

Sections 510(j)(1), (i), and (p), and 701(a) of the act also give us the discretion to require that registration and listing information be submitted in electronic format. Electronic receipt of registration and listing information would enable us to shift resources from more ministerial tasks, such as data entry, to the important public health objectives described previously in this document. Additional authority for requiring that content of labeling be submitted in electronic form stems from, among others, sections 201(n) and (p), 501, 502, 503, 505, 510(j)(1)(A) and (j)(1)(B), and 512 of the act. The certification requirement would help us with the efficient enforcement of the act because we would be able to distinguish between situations where there has been noncompliance with registration and listing requirements from situations where there have been no changes in information. The failure to register or list is a prohibited act under section 301(p) of the act and the failure to do either renders a drug misbranded under section 502(o) of the act.

We also have the authority to require the appropriate NDC number (in human-readable form) on certain drug labels for the efficient enforcement of various sections of the act. The appropriate NDC number in human readable form would, among other things, serve as a backup for the appropriate NDC number encoded in the bar code. That is, the human readable form of the NDC number could be manually keyed into a computer system by a health care provider if the bar code is damaged, cannot be read, or is otherwise illegible. Our legal authority to impose the human readable NDC number requirement, at least in part, is similar to that for requiring bar codes on labels (69 FR 9120, 9147–9149). These sections include sections 201(n) and (p), 501, 502, 503, 505, and 701(a) of the act, and sections 351 and 361 of the PHS Act.

Other sections of the act also provide authority for the human-readable NDC number requirement. The failure to register and list are prohibited acts and render drugs misbranded under sections 301(p) and 502(o) of the act. It would be possible for FDA investigators to read the NDC number on the drug's label and review information in our database to ascertain compliance with registration and listing requirements. Where a drug does not bear the appropriate NDC number, investigators can conduct further followup to discern, for example, whether there has been a failure to comply with registration and listing requirements (including those for NDC numbers). Accordingly, sections 201, 301(p), 502(o), 510, and 701(a) of the act provide additional authority for requiring the appropriate NDC number in human readable form on certain drug labels.

There is also additional legal authority for the rule's requirements as to biological products regulated under the PHS Act. Section 351(a) of the PHS Act provides for the approval, as well as the suspension and revocation, of biologics license applications. The human-readable NDC requirement for biological drugs and blood and blood components is designed to ensure the continued safe and effective use of licensed biological products. Additionally, section 361 of the PHS Act authorizes regulations necessary to prevent the introduction, transmission, or spread of communicable diseases. With specific regard to blood and blood components, the human-readable NDC number requirement will aid in the control of units that are at risk of spreading communicable diseases.

VI. Analysis of Economic Impacts

A. Introduction

We have examined the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4), and the Congressional Review Act.

Executive Order 12866 directs regulatory 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). This proposed rule is not considered economically significant under Executive Order 12866.

Under the Regulatory Flexibility Act (as amended by the Small Business Regulatory Enforcement Fairness Act), if a regulation has a significant economic impact on a substantial number of small entities, we must analyze regulatory options that would minimize the impact on small entities. We have conducted a preliminary regulatory flexibility analysis for the proposed rule, and we believe it will not have a significant impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 (UMRA) requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in expenditures by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any one year. Currently, such a statement is required if costs exceed about \$115 million for any one year. UMRA does not require us 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 \$115 million.

The Congressional Review Act requires that regulations determined to be major must be submitted to Congress before taking effect.

We contracted with the Eastern Research Group, Inc. (ERG), to collect data, interview industry experts, and estimate the costs and benefits of the proposed rule. The analysis and references in support of the effects of the proposed rule are summarized in table 2 and are included in the docket as Reference 3. Although we were unable to quantify specific benefits attributable to the proposed rule, we believe the ultimate use of electronic registration and listing data justify taking this action.

TABLE 2.—SUMMARY OF ANNUAL COSTS AND BENEFITS OF THE PROPOSED RULE¹

Annual Discount Rate	Average Annual Costs (in Millions)	Average Annual Benefits	Average Annual Net Benefits
3%	\$5.6	Unquantified. Benefits accrue by having accurate and unique identification of drugs that would allow greater use of technology.	N/A
7%	\$5.8	Unquantified. Benefits accrue by having accurate and unique identification of drugs that would allow greater use of technology.	N/A

¹Based on 10-year evaluation period.

B. Objective

The objective of the proposed regulation is to update our process for registering drug establishments and listing drugs. The current system does not allow for timely updates of important information and the current system for NDC numbers has introduced the potential for the misidentification and mistaken administration of drugs. We believe that electronic submission of registration and listing information, as well as our assignment of specific identifiers (i.e., the NDC number), would improve the quality and timeliness of information available to health care professionals and consumers. We further believe that these quality improvements would result in safer and more effective use of drugs by providing up-to-date and easily accessible relevant

information. We also believe that we should develop and maintain a high quality database of drugs available on the market to enhance future uses of technology in the delivery of health care.

C. Baseline Conditions and Scope

As discussed elsewhere in this preamble, we currently maintain databases that contain establishment registration and drug listing information. However, these databases rely on paper forms that manufacturers, repackers, relabelers, drug product salvagers, and private label distributors of drugs (both human and animal) must submit to us. The completed forms are then entered into our databases. These databases are intended to include identification of establishments involved in the manufacturing, preparation, propagation, compounding or processing of drugs, including the repacking, relabeling, and salvaging of drugs (human and animal prescription and OTC drugs, as well as active pharmaceutical ingredients), the procedures that take place at each establishment (e.g., repacking, or relabeling), and a list of each drug being manufactured, prepared, propagated, compounded, or processed for commercial distribution at each site. We rely on these databases to identify manufacturers, repackers, relabelers, drug product salvagers, and private label distributors, of human and animal drugs, specific drugs or ingredients, to facilitate recalls or information alerts in the case of potential safety concerns, and to otherwise exercise competent oversight of this important industry.

The quality and completeness of these databases depends on prompt submission of updated information from manufacturers, repackers, relabelers, drug product salvagers, and (currently) private label distributors, as well as our immediate inclusion of the data into our system. We are currently unable to verify the accuracy of the information submitted, and some manufacturers,

repackers, relabelers, drug product salvagers, and private label distributors are not prompt in informing us of changes. For example, some changes in processing or packaging might be submitted periodically rather than when such changes actually occur. In addition, forms may be mishandled, or even lost, which further reduces confidence in the databases.

Using a 5-digit labeler code, we estimate that we have the capacity for NDC numbers for up to 100,000 registered establishments, each having a capacity for up to 100,000 product/package size combinations (using the 5 remaining digits). If a registered establishment requires more than 100,000 product/package size codes, we could issue that establishment an additional labeler code. We currently have about 25,000 active establishments in our registration database, utilizing less than half of the 5-digit labeler code capacity. We currently issue about 1,000 new labeler codes annually. If we reach NDC number capacity (possibly in 30 to 50 years), we could propose to either add alphanumeric capability or expand the number of numeric digits to 11 or 12 (current § 207.35(b)(2)(i) states that FDA will go from a 5- to 6-digit labeler code if needed). This change in NDC numbers will necessitate advances in current UPC technology (due to the need for bar code reading), which we anticipate will likely occur prior to our reaching the 10-digit NDC numeric capacity.

TABLE 2A.—COUNT OF POTENTIALLY AFFECTED HEALTHCARE ENTITIES

Type of Entity	Establishments	Source	Additional Comment
Pharmaceutical manufacturers (human)	666	Orange Book, 2003	Includes only those pharmaceutical firms that have at least one currently marketed product in the United States. Might be an overestimate due to the possibility of applicant name duplication in the database. Does not include firms that only manufacture unapproved drug products.
Pharmaceutical manufacturers (animal)	80	Census, 2004	Includes firms that own establishments that manufacture animal drugs. Includes some firms that manufacture both human and animal drugs, so overstates the number that manufacture animal drugs exclusively. Does not include firms that only manufacture unapproved drug products.
Pharmacies	67,434	Listed below	Sum of pharmacy categories (chain store headquarters offices are not counted in this total)
Chain store (headquarters office)	25	NWDA, 2000	Covers headquarters for firms ranging from CVS (4,100 stores) to companies operating over approximately 35 stores.
Chain	20,493	NACDS, 2001	National Association of Chain Drug Stores Web site (http://www.nacds.org)
Independent	24,500	NCPA, 2002	National Community Pharmacists Association Web site (http://www.ncpanet.org)
Mass merchant	5,910	NACDS, 2001	National Association of Chain Drug Stores Web site (http://www.nacds.org)

TABLE 2A.—COUNT OF POTENTIALLY AFFECTED HEALTHCARE ENTITIES—Continued

Type of Entity	Establishments	Source	Additional Comment
Supermarket	8,531	NACDS, 2001	National Association of Chain Drug Stores Web site (http://www.nacds.org)
Institutional	7,950	ERG, 2001	Profile of the Pharmaceutical Compounding Industry: Draft Final Report. Submitted to FDA, Office of Policy, Planning, and Legislation, Office of the Commissioner, August 27, 2001.
Mail order	50	ERG, 2001	Based on discussions with Winkelman (2004)
Pharmacy benefit management companies (PBMs)	76	ERG, 2001	Profile of the Prescription Drug Wholesaling Industry: Final Report, February 12, 2001. Submitted to Office of Policy, Planning, and Legislation, Office of the Commissioner, FDA. The figure is reported by SMG Marketing Group, Inc.
Hospitals	6,116	AHA, 2002	American Hospital Association Web site (http://www.ahadata.org)
Compendium companies	5	ERG, 2004	Estimate based on discussions with Winkelman (2004)
Wholesalers/distributors	6,500	ERG, 2001	Profile of the Prescription Drug Wholesaling Industry: Final Report, February 12, 2001. Submitted to Office of Policy, Planning, and Legislation, Office of the Commissioner, FDA. The report notes that this is probably an underestimate.
Group purchasing organizations	701	ERG, 2001	See note in previous row.
State Medicare agencies	50	ERG, 2003	Allocated one per State.
Physician offices	195,655	Census, 2000	NAICS 62111 from County Business Patterns 2000, U.S. Census Bureau.
Dentist offices	116,494	Census, 2000	NAICS 62121 from County Business Patterns 2000, U.S. Census Bureau.

Note: ERG did not include various health care facilities, such as nursing homes and rehabilitative care facilities, that generally do not have on-site pharmacies.

The pharmaceutical and biological products industries (as defined by the North American Industrial Classification System (NAICS)) consist of 1,218 establishments (NAICS 325412 and NAICS 325414). ERG examined the 2003 “Approved Drug Products With Therapeutic Equivalence Evaluations” (the “Orange Book”) to estimate the number of companies currently operating establishments that are marketing drugs. While the Orange Book covers only products approved under section 505 of the act, there is sufficient overlap between manufacturers of products listed in the Orange Book and manufacturers of other types of products (e.g., manufacturers of OTC monograph products and animal drugs) to provide a basis for estimating the industry sector affected by the proposed rule. ERG estimates that a total of 666 companies own and operate manufacturing establishments. In addition, according to U.S. Census data, there are an estimated 80 companies that manufacture animal drugs in the United States. (There is likely overlap between human and animal drug companies.) Finally, the packaging and

labeling services industry (NAICS 561910) consists of 229 companies. Each of these establishments would be affected by the proposed rule.

Several provisions of the proposed rule affect establishments rather than companies. We used FDA's drug registration system to estimate that there are approximately 9,700 domestic sites.

There are approximately 200,000 distinct packaged products of human and animal (both prescription and OTC) drugs. The information generated by the drug listing process is used by many organizations for many purposes. Each specific drug is entered into our listing database. If the drug is later withdrawn from the market, for example, this is also noted. The pharmaceutical industry is undergoing corporate changes through mergers, acquisitions, and closings. These activities result in additional reporting requirements (via the current paper system) to keep our databases up-to-date. However, the magnitude of information required to keep the system current and the number of activities that would generate changes in the data have weakened our ability to rely on the current database.

In addition, the current drug listing system includes the use of the NDC system. Using this system, manufacturers, repackers, and relabelers of drugs (including human prescription, human OTC, certain biologics, and animal drugs) assign unique NDC numbers to each drug. An NDC number consists of 10 characters, including a 4- or 5- character labeler code, a 4- or 3- character product code, and a 1- or 2- character package code, and is presented in one of three formats (4-4-2, 5-3-2, or 5-4-1). Manufacturers, repackers, and relabelers notify us of the assigned NDC number at the time of drug listing, and the numbers may be printed on the label and labeling of each drug.

As discussed earlier in this document, we currently assign the labeler code to registered manufacturers, repackers, and relabelers of drugs. The manufacturer, repacker, or relabeler assigns the product code and package code to its drugs and must report the NDC number to us. Currently, when a manufacturer, repacker, or relabeler withdraws a drug from the distribution chain, NDC numbers for the discontinued drugs may be reused after 5 years.

This process and format for NDC numbers was introduced over 20 years ago as a means of identifying individual drugs by distinguishing, among other things, between specific strengths and package sizes for reimbursement purposes. Since the NDC system was created in 1969, a variety of uses for the NDC number have developed within the healthcare industry.

We have used the NDC number to facilitate recalls of drugs for a number of years. The identification system allows for notification throughout the distribution chain in the event of a recall or other warning about specific drugs.

The development of computerized systems and the ability to electronically transmit information have had a major effect on the ways NDC numbers are used. Because the NDC numbers are designed to be unique identifiers, many sectors of the industry have built systems to maximize the usefulness of this information. Compendium service companies assemble and distribute information to retail stores, hospitals, prescription benefit managers (PBMs), insurance companies, and electronic medical record companies among other users. These users rely on NDC numbers to identify drugs within their tracking or processing systems. The NDC numbers are incorporated into their internal software to facilitate scanning (such as by cashiers or hospital personnel) or for the operation of data processing systems for reimbursement (both private and public) or inventory management. In addition, these compendium

databases often include drug price information directly associated with the NDC numbers.

In some cases, the designers of the information systems that use NDC numbers convert the NDC number for use in industry databases. They add a zero to result in a consistent 11-digit format (5-4-2). Also, while visual use of NDC numbers uses hyphens to differentiate between the labeler-product-package codes, these hyphens are not read when scanned (as a bar code, for example). Because three formats are used within the current NDC system, removing hyphens introduces potential duplicates.

Other government entities, such as the Center for Medicare and Medicaid Services (CMS) and the Drug Enforcement Administration (DEA) use the NDC numbers to meet their mission requirements. The numbers are used to provide data for negotiated rebates or notification of distribution of controlled substances.

Companies are continually updating their drug information and price data. Generic relabeling companies and OTC manufacturers often repackage or remarket their products. These fairly constant revisions present a challenge to both compendium companies and us because maintaining the accuracy of the NDC database relies on prompt notification of any changes, but notification is not always prompt or consistent.

