new NDA's and ANDA's for systemic antibacterial drug products comply with the new labeling requirements. FDA regulations governing the submission and approval of NDA's and ANDA's, including the submission of product labeling, are in part 314 (21 CFR part 314). Recordkeeping and reporting requirements included in part 314 are approved by OMB until November 30, 2001, under OMB control number 0910–0001.

VII. Federalism

FDA has analyzed this proposed rule in accordance with Executive Order 13132. Executive Order 13132 requires Federal agencies to carefully examine actions to determine if they contain policies that have federalism implications or that preempt existing State law. As defined in the Order, ''policies that have federalism implications'' refers to regulations, legislative comments on proposed legislation, and other policy statements or actions that have substantial direct effects on the States, on the relationship between the national government and the States or on the distribution of power and responsibilities among the various levels of government.

The proposal would revise current regulations to require that all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use contain additional labeling information about the emergence of drug-resistant bacterial strains. Because enforcement of these labeling provisions is a Federal responsibility, there should be little, if any, impact from this rule, if finalized, on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. In addition, FDA does not believe that this proposed rule preempts any existing State law.

Accordingly, FDA has determined that this proposed rule does not contain policies that have federalism implications.

VIII. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this proposal by December 4, 2000. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Centers for Disease Control, ''Drug-Resistant Streptococcus Pneumoniae—Kentucky and Tennessee, 1993,'' *Journal of American Medical Association*, vol. 271, pp. 421–422, 1994.

2. Centers for Disease Control, ''Summary of Notifiable Diseases, United States, 1998,'' *Morbidity and Mortality Weekly Report*, 47 (53), December 31, 1999.

3. Centers for Disease Control, ''Public Health Focus: Surveillance, Prevention and Control of Nosocomial Infections,'' *Morbidity and Mortality Weekly Report*, vol. 41, pp. 783–787, 1992.

4. Fridkin, S., S. F. Welbel, and R. A. Weinstein, ''Magnitude and Prevention of Nosocomial Infections in the Intensive Care Unit,'' *Infectious Disease Clinics of North America*, vol. 11, pp. 479–495, 1997.

5. Centers for Disease Control, and American Academy of Pediatrics, edited by S. F. Dowell, ''Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections,'' Supplement to *Pediatrics*, vol. 101, pp. 163–164, January 1998.

6. Mainous, A. G., III, W. J. Hueston, and J. R. Clark, ''Antibiotics and Upper Respiratory Infection. Do Some Folks Think There Is a Cure for the Common Cold?,'' *The Journal of Family Practice*, vol. 42, pp. 357–361, 1996.

7. Gonzales, R., J. F. Steiner, and M. A. Sande, ''Antibiotic Prescribing for Adults with Colds, Upper Respiratory Tract Infections, and Bronchitis by Ambulatory Care Physicians,'' *Journal of American Medical Association*, vol. 278, pp. 901–904, 1997.

8. U.S. Congress, Office of Technology Assessment, *Impacts of Antibiotic-Resistant Bacteria*, OTA–H–269, U.S. Government Printing Office, Washington, DC, 1995.

9. McCaig, L. F., and J. M. Hughes, ''Trends in Antimicrobial Drug Prescribing Among Office-Based Physicians in the United States,'' *Journal of American Medical Association*, vol. 273, pp. 214–219, 1995.

10. World Health Organization, *Overcoming Antimicrobial Resistance*, WHO Report on Infectious Diseases, 2000, p. 27.

11. WHO Report, pp. 55–56.

12. Seppala, H. et al., ''The Effect of Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group A Streptococci in Finland,'' *The New England Journal of Medicine*, vol. 337, pp. 441–446, 1997.

13. Wenzel, R. P., and M. T. Wong, ''Editorial Response: Managing Antibiotic Use—Impact of Infection Control,'' *Clinical Infectious Diseases*, vol. 28, pp. 1126–1127, 1999.

14. Holmberg, S. D., S. L. Solomon, and P. A. Blake, ''Health and Economic Impacts of Antimicrobial Resistance,'' *Reviews of Infectious Diseases*, vol. 9, pp. 1065–1078, 1987.

15. Rubin, R. J. et al., ''The Economic Impact of*Staphylococcus Aureus* Infection in New York City Hospitals,'' *Emerging Infectious Diseases*, vol. 5, pp. 9–17, 1999.

16. Carmeli, Y. et al., ''Health and Economic Outcomes of Antibiotic Resistance in *Pseudomonas Aeruginosa*,'' *Archives of Internal Medicine*, vol. 159, pp. 1127–1132, 1999.

17. U.S. General Accounting Office Report, ''Antimicrobial Resistance: Data to Assess Public Health Threat from Resistant Bacteria Are Limited,'' GAO/HEHS/NSIAD/RCED–99–132, pp. 5–6, April 1999.