The NDC components (labeler, product, and package codes) have presented issues that may compromise the current database. For example, we assign only one labeler code to each manufacturer, repacker, or relabeler, but many companies have multiple labeler codes due to mergers and acquisitions and may use them to distinguish between different divisions within the new company. Pharmaceutical companies have taken different approaches to

handling product codes. For example, some firms assign product codes sequentially while others use predefined blocks of numbers for each operating division. Similarly, the methods used to assign package codes are not uniform.

Many repackers currently use the manufacturer's NDC number instead of their own when repacking drugs into smaller packages for pharmacies. Among the reasons such repackers do this is because Medicaid and other third-party payers use the NDC number presented on the drug to file rebate claims with the manufacturers. Such repackers sometimes present the manufacturer's NDC number in an effort to fall under the manufacturer's agreement with payers.

D. The Proposed Regulation

This proposed regulation would require the electronic submission of registration and listing information. The proposed rule would require, for example, drug product salvagers to list drugs and would not permit private label distributors to register establishments or list drugs, and would specifically define the responsibilities associated with each type of establishment covered by the proposal. The proposed rule would not permit manufacturers, repackers, and relabelers to assign the product code and package code for newly listed drugs. We would assign the entire NDC number for drugs.

Under the proposed rule, the electronic establishment registration and drug listing system must be used to enter and update all registration, listing, and NDC number information no later than 9 months after the effective date of a final rule. (We are proposing that any final rule based on the proposal become effective 90 days after publication in the **Federal Register**.) Manufacturers, repackers, and relabelers would have until 9 months after the effective date of a final rule to review and update the NDC number information

in our databases for each of their drugs to ensure that it complies with the proposal. In addition, manufacturers, repackers, and relabelers would have, for prescription drugs, 3 years after the effective date of a final rule and, for OTC drugs, 7 years after the effective date of a final rule, to ensure that the appropriate NDC number correctly appears on the label of each of their listed drugs, in accordance with the proposal. These costs have been accounted elsewhere in this analysis.

By requiring electronic drug registration and listing, this proposed rule would enhance the use of technology and provide the basis for efficiencies in the proper use of drugs. For example, the use of bar coded information to avoid adverse events associated with medication errors requires consistent information on the drug label. Other initiatives, such as electronic prescribing, may require the electronic accessibility of this information. This proposed rule would be an important step for the timely and useful availability of information that would benefit patients.

E. Costs

The major potential cost of the proposed rule is the assignment of NDC numbers by FDA. Although the proposed rule includes a selected alternative to minimize this cost, the potential impact could be very large, and is discussed in the Alternatives section of this document. Other costs associated with electronically submitting registration and listing information are discussed later. Costs have been analyzed and discounted using the methodology suggested by OMB's Circular A-4 (September 2003).

1. Costs of a Single Method of Assigning NDC Numbers

Currently, each manufacturer, repacker, and relabeler has its own method for assigning the product code and package code to its drugs. Under the

proposed rule, we would assign the product code and package code. Existing NDC numbers would not be affected, as long as they meet the proposed requirement for NDC numbers.

Because, the proposed changes to the NDC numbering system would affect product codes and package codes, and because NDC numbers are used by some sectors of the health care industry for reimbursement or inventory purposes, we expect that the proposed changes would have some effect on the data processing infrastructure. The primary area of impact would be in PBM tasks such as generation and maintenance of drug formularies for insurance coverage purposes. Other areas that would be affected include data analyses conducted by manufacturers, repackers, and relabelers, especially with respect to rebate predictions and market forecasts.

a. *Pharmaceutical manufacturers.* Changes to the NDC number would likely affect rebate processing by manufacturers as well as the ability of pharmaceutical firms to conduct market research analyses.

Common practice in the prescription pharmaceutical industry includes agreements that provide rebates from manufacturers to large insurance payers for use of a manufacturer's drugs by the insurer's enrollees. Medicaid and other large programs have negotiated these rebates with individual manufacturers. Each firm's staff reviews invoices, makes corrections, resolves disputes, and remits rebate payments to insurers based on reported volumes of sales to patients enrolled in the insurance plans. Most manufacturers use the current NDC numbers to identify the dispensed products during this process. A common practice among manufacturers is to group reimbursement data by product code in order to analyze payment history and resolve disputes with insurance carriers.

Because new product codes may be assigned without sequencing under the proposed rule, this may require manufacturers to devote more staff-time to manually group products for rebate processing. Additional data entry work would be required if, for example, an additional data field were added to reports in order to retain the ability to sort products on the basis of product codes.

Market research departments within the pharmaceutical industry also use the current configuration of NDC numbers when conducting analyses that affect product pricing and packaging. The ability to sort by product code allows for efficient use of data records, and randomization of product codes would result in additional staff-time to conduct rebate processing.

Initially, the loss of the ability to group products based on sequential product codes could require staff to either manually sort products or map the new randomized NDC number into another, internal sorting system. Over time, as new NDC numbers are assigned with new product codes and package codes, we expect that all manufacturers, repackers, and relabelers would eventually use automated mapping systems to track product codes. ERG has determined through interviews with industry information technology staff that it would take approximately 80 hours of programming to devise, validate, and introduce an automated mapping system for each affected company. In addition, ERG interviews determined that approximately 100 new packaged products are marketed per year for each manufacturer, and it would take approximately 0.083 hours (5 minutes) per product to map and validate the assigned NDC number to a new internal number for each internal database. ERG further determined that an average manufacturer is likely to have three internal databases that would utilize the new NDC numbers. Each manufacturer would

require about 25 hours of programmer time per year in maintenance of these systems. The 2003 Bureau of Labor Statistics (BLS) has published hourly pay and benefit rates of \$64 for senior computer programmers. Thus, each manufacturer would incur first-year costs of about \$5,100 (80 hours x \$64 per hour) and annual costs of about \$1,600 (100 product packages x 0.083 hours x 3 databases x \$64 per hour). During 2003, according to estimates based on FDA's Orange Book and the Census of Manufacturers, 746 manufacturing companies marketed at least one prescription, OTC, or animal drug product in the United States (666 domestic human drug manufacturers and 80 domestic animal drug manufacturers). These manufacturers would incur first-year costs of \$3.8 million (\$5,100 x 746 companies) and annual costs of \$1.2 million (\$1,600 x 746 companies) because of newly assigned product codes and package codes.

Although not included as a cost of the proposed regulation, we estimate that foreign manufacturers of drug and biological products would incur first-year and annual costs due to the proposed rule. The magnitude of any costs would depend on the specific prevailing wage rate for computer programmers in the respective countries. We note that foreign establishments would also experience some increase in costs because of the proposed rule. OMB Circular A-4 allows for the consideration of regulatory costs to foreign establishments, and requires such an analysis if the costs are significant. However, the relatively small marginal costs of the proposed rule and the uncertainty of the effect, if any, on consumer prices convinced us to limit the analysis on the costs to domestic establishments and companies.

b. *Pharmacies.* We believe that retail pharmacies (that would not be required to register or list) would generally be unaffected by the proposed rule

because most pharmacy processing systems do not use the internal component of NDC codes. In those cases where pharmacies use the components, we believe software vendors will make any appropriate revisions.

However, ERG found that large pharmacy chains were concerned about possible changes in NDC numbers. Some large chains use the current NDC numbers for the adjudication of claims. ("Adjudication" refers to the process by which pharmacists submit reimbursement claims to customer health plans.) Most formularies are built and maintained by PBMs or individual State Medicaid plans, but the chains have noted an increase in smaller plans that are maintained by individual retail stores. In order to serve these small, local insurance plans, data entry staff at the participating stores enter NDC numbers of the requested drugs using "wild card" symbols (such as asterisks) to indicate that any number in the wild card position is acceptable. For example, the package code of an NDC number may be entered as a wild card symbol to indicate that any package or strength of the indicated product is acceptable for reimbursement under that specific insurance plan. This ability allows data entry clerks to add groups of products quickly.

The proposed assignment by us of product codes and package codes could affect this practice. Several executives in the chain drug industry asserted to ERG that this change would result in possibly hiring as many as four additional data entry clerks. Although other respondents felt that this claim overstated the expected increased effort, they could not provide alternative estimates. According to the BLS, the annual salary for a data entry operator in 2003 was \$33,240 plus about 38 percent in benefits. We have used approximately \$50,000 per year as typical annual compensation for this industry. Therefore,

using this estimate of additional staff, each affected chain would experience an increased annual cost of \$200,000 (4 additional clerks x \$50,000).

According to the National Wholesale Drug Association, there are 25 large chain headquarters offices of corporations that operate at least 35 separate retail drug store outlets. ERG expects that only 10 percent of these corporations would potentially be affected by the proposed rule because relatively few chain stores use software that enables the use of "wild card" data entry for portions of the NDC numbers. This results in total industry annual operating costs of \$500,000 (25 large chain operations x 0.10 x \$200,000).

c. Pharmaceutical benefit managers. PBMs are the entities that build formularies and adjudication services for insurance plans. The software used for these services usually makes use of the NDC number. For example, when a PBM builds a formulary for an insurance plan, the data entry staff may enter the NDC numbers of the selected drugs into processing software. As discussed previously in the section on the expected effect on retail pharmacy chains, wild card symbols may be used to indicate that any number in the position of the wild card symbol is acceptable to the formulary and, thus, reimbursable. This practice works in cases where the product code of the NDC number is in sequence. In some cases, only the labeler code may be entered and wild card symbols are used for the rest of the NDC number to signify that any product from that company (i.e., manufacturer, repacker, relabeler, or private label distributor) is acceptable. This use of wild card symbols allows data entry clerks to quickly add groups of products, and according to respondents of ERG interviews, saves substantial time. Several managers of PBMs suggested that manual entry of all NDC numbers would be similar to those of pharmacy chain operators and could result in hiring as many as four additional employees

(FTEs) per year. Using the BLS data, the annual salary of \$33,240 and industry benefits of approximately 38 percent of salary results in typical compensation of around \$50,000 per FTE. If so, then increased costs to PBMs would be approximately \$200,000 per year per affected PBM (4 additional clerks x \$50,000).

However, not all PBMs would be affected by this change in NDC numbers. In discussions with ERG, only one supplier of adjudication software was identified as providing the "wild card" feature. This provider estimated that his clients constituted about 10 percent of the industry, so we have assumed that about 10 percent of the PBMs use this feature. Therefore, ERG has estimated that only 10 percent of PBMs would likely experience increased costs because of the proposed rule. ERG identified 76 PBMs for a 2001 profile of the prescription drug wholesaling industry (Ref. 4). Using this estimate, annual costs of the proposed rule for this industry segment are estimated to be \$1.5 million (76 PBMs x 0.10 affected by the proposed rule x \$200,000).

d. *Other entities.* ERG examined the potential effect of the proposed revisions to the NDC number on hospitals, compendium companies, wholesalers/distributors, group purchasers, State Medicaid agencies, physician offices, and dental offices. None of these sectors were identified as being significantly affected by the proposed rule. These sectors maintained that as long as the NDC number maintained its format, any adjustments would be minimal. In particular, respondents asserted that preservation of the labeler code in the NDC number would be sufficient for many of these users of NDC numbers. Other users of the NDC numbers (such as hospitals) are expected to be able to accommodate any changes without major modifications to their data systems.

e. *Total costs of NDC number revision.* Overall, we expect that revising the process by which NDC numbers are assigned will have a one-time cost during the first year of \$3.8 million and annual, recurring costs of \$3.2 million.

2. Other Costs of the Proposed Rule

Potential costs of the proposed rule also include: (1) The costs and cost savings for obtaining NDC numbers and recurring electronic registration and listing submissions; (2) the costs of label revisions for some drugs to include NDC numbers; (3) the costs of setting up electronic submissions of registration information, listing information, and content of labeling; and (4) the costs of continuing the submission of content of labeling. In addition, discussions with industry revealed two areas of potential concern that are not specific costs of the proposed rule. The first area of concern is potential delay in the assignment of NDC numbers, and the second area of concern is the use of repacker or relabeler NDC numbers on drug labels (rather than the manufacturer's NDC number) and the effect on negotiated reimbursements with third-party payers, including CMS.

a. *Costs and cost savings for obtaining NDC numbers and recurring electronic registration and listing submissions.* This category consists of eight types of identified costs or cost savings:

- Costs for prospectively obtaining NDC numbers for human prescription drug products, human OTC drug products, animal prescription drug products, animal OTC drug products, and active pharmaceutical ingredients.
- Costs for electronic submission of new drug listings.
- Costs for electronic submission of changes to drug listings.
- Costs to certify no drug listing changes.
- Costs for drug product salvagers to list.

- Costs to register new establishments electronically.
- Costs to review and update establishment registration electronically, including certifying no changes.

- Costs to obtain user accounts from FDA.

Currently, manufacturers, repackers, relabelers, and drug product salvagers register establishments and (except for salvagers) list their drugs. This can be a time-consuming procedure involving different forms that collect data for later computer entry. Forms must be completed by hand and changes to information to be submitted to us require that the entire form be redone.

With electronic submission of this information under the proposed rule, information may be keyed in and any changes may be made to the information submitted. Information would not have to be resubmitted each time. We expect the proposed rule will result in substantial time and cost savings in the use of electronic submissions.

New NDC numbers for drugs: ERG used FDA drug listing data to determine that over 11,000 new domestic drug listings occur each year (foreign drug listings are not counted in this analysis). The time required to submit information and coordinate with FDA for an NDC number is estimated to be 0.5 hours per drug (incremental to the time required for a firm to assign NDC numbers to themselves.) The BLS reports that the compensation (including benefits) for a mid-level manager within this industry is \$51.73. We expect the annual cost to obtain NDC numbers for new drugs to equal about \$0.3 million (11,000 new drug listings x 0.5 hours x \$51.73 per hour.)

Electronic submission of new drug listings: Currently, it takes approximately 2.5 hours to compile, copy, and mail drug listings to FDA. The annual cost for this activity is currently \$1.4 million (11,000 drug listings x

2.5 hours x \$51.73 per hour.) We expect that this activity will only require approximately 1 hour per drug listing if submitted electronically under the proposed rule. The annual cost would then be \$0.6 million (11,000 new drug listings x 1 hour x \$51.73 per hour.) Electronic submission of drug listings would result in annual cost savings of \$0.8 million.

Electronic submission of changes to drug listings: Currently, any changes to drug listings entail that the entire form be redone by hand. Therefore, approximately 2.5 hours is currently required to compile, copy, and mail any change to FDA. FDA's drug listing data estimate that there are approximately 36,000 changes to domestic drug listings each year. The current cost of this activity is \$4.7 million (36,000 annual changes x 2.5 hours x \$51.73 per hour.) Electronic submission of changes is expected to require only 0.5 hours per submission. The expected annual cost of using electronic submissions would be \$0.9 million (36,000 annual changes x 0.5 hours x \$51.73 per hour). Electronic submission of changes to drug listings would result in annual cost savings of \$3.8 million.

Electronic certification of no drug listing changes: As discussed earlier in this document, there are 83,600 domestic drug listings that must be reviewed twice a year to certify that there are no changes to the listing. There are approximately 36,000 annual changes to domestic drug listings, so we expect 131,200 annual certifications ((83,600 drug listings x 2 annual reviews)—36,000 changes). The time required to electronically certify that there have been no changes is not expected to be more than 0.25 hours (15 minutes.) The total cost of certification of no drug listing changes is \$1.7 million (131,200 annual certifications x 0.25 hours x \$51.73.)

Drug product salvagers: According to industry experts, only about 5 percent of all listed drugs may be salvaged during any year. According to our listing data, there are approximately 83,600 domestic drug listings (foreign listings are not counted here), so approximately 4,200 domestic drugs are estimated to be salvaged each year ($83,600 \times 0.05$.) Since the original manufacturer usually acts as the salvager, under the proposed rule, the original drug listing would be available electronically and could be easily copied to produce the drug listing for the salvaged drug. We expect that copying and submitting that drug listing (or withdrawal) would take 0.167 hours (10 minutes) and result in total annual costs of only \$36,000 ($4,200$ salvaged drugs \times 0.167 hours \times $\$51.73$ per hour.)

Electronic submission of new establishment registrations: According to our registration database, there are an average of approximately 1,100 new sites registered each year, of which about 900 are domestic. The current registration process for new establishments takes 2.5 hours. The annual cost to register new establishments is about \$0.1 million (900 new domestic registrations \times 2.5 hours \times $\$51.73$ per hour). The proposed rule will require new registrations to be done electronically and we expect this will take approximately 1 hour per registration. The cost of registering new establishments with the proposed rule would equal about \$47,000 (900 new domestic registrations \times 1 hour \times $\$51.73$ per hour.) The use of electronic submissions for new establishments would result in cost savings of about \$0.1 million.

Electronic review and update of establishment registration: There are currently 9,700 domestic registered sites that must reregister each year, including certification of no changes to their registration information, and there are about 1,500 annual updates to domestic registration forms. The current

estimate for this activity is 2.5 hours per submission for a current cost of about \$1.4 million ((9,700 registered sites + 1,500 annual updates) x 2.5 hours x \$51.73 per hour). We expect each annual registration will take 0.5 hours and each amendment will be expedited and take only 0.25 hours under the proposed rule. Annual registration would have a cost of about \$0.3 million (9,700 registered sites x 0.5 hours x \$51.73 per hour). FDA has estimated that expedited updates of changes to registration under the proposed rule would require only 0.25 hours (15 minutes) per update. The cost of this activity under the proposed rule would be only \$20,000 (1,500 annual updates x 0.25 hours x \$51.73 per hour.) This includes the costs to review and certify that there are no changes to registration information. The proposed rule is expected to result in annual cost savings of \$1.1 million from electronic review and update of establishment registration.

FDA user accounts: Prior to submitting electronic registration and listing information, the proposed rule requires manufacturers, repackers, relabelers, and drug product salvagers to obtain a user account from FDA. The proposed rule has us contacting each manufacturer, repacker, relabeler, and drug product salvager to request information to establish an account. FDA data suggest that 8,300 such requests would be made, based on primary registrants, of which 6,700 would be domestic firms. We expect each request to take about 0.25 hours (15 minutes.) The total one-time cost of this requirement is about \$0.1 million (6,700 companies x 0.25 hours x \$51.73 per hour.)

Total cost savings of electronic registration and listing: Overall, the proposed rule is expected to result in annual cost savings of approximately \$3.8 million due to electronic submission of registration and listing

information. There is a one-time cost of \$0.1 million for obtaining FDA user accounts.

Some manufacturers expressed concerns about potential time lags due to our assignment of product codes and package codes, but the electronic process should provide for prompt responses to requests for NDC numbers from FDA. Also, manufacturers commented that if labeler codes must be consolidated across subsidiaries or divisions, additional costs would occur.

We do not anticipate that we will receive requests for waiver of the requirement to submit registration and listing information electronically. However, if we receive waiver requests, we do not expect the costs to exceed those that would be incurred by paper submission of the information.

b. *Costs of label revisions to include NDC numbers.* The proposed rule would require that appropriate human-readable NDC numbers appear on the labels of all drugs that are required to be listed, including biological products and active pharmaceutical ingredients.

Prescription human drugs: Many manufacturers, repackers, relabelers and private label distributors, particularly those subject to the regulation addressing bar code label requirements (“Bar Code Label Requirements for Human Drug Products and Human Biological Products”; 69 FR 9120, February 26, 2004), already voluntarily include the NDC number in human-readable form under the barcode representation, as space permits. This proposed rule would require the appropriate human-readable NDC number to appear on drug labels for drugs subject to the listing requirements. Some packaging lines for prescription drugs have already been retooled to accommodate the unit-of-use requirement as set forth in the bar code rule. The costs of retooling these package lines have been analyzed in the bar code rule. However, we still expect as many

as 60 percent of all prescription separately packaged drug products¹² to be revised because of the proposed rule.

Currently, human-readable NDC numbers appear with an “N” or “NDC” prefix. The proposed rule would require use of only the “NDC” prefix. In addition, there are classes of prescription drugs that are exempt from the bar code rule that would be subject to the requirement in this proposed rule (i.e., that the drug labels for drugs subject to listing requirements bear the appropriate NDC number in human-readable form). There are some products (e.g. allergenic extracts) that do not currently print NDC numbers on labels that would be obligated to do so under the proposed rule.

We lack specific data on the proportion of affected labels, but believe that 50 percent would be revised to include the “NDC” prefix and an additional 10 percent may be accounted in one of the other categories. (Although the exact proportion of labels affected by this provision is unknown, we expect between 25 and 75 percent of all drug labels to require revisions. We have assumed that 50 percent of all labels will be affected for analytic purposes.) Therefore, ERG estimated that 46,800 separately packaged drug products would need revised relabels under the proposed rule.

Prescription drugs would be required to have revised labels that include appropriate human-readable NDC numbers within 3 years of the effective date of the final rule. Therefore, incremental regulatory costs would occur for any product label not revised during routine label changes that may occur during the 3-year period. (ERG has assumed that no incremental cost occurs if required label changes occur during other label revisions.) FDA has examined

¹² The number of separately packaged drug products is the number of drugs times the number of dosage forms times the number of concentrations times the number of package sizes. There are currently about 78,000 separate domestic prescription separately packaged drug products based on NDC number listings.

a number of prescription drug files and found that prescription products are sometimes revised as frequently as once a year. However, some prescription products rarely have label revisions in response to market conditions. We have assumed that 25 percent of prescription drug labels would not be revised during the 3-year implementation period in the absence of the proposed rule, or 11,700 separately packaged drug products.

ERG has estimated weighted label revisions as costing an average of about \$1,600 per separately packaged product (Ref. 5.) The cost of revising prescription human drug labels to include NDC numbers is estimated to total \$18.7 million (11,700 separately packaged drug products x \$1,600 per label revision.) However, these costs are not expected until 3 years after the implementation of the final rule because companies would not know if there would be market driven label changes and therefore wait until the end of the implementation period. The present values of the cost of these label revisions are \$17.1 million (using a 3-percent annual discount rate) and \$15.3 million (using a 7-percent annual discount rate.)

OTC human drugs: FDA has estimated that only 30 percent of all human OTC separately packaged products currently have human-readable NDC numbers printed on labels. However, the proposed rule allows for a 7-year implementation period for OTC drugs to include NDC numbers on labels. Based on previous studies of the OTC drug industry (Ref. 5), ERG has estimated that virtually all OTC drugs have label revisions within 6-year periods. Label changes over this period are mostly motivated by marketing trends and because ample space is usually available on most OTC labels, the inclusion of NDC numbers could be accommodated during these revisions at minimal additional cost.

However, ERG discussions with industry contacts raised concerns about the new label requirements as they apply at the OTC unit-of-use level (e.g., blister packs). Most drugs marketed as units-of-use, including those subject to the bar code rule, would require label changes, but not changes to packaging or printing equipment, and are of sufficient size to accommodate human-readable NDC numbers. However, some packaging lines for unit-of-use OTC products not subject to the bar code rule might need to be retooled to accommodate human-readable NDC numbers. These modifications are expected to be fairly challenging and the costs of applying NDC numbers to blister packs would be in addition to normal label revisions. ERG discussed the costs of these changes and found that line retooling costs to be approximately 150 percent of a normal label revision, or \$2,400 for each affected drug. Industry consultants estimated that as many as 5,000 units-of-use packaged OTC human drugs could be affected. The cost to label units-of-use drugs is \$12.0 million (5,000 drugs x \$2,400 per drug). Unlike voluntary label revisions, manufacturers are not expected to routinely retool production lines during the implementation period. Therefore, affected companies are expected to upgrade lines during the 7-year implementation period with an industry cost of \$1.7 million each year. The present values of this cost are equal to \$10.6 million (using a 3-percent annual discount rate) and \$9.2 million (using a 7-percent discount rate).

Prescription and OTC animal drugs: ERG estimated that each of the 2,100 registered domestic animal drug sites produce 4 separately packaged drug products and that normal label revisions occur at the same rate as for human drugs. In addition, industry consultants have estimated that approximately 40 percent of animal drugs currently have readable NDC numbers on labels and

would not be affected by the proposed rule. Thus, ERG expects that of the 60 percent of labels that would need revisions, 75 percent would be revised in the normal course of business during the 3 years after implementation of the final rule. Therefore, a total of approximately 1,300 animal drugs would require revised labels to include human readable NDC numbers (both prescription and OTC) (2,100 sites x 4 separately packaged products x 0.6 needing label revisions x 0.25). Using a weighted cost per labeling revision of \$1,600, the cost during the third year to the industry of applying NDC numbers to labels due to the proposed rule would be \$ 2.1 million (2,100 separately packaged products x \$1,600 per label change). The present value of this cost is \$1.9 million (using a 3-percent annual discount rate) and \$1.7 million (using a 7-percent discount rate). We do not believe there will be costs associated with retooling package lines for animal drugs.

Active pharmaceutical ingredients. Active pharmaceutical ingredients would be required to bear appropriate human-readable NDC numbers on drug labels under the proposed rule. Currently, many active pharmaceutical ingredients are shipped with bills of lading that are prepared for each shipment and an NDC number could be easily added for a negligible incremental cost. For the purposes of this analysis, we have assumed that 50 percent of all active pharmaceutical ingredients will be required to add human-readable NDC numbers as a result of this proposed rule. According to FDA's current registration and listing data, there are about 4,300 domestic bulk drug substances so about 2,150 are expected to require label changes because of the proposed rule. The costs of providing label changes for active pharmaceutical ingredients are assumed to be equal to the cost of label revisions for prescription drug products, or \$1,600 per revised label. The total cost of

revising active pharmaceutical ingredient labels is \$3.4 million (2,150 labels x \$1,600 per label). We have no data on voluntary label revisions for active pharmaceutical ingredients and have assumed that the revisions will occur throughout the implementation period (approximately \$1.1 million per year). The present values for this cost are \$3.2 million (using a 3-percent annual discount rate) and \$3.0 million (using a 7-percent annual discount rate).

Total costs of label revisions. The overall incremental costs of label revisions under the proposed rule have present values of \$34.0 million (using a 3-percent annual discount rate) and \$30.3 million (using a 7-percent discount rate).

c. Costs of setting up electronic submission of registration, listing, and content of labels. The proposed rule would require manufacturers, repackers, relabelers, and drug product salvagers of drugs, including human and animal drug products, active pharmaceutical ingredients, and biological products to register establishments, list drugs, and, for manufacturers, to provide the content of labeling electronically using specific software. Most, but not all, manufacturers of human prescription drug and biological drug products are already subject to requirements to submit content of labeling in electronic format, but manufacturers of OTC monograph and animal drug products not currently subject to these labeling requirements would not necessarily have this software. The current requirement to submit content of labeling in electronic form does not extend to repackers and relabelers. In addition, active pharmaceutical manufacturers producing ingredients for OTC drug products may not have the correct software to submit registration and listing information electronically.

According to discussions with industry consultants, approximately 75 percent of drug product manufacturers market only OTC monograph products. Using U.S. Census estimates of the industry, we believe about 550 firms would need to purchase needed software for electronic submissions for content of labeling. We note that this estimate is based on the first level of ownership and does not account for multiple layers of corporate hierarchy. We surveyed a range of prices for software (such as Adobe Acrobat Standard, for example) that would be expected to be used in a professional environment. The estimated price of this software is approximately \$250, with some variance for the specific desired features and sophistication. We note that this cost represents the marginal difference between any current software and new software with the capability to work with assigned NDC numbers, and is an incremental cost of the proposed rule. After discussing this estimate with industry IT personnel, we expect \$250 to represent a reasonable cost of software acquisition. In addition, training for 2 employees is expected to cost \$150 per employee. Training is expected to require 6 hours for each employee at a cost of \$51.73 per hour (based on fully loaded BLS wage rates for mid-level management within this industry). The total cost per firm is about \$1,000 ($\$250 + (2 \text{ employees} \times \$150) + (2 \text{ employees} \times 6 \text{ hours} \times \$51.73)$) for a total cost to the OTC monograph industry for software acquisition and training to be \$0.6 million to submit content of labeling electronically.

We expect similar costs of \$1,000 would accrue for all 350 companies that are predominantly involved in medicinal and botanical manufacturing (Census, 2004), which includes active pharmaceutical ingredient manufacturers, in order for these companies to electronically submit registration and listing information. According to Small Business

Administration data, as well as industry consultants, there are approximately 250 repackers and relabelers that serve the pharmaceutical industry. Each of these entities would require software and training in order to register and list. Finally, there are 80 firms that, according to U.S. Census data, predominantly or secondarily manufacture animal drugs that would require software and training to electronically submit content of labeling. The total costs of software acquisition and training for these segments is an additional \$0.7 million ((350 active pharmaceutical ingredient manufacturers + 250 repackers and relabelers + 80 animal drug manufacturers) x \$1,000).

The overall cost of software acquisition and training under the proposed rule is \$1.4 million.

d. *Costs of continuing submissions of content of labeling.* Additional costs might be incurred to submit the incremental content of labeling for a small proportion of drugs for which there have been labeling changes. The content of labeling, as described elsewhere in this proposal, must be submitted electronically. Makers of active pharmaceutical ingredients are not affected by this provision because they would not be expected to submit content of labeling electronically.