18. GAO Report, p. 16.

19. Graves, E. J., and B. S. Gillum, ''Detailed Diagnoses and Procedures, National Hospital Discharge Survey, 1995,'' National Center for Health Statistics Vital Health Statistics Series 13 (130):115.

20. Owings, M. F., and L. Lawrence, ''Detailed Diagnoses and Procedures, National Hospital Discharge Survey, 1997,'' National Center for Health

Statistics Vital Health Statistics Series 13 (145):118.

21. HCUPnet, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, Rockville, MD (http://www.ahrq.gov/data/hcup/hcupnet.htm).

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

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

PART 201—LABELING

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

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

2. Add § 201.24 to subpart A to read as follows:

§ 201.24 Labeling for systemic antibacterial drug products; required statements.

The labeling of all systemic drug products indicated to treat a bacterial infection, except a mycobacterial infection, must bear the following statements:

(a) At the beginning of the label, under the product name, the labeling must state:

Inappropriate use of (*insert name of antibacterial drug product*) may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of (*insert name of antibacterial drug product*) and related antimicrobial agents.

Use (*insert name of antibacterial drug product*) only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. See Indications and Usage section.

(b) In the ''Clinical Pharmacology'' section, the labeling must state:

Appropriate use of (*insert name of antibacterial drug product*) includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile.

(c) In the ''Indications and Usage'' section, the labeling must state:

Local epidemiology and susceptibility patterns of the listed micro organisms should direct initial selection of (*insert name of antibacterial drug product*) for the treatment of the indications listed below. Because of changing susceptibility patterns, definitive therapy should be guided by the results of susceptibility testing of the isolated pathogens.

(d) In the ''Precautions'' section, under the ''General'' subsection, the labeling must state:

Inappropriate use of (*insert name of antibacterial drug product*) may increase the prevalence of drug resistant microorganisms and may decrease the future effectiveness of (*insert name of antibacterial drug product*) and related antimicrobial agents.

(*Insert name of antibacterial drug product*) should only be used to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. See Indications and Usage section.

(e) In the ''Precautions'' section, under the ''Information for patients'' subsection, the labeling must state:

Patients should be counseled that (*insert name of antibacterial drug product*) should only be used to treat bacterial infections. It does not treat viral infections (e.g., the common cold).

Patients should also be told that the medication should be taken exactly as directed. Skipping doses and not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop that will not be treatable by (*insert name of antibacterial drug product*) in the future.

Dated: August 25, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 00–24007 Filed 9–18–00; 8:45 am]

BILLING CODE 4160–01–F

POSTAL SERVICE

39 CFR Part 111

Address Sequencing Service

AGENCY: Postal Service.

ACTION: Proposed rule with request for comment.

SUMMARY: This proposed rule amends section A920 of the Domestic Mail Manual (DMM) to enhance customer service and to provide notice of new safeguards to protect the ownership of customer address lists.

DATES: Comments must be received on or before October 19, 2000.

ADDRESSES: Written comments should be sent to Manager, Address Management, USPS, 6060 Primacy Pkwy, Ste 201, Memphis, TN 38188–0001. Copies of all written comments will be available for inspection and photocopying between 9 a.m. and 4 p.m., Monday through Friday, at the above address.

FOR FURTHER INFORMATION CONTACT: DeWitt Crawford, (901) 681–4612, or Susan Hawes, (901) 681–4661.

SUPPLEMENTARY INFORMATION: The manual address card sequencing process that has been available for many years has become too labor intensive and expensive for some mailers to maintain. An increasing number of customers have requested the adoption of a more efficient and cost-effective procedure for the sequencing of address lists. In response, the USPS is proposing an electronic address sequencing service for those customers who want to discontinue the production and processing of manual address cards. This proposal is an outgrowth of meetings the USPS conducted with saturation mailer groups and the Mailers Technical Advisory Committee (MTAC).

To ensure the integrity of the qualification process for the electronic sequencing service, all USPS-qualified walk sequence address files will contain seeded addresses known only to the list owner and the USPS. This will help guard against the fraudulent submission of rented lists for qualification. If a request for sequencing contains a seeded address, and all known possibilities of fraud cannot be ruled out, the request will be denied and the owner of the seeded address and the Postal Inspection Service will be notified. Notification will include requester's company name, ZIP Code, and level of address group requested for qualification.

Customers will be allowed three attempts to qualify a ZIP Code within a six-month period. Failure to qualify within this time frame will result in a suspension of one year from further attempts to qualify the ZIP Code.

To protect the integrity of customer address lists, and to add a level of security, all customer requests for DMM A920 card and electronic processing will be posted for 90 days on a password-secured USPS Address Sequencing Service Web site. Company name, ZIP Code, and requested address groups will be listed. This will enable USPS-qualified list owners to monitor possible misuse of their rented or leased address lists. Only USPS-qualified list owners will be able to access the Web site.

Summary of Proposed Change

Proposed DMM sections A920.1.0 through A920.6.4 provide an electronic address sequencing service for those customers who want to discontinue the production and processing of manual address cards.