For affected OTC drugs, we have assumed that two content of labeling submissions per listed drug will occur twice a year to account for the possibility of multiple dosage forms and concentrations in a product line. Animal products are expected to have an average of 1.5 content of labeling submissions per product twice a year. According to our drug listing system, there are about 30,400 domestic OTC drugs and about 4,200 domestic animal drugs. Using the assumption that each submission would entail 0.25 hours (15 minutes), and using the industry wage rate of \$51.73 per hour, the annual cost

of this provision is \$1.7 million (((30,400 domestic OTC drugs x 2 content of labeling submittals) + (4,200 domestic animal drugs x 1.5 content of labeling submittals)) x 2 times per year) x 0.25 hours per submission x \$51.73 per hour).

e. Delays in NDC Assignment. We understand from discussions with manufacturers that many manufacturing processes are dependent on timely assignment of NDC numbers. According to industry consultants, before drugs can be mass-produced, manufacturers of both prescription and OTC drug products need to know the NDC number for the production run. Currently, manufacturers control the assignment of NDC numbers once they have a labeler code, so this is not a problem that could affect the production process. There is concern about delays in production because new NDC numbers assigned by us might not be timely from a manufacturer's viewpoint and could result in major costs.

However, in discussions with several manufacturers, comments to ERG reflected that if the assignment of NDC numbers by FDA was done electronically and transmitted to the companies electronically, there would likely be a negligible impact on operations. Since FDA intends to assign and transmit NDC numbers electronically, we do not believe this provision would result in additional costs to industry.

f. Effect of the proposed rule on third-party reimbursement. Under the proposal, repackers and relabelers would not be allowed to use the manufacturer's human-readable NDC numbers on their drug labels. Many companies noted that reimbursement arrangements are contracted between drug manufacturers and third-party payers (including Medicaid programs) that provide for rebates for sales of a manufacturer's drug. Most reimbursement plans use NDC numbers as the appropriate billing code, and repackers and

relabelers note that they are not part of the negotiated rebate plans between manufacturers and third-party payers. Repackers and relabelers further claim that profit margins for their firms will not allow for such reimbursements. Thus, the process of negotiating these payments would be affected by the proposed rule, but we did not estimate the outcome of future negotiations.

g. Other potential costs. The proposed rule might have other impacts on various industry sectors. For example, the relationships between drug manufacturers and private label distributors may be altered because of the proposed registration, listing, and NDC requirements. Some industry sources have asserted that the proposed rule may make private label distributors unprofitable and that manufacturers would directly supply drugs to retailers. We are unable to assess this impact, and are unsure whether it would, in fact, result in market inefficiencies, but note that there would likely be changes in the current relationships between these sectors. We specifically request comment on any economic impact the proposal would have on this relationship between drug manufacturers and private label distributors.

3. Costs to FDA for Implementing the Proposed Rule

We do not expect a major increase in the need for internal resources associated with the proposed rule. Activities related to the assignment of NDC numbers are expected to be equivalent to our current activity of receiving notifications from industry and manually inputting the information into our databases. Similarly, we expect any increased workloads caused by increased submissions of registration or listing information or content of labeling to be approximately equivalent to the internal reduction in workload from electronically updating our databases. The database of NDC numbers for marketed drugs would require maintenance and updating to ensure the quality

of the data, and we would make this database available for other users, but the costs associated with activity have been accounted for in previous rule-making (see Bar Code Label Requirements for Human Drug Products and Human Biological Products, 69 FR 9120 at 9156). The registration and listing information will also be included in the database and we do not expect any additional costs to be associated with maintenance of this information.

However, the requirement that manufacturers, repackers, relabelers, and drug product salvagers obtain a user account from us would require increased use of our resources. We have estimated that 6,700 entities would be contacted in order to provide them with their user accounts, and that each contact would require 0.25 hours (15 minutes). This would require about 1,600 hours of FDA resources, or about 0.8 FTEs. The current weighted cost per FTE is approximately \$120,000, so the one-time cost to FDA for providing access codes for the proposed rule would be approximately \$0.1 million.

4. Total Costs of the Proposed Rule

Table 3 shows the initial investment costs and annual costs of the proposed rule over a 10-year period by cost category.

TABLE 3.—UNDISCOUNTED COSTS OF PROPOSED RULE BY CATEGORY (IN MILLIONS OF DOLLARS)

Cost Category	Initial Investment/One Time	Annual Costs/Recurring
Single Method of Assigning NDC Numbers	\$3.8	\$3.2
Electronic Drug Registration and Listing	\$0.2	(-\$3.8)
Label Revisions	\$36.2	—
Software Acquisition and Training	\$1.3	—
Continued COL Submissions	—	\$1.7

Table 4 shows the expected expenditures per year for the evaluation period and includes total present values based on 7 percent and 3 percent discount rates. Recurring costs include the retooling of OTC packaging systems

to provide NDC numbers for units-of-use during the first 7 years of the proposed regulation.

TABLE 4.—COSTS PER YEAR FOR THE PROPOSED RULE (IN MILLIONS OF DOLLARS)

Year	One-Time Costs	Recurring Costs
1	\$8.1	\$1.1
2	\$2.8	\$1.1
3	\$23.7	\$1.1
4	\$1.7	\$1.1
5	\$1.7	\$1.1
6	\$1.7	\$1.1
7	\$1.8	\$1.1
8	-	\$1.1
9	-	\$1.1
10	-	\$1.1
Present Value	3% - \$38.1	3% - \$9.4
	7% - \$33.0	7% - \$7.7

Average annualized costs of the proposed rule are estimated to be \$5.6 million using a 3 percent annual discount rate or \$5.8 million using a 7 percent annual discount rate.

F. Benefits

Benefits of the proposed rule will result because the improved processes in the proposed regulation would generate up-to-date, complete medication information, including NDC numbers, to support a growing number of medical and health information technology initiatives. The potential benefits of these initiatives are significant. For example, the final regulation that required bar coded NDC numbers on some human drugs and biological products (69 FR 9120) estimated benefits of approximately \$5 billion per year for the avoidance of over 500,000 adverse drug events associated with medication errors. These benefits are dependent on correct and unique NDC numbers being read by scanners at patient bedsides. The lack of accurate NDC numbers may delay the acceptance of this technology and decrease the potential patient benefits.

We have estimated that if the lack of reliable NDC numbers would delay the rate of technological acceptance by 1 year, the potential benefits of the bar code regulation would be reduced by about \$600 million per year and an average of 25,000 additional adverse drug events would occur.

We believe it is critical to other patient safety initiatives, such as DailyMed or electronic prescribing, that a reliable and consistent NDC numbering system be in place. The potential benefits of these initiatives could be similar to the benefits of the bar code rule, and any delay in implementing these programs because of the lack of electronic access to reliable identifying information could seriously limit their impacts.

The proposed rule would allow increased access to information in our databases. Increased use of these databases to efficiently treat patients would rely on the availability of information electronically. A key element for encouraging the use of technology to ensure public health will be the assurance that NDC numbers are unique and accurately identify drugs. The proposed rule would accomplish this by making assignment of NDC numbers our responsibility, rather than a responsibility diffused throughout the industry. In addition, by ensuring that these NDC numbers are available in human-readable format, patients and others would be able to access important patient safety information from the DailyMed system, the NDC Directory, or other drug information electronic systems without the use of bar code scanners. Human-readable NDC numbers would allow patients to report any adverse events easily and ensure that our adverse event reporting system is as accessible as possible. Also, the human-readable NDC number would enable us to trace the origin of each product (a particularly important issue when dealing with recalls or drug quality issues) and more easily identify drug products and their sources

(this is particularly important when dealing with import and counterfeiting issues). We specifically request comments on quantitative benefits resulting from the requirement that the NDC number be included on the drug label.

The proposed rule would increase the efficiency of the registration and listing process by eliminating most paper submissions. We would be able to review the submitted information more quickly and contact submitting firms immediately if any additional information were needed. The resulting database of registered establishments and listed drugs would provide the basis for increased patient safety by being complete and up-to-date. For example, an electronic database of drugs would allow for timely notification of any recalls of unsafe drugs and identification of affected manufacturers, repackers, relabelers, or drug product salvagers.

By changing the way that NDC numbers are assigned, we would increase the confidence that each drug being manufactured, repacked, or relabeled for commercial distribution has a unique identifier that we have assigned. After we have introduced increased oversight for new product codes and package codes, the likelihood of unsafe counterfeit drug products entering the supply chain would decline because would-be counterfeiters would be unsure of numerical sequences used for NDC numbers. Our assignment of NDC numbers would reduce the possibility of duplicate numbers appearing in various medical and reimbursement databases. Currently, firms have been reusing NDC numbers at times without informing us, and this practice has added uncertainty into these systems. There has been reported confusion about coverage of drugs for reimbursement and our control of the NDC system would ensure that only qualified drugs are subject to reimbursement.

In addition, the current NDC number makeup (using dashes to distinguish between the components) allows for potential duplicate numbers when the dashes are not read by scanners reading NDC numbers encoded in bar codes. This happens because the components used to indicate labeler codes, product codes, and package codes are of differing lengths, and are currently separated by hyphens. If those NDC numbers are barcoded, the differing components may lead to duplicate numbers since bar code scanners don't read hyphens. This would not happen under the proposed rule.

Although we know that the proposed rule will result in significant benefits, we are not able to quantify these benefits. We are confident that moving to electronic registration and listing processes, as well as assignment of NDC numbers, would encourage development of technology in the delivery of health care. We know that the successful development of medical and health information technology initiatives (such as the DailyMed, bar code label, and the electronic prescription drug program described below) will depend in large part on an accurate, reliable NDC number and that this proposed rule would further that development. Therefore, there are real benefits associated with the proposed changes to the NDC number and the NDC number assignment process. However, we are not able to quantify those benefits because they rely in part on further development of technology initiatives. Similarly, there are significant benefits associated with the proposed changes to the collection of registration and listing information. For example, ready access to complete and accurate registration and listing information helps to ensure the success of many of our programs, such as postmarketing surveillance (including FDA inspections), bioterrorism initiatives, responses to drug shortages, and user fee assessments. We know there are benefits associated with the efficiencies

achieved by improved access to more complete information, but we are not able to quantify those benefits.

We also note that continuation of a paper registration and listing system is likely to act as a deterrent to investment in new initiatives. As discussed earlier in this document, the recently issued final regulation that requires NDC numbers to be encoded in bar codes on certain prescription drugs, certain OTC products, and human blood products helps to avoid adverse drug events due to medication errors. The benefits for that rule would be reduced by as much as \$600 million per year if unique NDC numbers are not universally available and this results in delays in the use of this technology. Lack of universal identifiers would likely discourage investment in machine-readable technology and make access to electronic information difficult.

The proposed rule would provide necessary assurances to health professionals and patients that they have access to up-to-date labeling information and that the safety of the drug supply is assured. It would also encourage investment in installed scanners and readers at points of administration such as hospitals or physician clinics that rely on this information. The existence of this system may support the development of electronic prescribing or other efficiencies in health care that may save money and reduce medication errors that may cause adverse reactions in patients. The electronic prescription drug program (electronic prescribing) established by the Medicare Modernization Act promotes uniform standards that permit (among other things) electronic exchange of drug labeling and drug listing information maintained by us and by the National Library of Medicine. The goal behind the program is to reduce transcription and dispensing errors (which, in turn, lead to medication errors) and to prevent adverse drug interactions. The

proposal to assign the NDC number, resulting in an accurate and reliable NDC number, would also facilitate development of the DailyMed). The DailyMed is an up-to-date, computerized repository of medication information, including drug product labeling. The DailyMed, maintained by the National Library of Medicine in cooperation with FDA, is a new way to distribute current and comprehensive medication information in a computerized format for use in health care information systems. Health care information suppliers will be able to use the information from the DailyMed in their computer systems, allowing providers, patients, and the public access to reliable, up-to-date information on the medications they use. The DailyMed would enable drug product users and health care providers to have electronic access to up-to-date information about a drug.

Although the scope of the proposed rule does not extend beyond registration and listing, the high-quality, electronic database that would result from the proposed rule would enable future uses of technology for the public benefit.

G. Small Business Analysis and Discussion of Alternatives

We believe the proposed rule is unlikely to have a significant impact on a substantial number of small entities. Despite this, we have prepared an initial regulatory flexibility analysis and invite comment from affected entities.

1. Affected Sectors and Nature of Impacts

The proposed rule would directly affect manufacturers of pharmaceutical and biological products (NAICS 325412 and NAICS 325414), packaging services (NAICS 561910), retail pharmacy chains (NAICS 446110; Pharmacies), and prescription benefit managers (NAICS 524292; Insurance Plan Administrative Services, Third Party). We assessed data on these industries

from the 2002 Economic Censuses and estimated revenues per establishment. The affected establishments are shown in table 2a of this document. Although other economic measures, such as profitability, may provide preferable alternatives to revenues as a basis for estimating the significance of regulatory impacts in some cases, use of any reasonable estimate of profits would not change the results of this analysis. As discussed earlier in the Analysis of Economic Impacts (see section VI.B of this document), we are proposing this rule in order to improve the quality and timeliness of information available to patients and health care professionals. We believe this improvement would result in improved outcomes by providing better uses of medicines by patients.

a. *Pharmaceutical manufacturers (NAICS 325412)*. The Small Business Administration (SBA) has defined as small any entity in this industry with fewer than 750 employees. According to census data, 94 percent of the industry is considered small. The average annual revenue for these small entities is \$54.7 million per entity. Small entities would be affected by the proposed rule. We estimate the annualized compliance cost for small entities in this industry to average \$30,200. This is about 0.1 percent of their annual revenue. We believe this cost does not constitute a significant impact on a substantial number of small entities in this industry.

b. *Biological product manufacturers (NAICS 325414)*. The SBA has defined as small any entity in this industry with fewer than 750 employees. According to census data, 97 percent of the industry is considered small. The average annual revenue for these small entities is \$15.5 million per entity. Small manufacturers of biological products would be affected by the proposed rule. We estimate the annualized compliance cost for a small entity in this industry to be \$30,200. This is about 0.2 percent of their annual revenues. We believe

this does not constitute a significant impact on a substantial number of small entities in this industry.

c. *Packaging services (NAICS 561910)*. The SBA has defined as small any entity in this industry that has less than \$6.5 million in annual revenue. On this basis, almost 94 percent of the industry is considered small. The average annual revenue for small entities is \$1.4 million per entity. We have not identified specific regulatory costs of compliance to this industry. We have no confident data that the extent of electronic registration and listing would increase or decrease costs to these entities. At this point, we tentatively believe the proposed rule would not constitute a significant impact on a substantial number of small entities in this industry and solicit comment in this area.

d. *Retail pharmacy chains (NAICS 446110)*. The SBA has defined as small any entity in this industry that has less than \$6.5 million in revenue. On this basis, almost 100 percent of the industry is considered small. The average annual revenue for small entities is \$3.8 million per entity. We expect that some large pharmacy chains with 35 or more operations would experience increased operating cost of \$200,000 due to the proposed rule. However, these large chains do not meet the criteria for small entities because their annual revenues are at least \$133 million (\$3.8 million times 35 outlets). We do not believe this impact constitutes a significant impact on a substantial number of small entities in this industry.

We do not believe that independent retail pharmacies will be adversely affected by the proposed rule because most pharmacy systems do not use the internal component of NDC numbers. We found no evidence of any impacts, but specifically request comment on this issue.

e. *Prescription benefit managers (NAICS 524292)*. The SBA has defined as small any entity in this industry that has less than \$6.5 million in annual revenues. On this basis, over 92 percent of the industry is considered small. The average annual revenue for small entities is \$1.6 million per entity. We are unable to distinguish PBMs from other insurance administrative services, but have used aggregate industry data. Some PBMs would be expected to experience annual cost increases of \$200,000 due to the proposed rule. This constitutes 12.5 percent of annual revenues for the affected entities. However, of the 11,584 small entities in this industry (there are only 76 PBMs of any size) we expect that between 7 and 8 entities would be affected. We do not believe this constitutes a significant impact on a substantial number of small entities in this industry.

2. Alternatives

We considered several alternatives to the proposed rule. Each is discussed below.

a. *Completely reassign NDC numbers, including existing numbers*. We considered removing the existing format of the NDC number and reassigning randomized numbers for all products. We believe this would improve the robustness of the NDC and allow more numbers to be available for future drugs as well as improve our industry oversight responsibilities. However, discussions with industry representatives suggested that the first-year cost of such an approach could reach more than \$900 million. Pharmaceutical manufacturers would be required to completely remap the newly assigned NDC numbers so that existing data processing, rebate, and market analyses tasks could continue. While individual retail pharmacies would not likely be affected, chain stores and PBMs would require large internal reprogramming

in order to manage repayment options. Additional quality control procedures would be required to ensure proper reimbursement. Wholesalers and distributors would also require major internal reprogramming to account for the loss of sequential NDC numbers. For this alternative, each State Medicaid program would require an estimated \$3 million to reprogram reimbursement software so that each prescription could be tracked. This alternative is described in more detail in Reference 3.

b. Implementation period. We considered (and are still considering) different implementation periods. Under the proposal, manufacturers, repackers, and relabelers of prescription drugs would have 3 years to provide NDC numbers on their labels, while manufacturers, repackers, and relabelers of OTC drugs would have 7 years. We examined a total of 25 different implementation plans. These plans include prescription products having between 1 year and 5 years to comply and OTC products having between 5 years and 9 years to comply with the proposed rule. Table 5 shows the difference in average annualized costs between the current implementation plan and the other 24 combinations.

TABLE 5.—DIFFERENCES IN ANNUALIZED COSTS OF DIFFERING IMPLEMENTATION PERIODS (IN MILLIONS OF DOLLARS; 7 PERCENT DISCOUNT RATE)

	5 Year OTC	6 Year OTC	7 Year OTC	8 Year OTC	9 Year OTC
1 Year Prescription	+\$2.1	+\$2.0	+\$1.9	+\$1.9	+\$1.9
2 Year Prescription	+\$1.4	+\$1.2	+\$1.2	+\$1.2	+\$1.1
3 Year Prescription	+\$0.2	0	—	-\$0.1	-\$0.1
4 Year Prescription	-\$0.9	-\$1.0	-\$1.0	-\$1.0	-\$1.1
5 Year Prescription	-\$1.4	-\$1.5	-\$1.5	-\$1.6	-\$1.6

There was relatively little difference in changes to the OTC drug implementation period because of the ongoing normal revisions to labeling. Only if a 5-year implementation period is selected are there noticeable cost increases. However, shorter implementation periods for prescription products

increase costs by about 20 percent for a 2-year implementation period and about 33 percent for a 1-year period. Conversely, while longer implementation periods would reduce annualized costs by similar amounts, the delay in ensuring that medical information technologies would be able to use efficiencies expected from the proposed rule seemed high. Therefore, we selected the proposed implementation periods as a reasonable balance. We solicit public comment on the proposed implementation period and the effect on expected costs and benefits.

c. Exemption for small entities. We considered exempting small entities, but rejected the alternative due to the relatively modest impact of this initiative on small businesses and the lack of label standardization that would result. Any potential exemptions to this proposed rule would be on a product basis, not an entity basis. In addition, benefits of having a standardized identification system would be reduced by such blanket exemptions.

Outreach: We will specifically solicit comment from affected small entities on the proposed rule.

d. Conclusion. We have analyzed the expected impacts of the proposed rule. This proposal is expected to have average annualized costs of \$5.6 million (using a 3 percent annual discount rate) or \$5.8 million (using a 7 percent annual discount rate). The benefits include assurance of correct NDC numbers, which would also mean correct bar-coded information, and electronic access to important product information for patients that will improve public health. Despite the fact that we are unable to specifically quantify patient benefits directly attributable to the proposed rule, we believe the benefits would be greater than the expected costs and the proposed rule should be implemented.

VII. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). "Collection of information" includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown under this section with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

We invite comments on these topics: (1) Whether the collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs

Description: The proposed rule would reorganize, consolidate, clarify, and modify current regulations on registering establishments and listing human

and animal drugs under part 207, blood and blood products under part 607, and HCT/Ps under part 1271. The proposal describes when and how to register and list and what information must be submitted for registration and listing. The proposal makes certain changes to the NDC system for drugs and would require the appropriate NDC number to appear on drug labels (for drugs subject to the drug listing requirements). The proposed regulations would require the electronic submission of all registration and most listing information instead of the current use of paper forms.¹³

FDA currently reviews completed registration and listing forms and other submissions required under current parts 207, 607, and 1271. The information collection for current part 207 is approved by OMB until December 31, 2007, under OMB Control Number 0910-0045. The information collection for current part 607 and Form FDA 2830 is approved by OMB until March 31, 2009, under OMB Control Number 0910-0052. The information collection for current part 1271 and Form FDA 3356 is approved by OMB until July 31, 2007, under OMB Control Number 0910-0469.

FDA has estimated, in Tables 6, 7, and 8 of this document, the burden to comply with all of the information collection requirements for proposed parts 207, 607, and 1271. These estimates are based on FDA's experience in reviewing registration and listing submissions and on the number of submissions currently received, the number of respondents submitting this information, and the number of registered establishments and listed drugs, blood products, and HCT/Ps currently in FDA's database. The estimates discussed below are for each section of proposed parts 207, 607, and 1271 that contain a reporting burden under the PRA.

¹³ The electronic submission of registration and listing information would remain voluntary for blood products.

A. Registration Information Under Part 207

1. Proposed Requirements

Under proposed § 207.17, manufacturers, repackers, relabelers, and drug product salvagers must register establishments. This is consistent with current registration requirements, except that currently private label distributors may submit information (similar to registration information) to obtain a labeler code from FDA. In addition, the estimates include PET drug producers who would not be exempt from registration under the proposal.

Under proposed § 207.21, domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers must complete initial registration of each establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug. In addition, foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers must register each establishment before the drug is imported or offered for import into the United States. This is consistent with current registration requirements, except that the proposal would include additional foreign establishments as a result of the revocation of the exemption for drugs that enter a foreign trade zone and are re-exported from that foreign trade zone without having entered U.S. commerce, and for drugs imported under section 801(d)(3) of the act.

The information that must be provided to FDA for registration is described under proposed § 207.25. The information that would be required under proposed § 207.25 differs from the information currently required for registration. The following currently required information would not be required under the proposal: The kind of ownership or operation and the title of each corporate officer and director. New information required under the

proposal would be the type of operations performed at each establishment and contact information about the official contact and the United States agent, each importer of the drug that is known to the establishment, and each person who imports or offers for import the drug to the United States.

Under proposed § 207.29, manufacturers, repackers, relabelers, and drug product salvagers must review annually their registration information. During the review, manufacturers, repackers, relabelers, and drug product salvagers must report all changes to their registration information or certify that no changes have occurred. In addition to the annual review and update, manufacturers, repackers, relabelers, and drug product salvagers must submit expedited reports of certain changes within 30 calendar days of the change. Currently, manufacturers, repackers, relabelers, and drug product salvagers must renew their registration information annually and submit certain amendments to registration within 5 days of a change. Proposed § 207.29 differs from the current requirement to submit amendments to registration in the following ways: The proposal would lengthen the current time period for reporting changes to registration information from 5 days (10 business days for a change in United States agent information) to 30 calendar days. The proposal would revoke the current requirement to report a change in individual ownership and corporate or partnership structure, and the current requirement to submit a signed statement for a change in a registered establishment's firm name. New requirements under the proposal would be to certify that no changes have occurred and to report as expedited updates certain changes within 30 calendar days, such as the close or sale of an establishment. Modified requirements would be to submit within 30 calendar

days a change in the name or address of an establishment and a change in contact information for the official contact and United States agent.

2. Burden Estimates

Based on the number of new establishments that currently register each year by submitting Form FDA 2656, we estimate that approximately 987 manufacturers, repackers, relabelers, and drug product salvagers will provide electronically approximately 1,128 new establishment registrations annually. Based on the number of registered establishments in our database, we estimate that approximately 8,343 manufacturers, repackers, relabelers, and drug product salvagers will provide approximately 12,137 annual reviews and updates of registration information or reviews and certifications that no changes have occurred. Based on the number of changes to registration information that have been submitted annually on Form FDA 2656e, we estimate that approximately 775 manufacturers, repackers, relabelers, and drug product salvagers will provide approximately 1,921 expedited updates.

The estimates include the registration of establishments for both domestic and foreign manufacturers, repackers, relabelers, and drug product salvagers. The estimates for the number of manufacturers, repackers, relabelers, and drug product salvagers excludes the number of private label distributors currently in the database that submit information to receive a labeler code. The estimates include an additional 80 PET drug producers who would not be exempt from registration under the proposal, and approximately 30 manufacturers of plasma derivatives. In addition, the estimates include five additional foreign establishments that would be required to register as a result of the revocation of the exemption for drugs that enter a foreign trade zone and are reexported

from that foreign trade zone without having entered U.S. commerce, and for drugs imported under section 801(d)(3) of the act.

We estimate that it will take approximately 60 minutes to provide electronically the initial registration information for each new establishment. This estimate is only until manufacturers, repackers, relabelers, and drug product salvagers become familiar with using the electronic drug registration and listing system. We intend to lower this burden estimate to approximately 30 minutes when we submit to OMB the request to renew approval of this information collection.

We also estimate that it will take approximately 30 minutes for each annual review and update of registration information or each review and certification that no changes have occurred. This estimate is only until manufacturers, repackers, relabelers, and drug product salvagers become familiar with using the electronic drug registration and listing system. We intend to lower this burden estimate to approximately 15 minutes when we submit to OMB the request to renew approval of this information collection.

We also estimate that it will take approximately 15 minutes to provide each expedited update. This estimate is only until manufacturers, repackers, relabelers, and drug product salvagers become familiar with using the electronic drug registration and listing system. We intend to lower this burden estimate to approximately 5 minutes when we submit to OMB the request to renew approval of this information collection.

The burden hour estimates above are based on our familiarity with the content of current registration forms and submissions and the times required by industry volunteers to input registration information during our electronic drug registration and listing system pilot project (discussed in section IV.E.3

of this document). The estimates are an average of the time it would take to register a domestic or foreign establishment and an average of the time it would take to review registration information and update several registration items in the database or review registration information and only certify that no changes have occurred. We note that these estimates for the electronic submission of this information would be a reduction in the currently approved estimate of 2.50 hours (OMB Control Number 0910-0045) for preparing and mailing to FDA Form FDA 2656.

We intend to migrate into our new database current registration information that had been submitted using paper forms. As a result, current manufacturers, repackers, relabelers, and drug product salvagers would require additional time to review in the new database all current registration information and make any necessary revisions. We assume that this one-time initial review will be the first annual review and update using the electronic system, and we estimate it will take an average of 30 minutes for each review and update.

B. Listing Information Under Part 207

1. Proposed Requirements

Under proposed § 207.41, manufacturers, repackers, relabelers, and drug product salvagers must list drugs they manufacture, repack, relabel, or salvage for commercial distribution (this includes drugs they manufacture, repack, relabel, or salvage for a private label distributor). This proposed requirement is consistent with the current listing requirements, except that drug product salvagers are not currently required to list under part 207 and private label distributors may submit listing information directly to FDA.

Under proposed § 207.45, manufacturers, repackers, relabelers, and drug product salvagers must list, at the time of initial registration of an establishment, any drug being manufactured, repacked, relabeled, or salvaged for commercial distribution at that establishment. This is consistent with the current listing requirements, except that drug product salvagers are not currently required to list under part 207.

Under the proposal, the human-readable NDC number must appear on the drug's label (for drugs subject to the listing requirements). The information that must be provided electronically to us by manufacturers, repackers, and relabelers (including drug product salvagers who repack and relabel) to receive an NDC number is described under proposed § 207.33. Currently, the human-readable NDC number is not required to appear on the drug's label, but most prescription drugs and about one-third of the OTC drug products have the NDC number on the label. We currently assign a labeler code to each manufacturer, repacker, relabeler, and private label distributor to be part of the NDC number, and the manufacturer, repacker, relabeler, and private label distributor assigns the remainder of the NDC number to each drug product. Under the proposal, for drugs listed after the effective date of the proposal, the NDC number for a drug must be obtained from us before (or at the time) that drug is listed. Some of the information currently required to list the drug would be submitted under the proposal to receive the NDC number. The assigned NDC number would be submitted as part of the listing information and would serve as a link to the information already submitted for the drug to obtain the NDC number.

The information that must be provided electronically to us by manufacturers, repackers, and relabelers to list a drug is described under

proposed §§ 207.49, 207.53, 207.54, 207.55, and 207.61. As mentioned previously in this document, drug product salvagers are not currently required to list the drugs they salvage. The listing information and the NDC number information required under the proposal is consistent with the information currently submitted to FDA on Forms FDA 2657 or 2658, except for the following: (1) The proposal would require identification information about the name of each importer of the drug that is known to the establishment and each person who imports or offers for import a drug to the United States (importer information is currently required under the Bioterrorism Act); (2) the content of labeling would be submitted electronically (for approved human drugs, the information collection burden for this requirement is accounted for under current § 314.50(l)(1)(i), approved under OMB Control Number 0910-0001); (3) the quantity of the active pharmaceutical ingredient would be required for all drugs subject to the listing requirements (unless the approved application number is provided) (this requirement is substantially the same as the current requirement); (4) the name of the inactive ingredients for certain drugs would be required under the proposal (unless the approved application number is provided); (5) repackers and relabelers would be required to submit the NDC number assigned to the drug immediately before they received the drug; (6) additional information to identify the manufacturer, repacker, relabeler, and drug product salvager would be required (such as e-mail address, fax number, and labeler code); (7) the submission of a representative sampling of labeling would include advertisements under § 202.1(l)(1); (8) certain listing information would not have to be submitted if the approved U.S. application number for the drug is provided; (9) the DMF number would be submitted by the manufacturer to obtain an NDC number for an active pharmaceutical

ingredient; and (10) drug product salvagers (who do not repack or relabel) would submit the lot number and expiration date and NDC number assigned to the drug immediately before the drug is received by the drug product salvager.

Under proposed § 207.57, manufacturers, repackers, relabelers, and drug product salvagers must review each June and December all drug listing information that has been provided to us and must report all material changes or certify that no changes have occurred. Manufacturers, repackers, and relabelers must also notify us at this time if any listed drug has been discontinued from marketing or if any discontinued drug has resumed marketing and provide listing information for any drug not yet listed. Under the proposal, all manufacturers, repackers, relabelers, and drug product salvagers must review the listing information for each drug listed and report any material changes. Current regulations do not specify that the information for each listed drug needs to be reviewed, nor is a certification required if there are no changes. Only material changes to listing information must be reported. Under the proposal and consistent with section 510 of the act, manufacturers, repackers, relabelers, and drug product salvagers must also update their listing information for drug products that have not been previously listed at the time registration information for each establishment is updated.

Under proposed § 207.33(f), manufacturers, repackers, and relabelers must notify us of a change in any of the drug characteristics (except certain identifying information) for an NDC number in § 207.33, and we would assign a new NDC number for that drug.

Under proposed § 314.81(b)(3)(iii), applicants under part 314 must report electronically within 30 calendar days the withdrawal of an approved drug product from sale (the current requirement is to report within 15 days).

2. Burden Estimates

Based on the current receipts of Forms FDA 2657 and 2658 for new listings, we estimate that approximately 1,812 manufacturers, repackers, relabelers, and drug product salvagers will provide electronically approximately 13,821 new listings annually.

Based on the number of drugs in our listing database and the current receipts of Forms FDA 2657 and 2658 for changes to listing information (and, until recently, the number of receipts of compliance verification reports), we estimate that approximately 2,278 manufacturers, repackers, relabelers, and drug product salvagers will provide approximately 22,568 June and 22,568 December reviews and updates of listing information (a total of 45,136 submissions annually), and that approximately 5,594 manufacturers, repackers, relabelers, and drug product salvagers will provide approximately 81,980 June and 81,980 December reviews and certifications that no changes have occurred (a total of 163,960 submissions annually).

The estimates for the number of drug listings submitted by manufacturers, repackers, relabelers, and drug product salvagers include both domestic and foreign listings and the listings that would be submitted by manufacturers, repackers, relabelers, and drug product salvagers for private label distributors. The estimates also include the time for submitting information for an NDC number under proposed § 207.33. The drugs that would be listed include PET drugs, an additional 57 drugs listed by approximately 5 foreign establishments as a result of the revocation of the exemptions for foreign establishments, and

approximately 30 plasma derivatives. The estimates for the number of June and December reviews and updates of listing information or reviews and certifications that no changes have occurred would include the number of changes to drug characteristics submitted to obtain a new NDC number under proposed § 207.33(f) and the reports of the withdrawal of an approved drug from sale under § 314.81(b)(3)(iii) and, for biological products, under § 601.2(f).

Based on our familiarity with the content of current listing forms and submissions and the time required to input listing information during our electronic drug registration and listing system pilot project, we estimate that it will take manufacturers, repackers, relabelers, and drug product salvagers approximately 1 hour and 30 minutes to provide electronically information for each drug they list for the first time (for both foreign and domestic listings). This estimate is an average of the time it will take manufacturers, repackers, relabelers, and drug product salvagers, with drug product salvagers taking considerably less time than manufacturers. This estimate includes the time for submitting the content of labeling in electronic format under proposed § 207.61(a)(2) and for submitting other labeling and advertisements in paper or electronic format under proposed §§ 207.49(g) and (h) and 207.53(d) and (e). This estimate is only until manufacturers, repackers, relabelers, and drug product salvagers become familiar with using the electronic drug registration and listing system. We intend to lower this burden estimate to approximately 45 minutes when we submit to OMB the request to renew approval of this information collection.

We also estimate that it will take approximately 30 minutes for each June and December review and update of listing information, and approximately 15 minutes for each review and certification that no changes have occurred.

These estimates include the time for submitting any labeling and advertisements for each drug, changes to the drug's characteristics submitted for a new NDC number under proposed § 207.33(f), and reports of the withdrawal of an approved drug from sale under § 314.81(b)(3)(iii). This estimate is only until manufacturers, repackers, relabelers, and drug product salvagers become familiar with using the electronic drug registration and listing system. We intend to lower this burden estimate to approximately 15 minutes for each review and update and approximately 5 minutes for each review and certification when we submit to OMB the request to renew approval of this information collection. We note that these estimates for the electronic submission of this information would be a reduction in the currently approved estimate of 2.50 hours (OMB Control Number 0910-0045) for preparing and mailing to FDA Form FDA 2657 and FDA Form FDA 2658.

We intend to migrate into our new electronic drug registration and listing system current listing information that had been submitted using paper forms. As a result, current manufacturers, repackers, relabelers, and drug product salvagers will need additional time to review all current listing information in the new database and make any necessary revisions. We estimate that it will take on average 45 minutes to review and update each drug's listing information (the listing information includes information submitted for an NDC number).

C. Registration and Listing Information Under Part 607

1. Proposed Requirements

Under proposed § 607.22, manufacturers may electronically obtain, complete, and submit to FDA Form FDA 2830 (Blood Establishment Registration and Product Listing) or may request a copy of the form by e-mail.

Currently, under § 607.22, manufacturers must register establishments and list blood products on Form FDA 2830. The proposal is consistent with the current requirement to register establishments and list products approved under OMB Control Number 0910-0052.

Under proposed § 607.25(b)(1), blood establishments are required to list blood products by the established and proprietary name. This proposal is consistent with the current listing requirement approved under OMB Control Number 0910-0052. Currently, blood establishments list bulk product substances as well as finished dosage forms under both parts 607 and 207 to obtain an NDC number. The proposal would reduce reporting burden by requiring blood establishments to list only under part 607. To be consistent with part 207, we are also proposing to delete the reference in part 607 to Form FDA 2250 (National Drug Code Directory Input) because this form is no longer being used by CDER or CBER.

Under proposed § 607.40, foreign establishments must register each establishment before their blood product enters a foreign trade zone and are reexported from that foreign trade zone without having entered U.S. commerce. This proposal is consistent with the current registration requirement in that establishments must register before their blood products are imported or offered for import into the United States. The proposal would also include additional foreign establishments as a result of the revocation of the exemption under section 801(d)(4) of the act for blood products that enter a foreign trade zone and are reexported from that foreign trade zone without having entered U.S. commerce. Under the proposal, we are requiring additional information for each foreign establishment. The proposal would also require the foreign establishment to report to FDA changes in the United States agent's name,

address, telephone and fax numbers, and e-mail address within 30 calendar days of the change. The proposal would lengthen the time period from 10 business days to 30 calendar days for reporting changes in the United States agent to FDA.

2. Burden Estimates

Based on the number of new establishments that currently register with FDA each year, we estimate that approximately 15 foreign establishments would provide new establishment registrations annually. Based on the number of registered establishments in our database, we estimate that approximately 21 foreign establishments would provide approximately 105 annual reviews and updates of registration information or reviews and certifications that no changes have occurred. Based on the number of changes to registration information that have been submitted annually on Form FDA 2830, we estimate that approximately 21 foreign establishments would provide approximately 80 product listing updates.

The estimates above include 10 foreign establishments with blood products that enter a foreign trade zone and are reexported from that foreign trade zone without having entered U.S. commerce under section 801(d)(4) of the act. We estimate that it would take approximately 60 minutes to provide the initial registration and listing information for each new establishment.

We estimate that it would take approximately 30 minutes for each annual review and update of registration and listing information, including each review and certification that no changes have occurred.

We estimate that it would take approximately 15 minutes to provide the product listing update for each establishment.

The burden hour estimates above are based on institutional experience with the current registration and listing requirements. The estimates are an average of the time it would take to register a foreign establishment and an average of the time it would take to review registration and listing information and update several registration and listing items in the database or review information and only certify that no changes have occurred.

D. Registration and Listing Information Under Part 1271

1. Proposed Requirements

Under proposed § 1271.22, establishments must register, list products, and provide updates electronically. The current regulation requires registration, listing, and updates either electronically or in paper form using Form FDA 3356 and is approved under OMB Control Number 0910-0469.

Under proposed § 1271.25, establishments would submit the telephone and fax numbers, and e-mail address of the reporting official. Each foreign establishment would submit the name, the address, telephone and fax numbers, and e-mail address of each importer that is known to the establishment and the name of each person who imports or offers for import such HCT/P to the United States. Foreign establishments would also submit the name, the address, telephone and fax numbers, and e-mail address of their United States agent.

Under proposed § 1271.26, establishments must report a change to the United States agent's name, address, telephone and fax number, and e-mail address. The proposal would also lengthen to 30 calendar days the current requirement of reporting the changes within 5 days.

2. Burden Estimates

Based on the number of new establishments that currently register with FDA each year, we estimate that approximately 300 establishments would provide new establishment registration annually. Based on information from FDA's database, we estimate that approximately 2,000 establishments are registered and listed with FDA. The number of establishments that currently register and list with FDA include both foreign and domestic establishments. Based on information from FDA's database, we estimate that approximately 1,400 establishments would provide establishment and listing updates. If no change has occurred, an update is not required. Based on the number of establishments from FDA's database, we estimate that approximately 1,800 establishments would provide approximately 2,100 changes to establishment ownership or location, or changes to the United States agent's information.

We estimate that it would take approximately 45 minutes to provide the initial registration and listing information for each new establishment.

We estimate that it would take approximately 30 minutes for each annual review and update of registration and listing information for each establishment.

We estimate that it would take approximately 15 minutes for each establishment to provide a change in ownership and location, or a change to the United States agent's information.

The burden hour estimates above are based on institutional experience with the current registration and listing requirements. The estimates are an average of the time it would take to register an establishment, and an average of the time it would take to review registration and listing information, and update several registration and listing items in the database.

E. User Account Information for Electronic System

Under proposed § 207.61, establishment registration and drug listing information must be submitted to us in electronic format. In addition, the content of labeling must be submitted in electronic format. Other labeling and advertisements may be provided in paper or electronic format. Electronic format submissions must be in a form that we can process, review, and archive. Prior to accepting registration and listing information from the online system, we may need to authenticate the source (that is, manufacturer, repacker, relabeler, or drug product salvager) providing the data. We are proposing to authenticate entry into the electronic drug registration and listing system by establishing user accounts based on the current registration information. We would contact currently registered manufacturers, repackers, relabelers, or drug product salvagers and request that they provide electronic contact information to establish an administration account.

We estimate that approximately 8,343 manufacturers, repackers, relabelers, and drug product salvagers will provide this information (approximately 8,343 submissions) and that it will take approximately 15 minutes to provide the requested information.

F. Waiver Request Information

1. Part 207

Under proposed § 207.65, manufacturers, repackers, relabelers, and drug product salvagers may request a waiver from the requirement in § 207.61 that information must be provided to us in electronic format. We expect very few waiver requests because only a computer, Internet access, and an email address are needed to register and list.

We estimate that approximately two manufacturers, repackers, relabelers, or drug product salvagers would request a waiver annually, and that each request would take approximately 1 hour to prepare and submit to us.

In those instances when we grant a request for a waiver, we intend to make available to the manufacturer, repacker, relabeler, or drug product salvager paper forms—revised Form FDA 2656 for registration and revised Form FDA 2657 for listing (the listing form would include a section for submitting the information required to obtain an NDC number). We intend to request public comment and OMB approval for the revised forms before the effective date of any final rule. The proposed form will be available from the Division of Compliance Risk Management and Surveillance, Office of Compliance, Center for Drug Evaluation and Research (HFD-330), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-8920, herbert.gerstenzang@fda.hhs.gov or john.gardner@fda.hhs.gov.

2. Part 607

Under proposed § 607.40(f)(1), foreign establishments may request a waiver from the requirement in § 607.40(e) that information must be provided to FDA in electronic format. We expect very few waiver requests because only a computer, Internet access, and an e-mail address are needed to register and list.

We estimate that approximately two manufacturers would request a waiver annually, and that each request would take approximately 1 hour to prepare and submit to us.

In those instances when we grant a request for a waiver, we intend to make available to the manufacturer the paper form—Form FDA 2830 for registration and listing.

3. Part 1271

Under proposed § 1271.23, manufacturers may request a waiver from the requirement in § 1271.22 that information must be provided to FDA in electronic format. We expect few waiver requests because only a computer, Internet access, and an e-mail address are needed to register and list.

We estimate that approximately 100 manufacturers would request a waiver annually, and that each request would take approximately 1 hour to prepare and submit to FDA.

In those instances when we grant a request for a waiver, we intend to make available to the manufacturer the paper form—revised Form FDA 3356 for registration and listing. We intend to request public comment and OMB approval for the revised form before the effective date of any final rule.

G. Public Disclosure Exemption Requests

Under proposed § 207.81(c), manufacturers, repackers, relabelers, and drug product salvagers may request that certain information in proposed § 207.81(a) not be made available from their registration and listing information. Based on our experience with registration and listing information inspection requests under current § 207.37, we estimate that approximately 100 manufacturers, repackers, relabelers, or drug product salvagers would submit this request annually, and that each request would take approximately 1 hour to prepare and submit to us.

H. Revised Labeling Submitted With Annual Report

Under the proposal, the NDC number must appear on all drug labels for drugs subject to the listing requirements. Manufacturers, repackers, and relabelers for drug products that do not already have an NDC number on the label would be required to include the NDC number assigned by us.

Manufacturers, repackers, and relabelers for drug products that have an NDC number on the label as it is currently required would be required to examine their current NDC number to ensure that it complies with the NDC number requirements in proposed §§ 201.2, 207.33, and 207.37, and would have to obtain a new NDC number from us if necessary.

When there is a change in the NDC number on a drug label, or when an NDC number is added to a label, application holders must submit revised labeling to us with their annual reports under § 314.81(b)(2) for human drugs, § 514.80(b)(4) for animal drugs (“periodic reports” are required instead of “annual reports”), and § 601.12(f)(3) for biological drugs. The submission of annual reports (or periodic reports for animal drugs) under these regulations is already approved by OMB under Control Number 0910–0001 for human drugs (approval expires 5/31/08), Control Number 0910–0284 for animal drugs (approval expires 9/30/06), and Control Number 0910–0338 for biological products (approval expires 9/30/08). There would be no additional information collection burden associated with any labeling revision because of a new NDC number assigned by us because it would be “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” and exempt under the PRA (5 CFR 1320.3(c)(2)). However, we have estimated a burden of approximately 5 minutes per annual report as the time required to state in the annual report that the labeling has been revised to include a new NDC number and the additional time required to submit to us the revised labeling with the annual report. For the number of submissions, we estimate that no more than approximately one-half of all annual reports submitted for products already listed with FDA on the effective date of the final rule would include this information.

I. Capital Costs

There are one-time capital costs associated with this proposed rulemaking. These costs are discussed in section VI of this document, "Analysis of Economic Impacts."

We specifically request comments on the burden hour estimates described previously in this document and in tables 6, 7, and 8 of this document.

Description of Respondents: Manufacturers, repackers, relabelers, and drug product salvagers.

Burden Estimate: Tables 6, 7, and 8 of this document provide an estimate of the annual reporting burden for the proposed registration and listing requirements.

TABLE 6.—ESTIMATED ANNUAL REPORTING BURDEN UNDER PROPOSED PART 207

21 CFR Sections and Reporting Requirements	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Hours Per Registration and Listing	Total Hours
Initial Establishment Registration (207.25)	987	1.14	1,128	1 hour	1,128
Annual Review and Update of Registration Information (207.29)	8,343	1.45	12,137	.50 hours	6,068.5
Expedited Updates (207.29)	775	2.46	1,921	.25 hours	480.25
Initial Listing and NDC Number Information (207.33, 207.49, 207.53, 207.54, 207.55)	1,812	7.63	13,821	1.50 hrs.	20,731.50
Review and Update of Listing Information (June and December) (207.33, 207.37, 207.57, 314.81(b)(3)(iii), 601.2(f))	2,278	19.81	45,136	.50 hours	22,568
Review and Certification of Listing Information (June and December) (207.57, 601.2(f))	5,594	29.29	163,960	.25 hours	40,990
Review of registration information already in FDA database on effective date of final rule	8,343	1.45	12,137	.50 hours	6,068.5
Review of listing information already in FDA database on effective date of final rule	7,962	13.13	104,548	.75 hours	78,411
User accounts for electronic system	8,343	1	8,343	.25 hours	2,085.75
Waiver requests (207.65) Revised Forms FDA 2656 and 2657	2	1	2	1 hour	2
Public disclosure exemption requests (207.81(c))	100	1	100	1 hour	100
Annual report revision for new NDC number (314.81(b)(2), 514.80(b)(4), 601.12(f)(3))	3,981	13.13	52,289	5 minutes	871.5
Total Reporting Burden					179,505

TABLE 7.—ESTIMATED ANNUAL REPORTING BURDEN UNDER PROPOSED PART 607

21 CFR Sections	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Hours Per Registration and Listing	Total Hours
Initial Establishment Registration and Blood Product Listing (607.40)	15	1	15	1	15
Annual Review and Update of Establishment Registration and Blood Product Listing (607.40)	21	5	105	0.5	52.5
Product Listing Update (607.40)	21	3.8	80	0.25	20
Waiver requests (607.40(f)(1)) Revised Form FDA 2830	2	1	2	1	2

TABLE 7.—ESTIMATED ANNUAL REPORTING BURDEN UNDER PROPOSED PART 607—Continued

21 CFR Sections	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Hours Per Registration and Listing	Total Hours
Total Reporting Burden					89.5

TABLE 8.—ESTIMATED ANNUAL REPORTING BURDEN UNDER PROPOSED PART 1271

21 CFR Sections	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Hours Per Registration and Listing	Total Hours
Initial Establishment Registration and Listing (1271.25)	300	1	300	0.75	225
Annual Review and Update of Establishment Registration and Listing (1271.25)	2,000	1.4	1,400	0.5	501.5
Waiver requests (1271.23) Revised Form FDA 3356	100	1	100	1	100
Amend Establishment Registration (1271.26)	1800	1.16	2100	0.25	525
Total Reporting Burden					1550.5

In compliance with section 3507(d) of the PRA, we have submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to fax comments regarding information collection to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington DC 20503, Attn: Desk Officer for FDA, FAX: (202) 395-6974.

VIII. Environmental Impact

We have determined under 21 CFR 25.30(h) and 25.30(k) 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.

IX. Proposed Effective Date

We propose that any final rule based on this proposal become effective 90 days after publication in the **Federal Register**.

X. Proposed Compliance Dates

We are proposing that our electronic drug registration and listing system be used to enter and update all registration, listing, and NDC number information no later than 9 months after the effective date of a final rule. As

discussed in section IV.C.4.a of this document, manufacturers, repackers, and relabelers would have until 9 months after the effective date of a final rule to review and update the NDC number information in our database for each of their drugs to ensure that it complies with proposed §§ 201.2, 207.33, 207.37, 610.60, and 610.61. In addition, as discussed in section IV.C.4.b of this document, manufacturers, repackers, and relabelers would have, for prescription drugs, 3 years after the effective date of a final rule and, for OTC drugs, 7 years after the effective date of a final rule, to ensure that the appropriate NDC number correctly appears on the label of each of their listed drugs, in accordance with the requirements in proposed §§ 201.2, 207.33, 207.37, 610.60, and 610.61. We are considering shortening the compliance dates by which the appropriate NDC number must appear on drug labels to 2 years after the effective date of a final rule for prescription drugs and 5 years after the effective date of a final rule for OTC drugs. We discuss this issue further in section VI of this document, "Analysis of Economic Impacts."

We specifically request comments on these proposed compliance dates.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies 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. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this proposal. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper 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 Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XIII. References

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

1. Letter from John M. Coster, Vice President, Policy and Programs, NACDS, and Lisa Clowers, Senior Vice President, Industry Relations, HDMA, to Michael D. Jones, FDA, dated September 27, 2004.
2. Letter from the Deputy Director, Division of Prescription Drug Compliance and Surveillance, CDER, FDA to John M. Coster, National Association of Chain Drug Stores, August 24, 1997.
3. Eastern Research Group, Inc., Foreign and Domestic Establishment Registration and Listing Requirements for Human Drugs, Certain Biological Drugs, and Animal Drugs, August 2005.
4. Eastern Research Group, Inc., Profile of the Prescription Drug Wholesale Industry, February 2001.
5. Eastern Research Group, Inc., Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Regulation, March 1999.

List of Subjects

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 207

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 314

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

21 CFR Part 330

Over-the-counter drugs.

21 CFR Parts 514 and 515

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 607

Blood.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 1271

Biologics, Drugs, Human cells and tissue-based products, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 20, 201, 207, 314, 330, 514, 515, 601, 607, 610, and 1271 be amended as follows:

PART 20—PUBLIC INFORMATION

1. The authority citation for 21 CFR part 20 continues to read as follows:

Authority: 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 321–393, 1401–1403; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–l.

§ 20.100 [Amended]

2. Section 20.100 is amended in paragraph (c)(9) by removing “§ 207.37” and by adding in its place “§ 207.81”.

3. Section 20.116 is revised to read as follows:

§ 20.116 Drug and device registration and listing information.

Information submitted to the Food and Drug Administration pursuant to section 510(a) through (j) of the act shall be subject only to the special disclosure provisions established in §§ 207.81 and 807.37 of this chapter.

PART 201—LABELING

4. 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.

§ 201.1 [Amended]

5. Section 201.1 is amended in paragraph (f) by removing “§ 207.3(b)” and by adding in its place “§ 207.1”.

6. Section 201.2 ^{is} ~~and the section heading~~ are revised to read as follows:

§ 201.2 Drugs; National Drug Code (NDC) number.

(a) What drugs must have an NDC number in human-readable form on the label? Drugs subject to the drug listing requirements of part 207 of this chapter must have labels that bear the appropriate NDC number in human-readable form, in accordance with the provisions of this section.

(b) What is the appropriate NDC number? The appropriate NDC number is the NDC number of the manufacturer, repacker or relabeler (including a drug product salvager who repacks or relabels the drug), or private label distributor, as defined in § 207.1 of this chapter, that is the last manufacturer, repacker, relabeler, or private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer. The appropriate NDC number is assigned to the drug as described in §§ 207.33 and 207.37 of this chapter. The unique NDC number assigned to each package size and type of a drug must appear on the corresponding label for the particular package size and type of the drug.

(c) May any other NDC number appear on the label? No. Only the appropriate NDC number required by paragraph (b) of this section to appear on the label may appear on the label.

(d) What prefix must be used to identify the NDC number on the label? The NDC number in human-readable form must be immediately preceded by the letters NDC.

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(e) Must the NDC number appear at a specific location on the label? No.

However, the appropriate NDC number must appear clearly on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act.

7. Section 201.25 is amended in paragraph (c)(1) ^{introductory text} by adding a sentence after the first sentence and by adding paragraph (e) to read as follows:

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§ 201.25 Bar code label requirements.

* * * * *

(c) * * *

(1) * * * For purposes of this section "appropriate NDC number" is described in § 201.2(b). * * *

* * * * *

(e) Can a drug that is not subject to the bar code requirement display a bar code? A drug product that is subject to the drug listing requirements of part 207 of this chapter but is not subject to this section may display a bar code on the label only if the bar code meets the requirements of paragraph (c) of this section.

8. Part 207 is revised to read as follows:

PART 207—REQUIREMENTS FOR FOREIGN AND DOMESTIC ESTABLISHMENT REGISTRATION AND LISTING FOR HUMAN DRUGS, INCLUDING DRUGS THAT ARE REGULATED UNDER A BIOLOGICS LICENSE APPLICATION, AND ANIMAL DRUGS

Subpart A—General

Sec.

207.1 What definitions and interpretations of terms apply to this part?

207.5 What is the purpose of this part?

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Subpart B—Registration

207.17 Who must register?

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Subpart C—National Drug Code Number

207.33 What is the National Drug Code (NDC) number, who must obtain it, and what information must be submitted?

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Subpart D—Listing

207.41 Who must list drugs?

207.45 When must initial listing information be provided?

207.49 What listing information is required for manufacturers?

207.53 What listing information is required for repackers and relabelers?

207.54 What listing information is required for drug product salvagers who are not repackers or relabelers?

207.55 What additional drug listing information may be required?

207.57 What are the requirements for reviewing and updating listing information?

Subpart E—Electronic Format for Registration and Listing

207.61 How is registration and listing information provided to FDA?

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Subpart F—Miscellaneous

207.69 What are the requirements for an official contact and a United States agent?

207.77 What legal status is conferred by registration and listing?

207.81 What registration and listing information will we make available for public disclosure?

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360b, 371, 374, 381, 393;
42 U.S.C. 262, 264, 271.
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SUBPART A—GENERAL

§ 207.1 What definitions and interpretations of terms apply to this part?

The definitions and interpretations of terms in section 510 of the act apply to the terms used in this part. The following definitions also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (52 Stat. 1040, *et seq.*, as amended (21 U.S.C. 301, *et seq.*)), except as otherwise provided.

Active pharmaceutical ingredient means any substance that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance.

Commercial distribution means any distribution of a human drug except for investigational use under part 312 of this chapter, and any distribution of an animal drug or an animal feed bearing or containing an animal drug for noninvestigational uses, but the term does not include internal or interplant transfer of an active pharmaceutical ingredient between registered establishments within the same parent, subsidiary, and/or affiliate company. For foreign manufacturers, foreign repackers, foreign relabelers, foreign drug product salvagers, foreign private label distributors, and foreign establishments, the term “commercial distribution” has the same meaning except the term does not include distribution of any drug that is neither imported nor offered for import into the United States.

Content of labeling means: (1) For human prescription drugs that the manufacturer regards as subject to section 505 of the act or section 351 of the Public Health Service Act: The content of the prescription drug labeling (as specified in §§ 201.56, 201.57, and 201.80 of this chapter), including all text, tables, and figures.

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(2) For human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the Public Health Service Act: The labeling equivalent to the content of the prescription drug labeling (as specified in §§ 201.56, 201.57, and 201.80 of this chapter), including all text, tables, and figures.

(3) For human over-the-counter (OTC) drugs: The content of the drug facts labeling required by § 201.66 of this chapter, including all text, tables, and figures.

(4) For animal drugs (including, but not limited to, drugs that the manufacturer regards as subject to section 512 of the act): The content of the labeling that accompanies the drug that is necessary to enable safe and proper administration of the drug (e.g., the labeling specified in §§ 201.1 and 201.5 of this chapter), including all text, tables, and figures.

Domestic for the purposes of registration and listing under this part, when used to modify the term “manufacturer,” “repacker,” “relabeler,” “drug product salvager,” “private label distributor,” or “establishment,” refers to a manufacturer, repacker, relabeler, drug product salvager, private label distributor, or establishment within any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

Drug(s) for the purposes of registration and listing under this part, has the meaning given in section 201(g)(1) of the act.

* place here → *Drug product salvaging* means applying manufacturing controls such as those required by current good manufacturing practice in parts 210 and 211 of this chapter to drug products and segregating out those drug products that may have been subjected to improper storage conditions (such as extremes in

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temperature, humidity, smoke, fumes, pressure, age, or radiation) for the purpose of returning the products to the marketplace.

Drug product salvager means a person who owns or operates an establishment that engages in drug product salvaging. When not modified by “domestic” or “foreign,” the term includes both domestic drug product salvagers and foreign drug product salvagers.

Establishment for purposes of registration and drug listing means a place of business under one management at one geographic location. One geographic location may include separate buildings within the same city if their activities are closely related to the same business enterprise and are under the supervision of the same local management. When not modified by “domestic” or “foreign,” the term includes both domestic and foreign establishments.

Establishment registration number means the number assigned by FDA to the establishment during the establishment registration process required in this part.

Foreign for the purposes of registration and listing under this part:

(1) When used to modify the term “manufacturer,” “repacker,” “relabeler,” “drug product salvager,” or “private label distributor” refers to a manufacturer, repacker, relabeler, drug product salvager, or private label distributor who is located in a foreign country and who manufactures, repacks, relabels, salvages, or distributes a drug that is imported or offered for import into the United States.

(2) When used to modify the term “establishment” refers to an establishment that is located in a foreign country and is the site where a drug that is imported or offered for import into the United States was manufactured, repacked, relabeled, salvaged, or distributed.

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Importer means, for purposes of this part, a company or individual in the United States that is an owner, consignee, or recipient, even if not the initial owner, consignee, or recipient, of the foreign establishment's drug that is imported into the United States. An importer does not include the consumer or patient who ultimately purchases, receives, or is administered the drug, unless the foreign establishment ships the drug directly to the consumer or patient.

Manufacture means each step in the manufacture, preparation, propagation, compounding, or processing of a drug. Manufacture includes the making by chemical, physical, biological, or other procedures or manipulations of a drug, including control procedures applied to the final product or to any part of the process. Manufacture includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process, including, for example, analytical testing of drugs, for another registered establishment's drug. For purposes of this part, and in order to clarify the responsibilities of the different parties, the term manufacture is defined and used separately from the terms relabel, repackage, and salvage, although the term "manufacture, preparation, propagation, compounding, or processing," as used in section 510 of the act, includes relabeling, repackaging, and drug product salvaging activities.

Manufacturer means a person who owns or operates an establishment that manufactures a drug. This term includes, but is not limited to, control laboratories, contract laboratories, contract manufacturers, contract packers, contract labelers, and other entities that manufacture a drug as defined in this paragraph. For purposes of this part, and in order to clarify the responsibilities of the different parties, the term manufacturer is defined and used separately

from the terms relabeler, repacker, and drug product salvager, although the term “manufacture, preparation, propagation, compounding, or processing,” as used in section 510 of the act, includes the activities of relabelers, repackers, and drug product salvagers. Repackers, relabelers, and drug product salvagers are subject to the provisions of this part that are applicable to repackers, relabelers, and drug product salvagers, but are not subject to the provisions of this part that are applicable to manufacturers. When not modified by “domestic” or “foreign,” the term includes both domestic manufacturers and foreign manufacturers.

Material change means any change in any drug listing information, as required under §§ 207.49, 207.53, 207.54, 207.55, or 207.57 except changes in arrangement or printing of labeling, labeling changes of an editorial nature, or inclusion of a bar code or NDC number on the label.

Person who imports or offers for import means, for purposes of this part, an agent, broker, or other entity, other than a carrier, that the foreign establishment uses to facilitate the import of its drug into the United States.

Private label distributor means a person who owns or operates an establishment that commercially distributes, under its own label or trade name, any drug manufactured, repacked, relabeled, or salvaged by a registered establishment. When not modified by “domestic” or “foreign,” the term includes both domestic private label distributors and foreign private label distributors.

Relabel means to change the label or labels on a drug or drug package, or add to the labeling for a drug or drug package, without repacking the drug or drug package.

Relabeler means a person who owns or operates an establishment that relabels a drug. When not modified by “domestic” or “foreign,” the term includes both domestic relabelers and foreign relabelers.

Repack means to repack or repackage or otherwise change the container or wrapper of a drug or drug package.

Repacker means a person who owns or operates an establishment that repacks a drug or drug package. When not modified by “domestic” or “foreign,” the term includes both domestic repackers and foreign repackers.

Representative sampling of advertisements means typical advertising material (including the promotional material described in § 202.1(l)(1) of this chapter, but excluding labeling as determined in § 202.1(l)(2) of this chapter), that gives a balanced picture of the promotional claims used for the drug.

Representative sampling of any other labeling means typical labeling material (including the promotional material described in § 202.1(l)(2) of this chapter, but excluding labels and package inserts) that gives a balanced picture of the promotional claims used for the drug.

§ 207.5 What is the purpose of this part?

Establishment registration information helps us to identify who is manufacturing, repacking, relabeling, or salvaging drugs and where those operations are being performed. Drug listing information gives us a current inventory of marketed drugs. Both types of information facilitate our implementation and enforcement of the act and are used for many important public health purposes.

§ 207.9 Who does this part cover?

(a) This part applies to domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers, not exempt under

section 510(g) of the act or § 207.13, regardless of whether their drugs enter interstate commerce.

(b) This part applies to foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers, not exempt under §§ 207.13(c) through (h).

(c) This part applies to certain manufacturers of drugs regulated under a biologics license application (BLA):

(1) Except as provided in paragraphs (c)(2) and (c)(3) of this section, this part applies to manufacturers of drugs regulated under a BLA, including but not limited to the following:

(i) Plasma derivatives such as albumin, Immune Globulin, Factor VIII and Factor IX, and recombinant versions of plasma derivatives or animal derived plasma derivatives;

(ii) Vaccines;

(iii) Allergenic products;

(iv) Bulk product substances such as fractionation intermediates or pastes;

and

(v) Therapeutic biological products.

(2) This part, as well as part 1271 of this chapter, applies to establishments solely engaged in the manufacture (as defined in § 1271.3(e) of this chapter) of human cells, tissues, and cellular and tissue-based products (HCT/Ps) (as defined in § 1271.3(d) of this chapter) that, under § 1271.20 of this chapter, are also drugs regulated under section 351 of the Public Health Service Act or section 505 of the act. These establishments must:

(i) Register and list those HCT/Ps with the Center for Biologics Evaluation and Research by following the procedures described in subpart B of part 1271

of this chapter, instead of the procedures for registration and listing described in this part, and

(ii) Submit to the Center for Biologics Evaluation and Research the information specified in §§ 207.33(c)(2)(i) and (c)(2)(ii), 207.49(a), (b), (g), and (h)(2), 207.53(a), (c), (d), and (e)(2), 207.54(b)(1), and 207.55.

(3) This part does not apply to owners and operators of human blood and blood product establishments, except as provided in paragraphs (c)(1)(i) and (c)(1)(iv) of this section. Establishments that collect or process whole blood and blood products as well as establishments involved in testing of whole blood and blood products must register and list under part 607 of this chapter. Manufacturers of licensed devices and manufacturers of licensed biologic components used in a licensed device must register and list under part 607 of this chapter.

(d) This part does not apply to establishments that solely manufacture, prepare, propagate, compound, assemble, or process medical devices. Registration and listing regulations for such establishments are codified in part 807 of this chapter.

§ 207.13 Who is exempt from the registration and listing requirements?

Except as provided in § 207.13(i), the following classes of persons are exempt from registration and drug listing in accordance with this part under section 510(g) of the act or because we have found, under section 510(g)(5) of the act, that their registration is not necessary for the protection of the public health. This exemption is limited to establishment registration and drug listing requirements and does not relieve a person from other statutory or regulatory obligations.

(a) *Pharmacies.* (1) Pharmacies that:

(i) Operate in conformance with all applicable local laws regulating the practice of pharmacy, including all applicable local laws regulating the dispensing of prescription drugs;

(ii) Regularly engage in dispensing prescription drugs upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care; and

(iii) Do not manufacture (as defined in § 207.1), repack, or relabel drugs for sale other than in the regular course of the practice of pharmacy, including dispensing and selling drugs at retail.

(2) The exemption in paragraph (a) of this section is limited to pharmacies located in any State as defined in section 201(a)(1) of the act.

(b) *Hospitals, clinics, other health care entities, and public health agencies.* (1) Hospitals, clinics, other health care entities, and public health agencies that:

(i) Operate establishments in conformance with all applicable local laws regulating the practice of pharmacy and medicine, including all applicable local laws regulating the dispensing of prescription drugs;

(ii) Regularly engage in dispensing prescription drugs, other than human blood or blood products, upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care; and

(iii) Do not manufacture (as defined in § 207.1), repack, or relabel drugs other than in the regular course of the practice of pharmacy, including dispensing.

(2) The exemption in paragraph (b) of this section is limited to hospitals, clinics, other health care entities, and public health agencies located in any State as defined in section 201(a)(1) of the act.

(c) Practitioners who are licensed by law to prescribe or administer drugs and who manufacture, repack, or relabel drugs solely for use in their professional practice.

(d) Manufacturers, repackers, relabelers, or drug product salvagers who manufacture, repack, relabel, or salvage drugs solely for use in research, teaching, or chemical analysis and not for sale.

(e) Manufacturers, repackers, relabelers, and drug product salvagers of harmless inactive ingredients that are excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs.

(f) Manufacturers, repackers, relabelers, or drug product salvagers of Type B or Type C medicated feeds, except for manufacturers, repackers, relabelers, or drug product salvagers of Type B or Type C medicated feeds made from Category II, Type A medicated articles. This exemption does not apply to persons that would otherwise be required to register (such as manufacturers, repackers, relabelers, or drug product salvagers of certain free-choice feeds, as defined in § 510.455 of this chapter, or certain liquid feeds, as defined in § 558.5 of this chapter, where the specifications and/or formulas are not published and a feed mill license is required). All manufacturers, repackers, relabelers, or drug product salvagers of Type B or Type C medicated feeds are exempt from listing.

(g) Any manufacturer, repacker, relabeler, or drug product salvager of a virus, serum, toxin, or analogous product intended for the treatment of domestic animals who holds an unsuspended and unrevoked license issued by the Secretary of Agriculture under the animal virus-serum-toxin law of March 4, 1913 (37 Stat. 832 (21 U.S.C. 151 *et seq.*)), provided that this

exemption from registration applies only to the manufacturer, repacker, relabeler, or drug product salvager of that animal virus, serum, toxin, or analogous product.

(h) Carriers, in their receipt, carriage, holding, or delivery of drugs in the usual course of business as carriers.

(i) The exemptions provided in paragraphs (a) through (h) of this section do not apply to such persons if they:

(1) Manufacture (as defined in § 207.1), repack, relabel, or salvage compounded positron emission tomography drugs as defined in section 201(ii) of the act.

(2) Manufacture (as defined in § 600.3(u) of this chapter) a biological product subject to licensing under section 351 of the Public Health Service Act;

(3) Manufacture (as defined in § 1271.3(e) of this chapter) an HCT/P that, under § 1271.20 of this chapter, are also drugs regulated under section 351 of the Public Health Service Act or section 505 of the act; or

(4) Engage in activities that would otherwise require them to register under this part.

SUBPART B—REGISTRATION

§ 207.17 Who must register?

(a) All manufacturers, repackers, relabelers, and drug product salvagers must register establishments in accordance with this part. When operations are conducted at more than one establishment and joint ownership and control among all the establishments exists, the parent, subsidiary, and/or affiliate company may submit registration information for all establishments.

(b) Private label distributors must not register with us unless they also manufacture, repack, relabel, or salvage drugs and are required to register under paragraph (a) of this section.

§ 207.21 When must initial registration information be provided?

Domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers must register each establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug. Foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers must register each establishment before a drug manufactured, repacked, relabeled, or salvaged at the establishment is imported or offered for import into the United States.

§ 207.25 What information is required for registration?

Manufacturers, repackers, relabelers, and drug product salvagers must provide the following information to us:

(a) Name of the owner or operator of each establishment; if a partnership, the name of each partner; if a corporation, the name of each corporate officer and director, and the place of incorporation;

(b) Name of each establishment;

(c) Any trade name(s) of the establishment, names under which the establishment conducts business, and additional names by which the establishment is known;

(d) Address of each establishment;

(e) Registration number of each establishment, if previously assigned by us; if not previously assigned by us, we will assign a registration number after we receive the registration information;

(f) Type of operations performed at each establishment (for example, manufacturing, repacking, relabeling, or salvaging);

(g) Name, address, telephone and fax numbers, and e-mail address of the official contact, as provided in § 207.69(a), for each establishment; and

(h) With respect to foreign establishments only, for drugs manufactured, repacked, relabeled, or salvaged at the establishment, the name, address, telephone and fax numbers, and e-mail address must also be provided for:

(1) The United States agent, as provided in § 207.69(b);

(2) Each importer of such drug in the United States that is known to the establishment; and

(3) Each person who imports or offers for import such drug to the United States.

§ 207.29 What are the requirements for reviewing and updating registration information?

(a) *Expedited updates.* Manufacturers, repackers, relabelers, and drug product salvagers must update their registration information no later than 30 calendar days after:

(1) Closing or selling an establishment;

(2) Changing an establishment's name or address; or

(3) Changing the name, address, telephone and fax numbers, or e-mail address of the official contact or the United States agent. A manufacturer, repacker, relabeler, and drug product salvager, official contact, or United States agent may notify us about a change of information for the designated official contact or United States agent, but only a manufacturer, repacker, relabeler, or drug product salvager may designate a new official contact or United States agent.

(b) *Annual review and update of registration information.* Manufacturers, repackers, relabelers, and drug product salvagers must review and update all registration information required under § 207.25 for each establishment.

(1) The first review and update must occur no later than 1 year after the date of initial registration, and subsequent reviews and updates must occur no later than annually thereafter from the date of initial registration.

(2) The updates must reflect all changes that have occurred since the last annual review and update.

(3) If no changes have occurred since the last annual registration (accomplished through the review and update of registration information), manufacturers, repackers, relabelers, and drug product salvagers must certify that no changes have occurred.

SUBPART C—NATIONAL DRUG CODE NUMBER

§ 207.33 What is the National Drug Code (NDC) number, who must obtain it, and what information must be submitted?

(a) *What is the NDC number?* The NDC number is a unique 10 digit number with 3 segments. The three segments are the labeler code, the product code, and the package code. We will assign the complete NDC number (that will include the existing labeler code, if any) to each drug that is subject to the listing requirements in this part.

(b) *Who must obtain an NDC number?*

(1) Manufacturers, repackers, or relabelers, must obtain an NDC number from us for each drug that is subject to the drug listing requirements in this part.

(2) Drug product salvagers must obtain an NDC number from us for each drug that is subject to the drug listing requirements in this part only if they repack or relabel the salvaged drug. Drug product salvagers must follow the requirements for repackers and relabelers in paragraphs (d), (e), (f), and (g) of this section.

(3) If you are a private label distributor, the manufacturer, repacker, relabeler or drug product salvager (described in paragraph (b)(2) of this section) who manufactures, repacks, or relabels a drug for you is responsible for obtaining an NDC number from us for each drug that is subject to the drug listing requirements in this part.

(c) *What information must a manufacturer submit before we will assign an NDC number to a drug?* Before we assign an NDC number to a drug, the manufacturer must submit the information required under paragraphs (c)(1), (c)(2), or (c)(3) of this section. If that information changes (or as otherwise specified in paragraph (f) of this section), we will assign a new NDC number as described in paragraph (f) of this section.

(1) *Assigning an NDC number to an active pharmaceutical ingredient.* We will assign a unique NDC number to a drug that is an active pharmaceutical ingredient when the manufacturer provides the following information for the drug:

(i) The manufacturer's name, address, telephone and fax numbers, e-mail address, and labeler code;

(ii) The drug's established name and proprietary name, if any;

(iii) The package size and type; and

(iv) The Drug Master File number or Veterinary Master File number, if any, assigned to the active pharmaceutical ingredient.

(2) *Assigning an NDC number to a manufacturer's drug other than an active pharmaceutical ingredient.* We will assign a unique NDC number to a drug when the manufacturer provides, in addition to the information described in paragraphs (c)(1)(i) and (c)(1)(ii) of this section, the following information for the drug:

(i) The name and quantity of each active pharmaceutical ingredient unless the approved U.S. application number is provided;

(ii) Unless the approved U.S. application number is provided, the name of each inactive ingredient for each human and animal drug that the manufacturer regards as subject to section 505 or section 512 of the act or section 351 of the Public Health Service Act, and for each human over-the-counter drug that the manufacturer regards as not subject to section 505 of the act, and whether the name of the inactive ingredient falls under § 20.61 of this chapter or is otherwise prohibited from disclosure and, if so, why;

(iii) The dosage form;

(iv) The package size and type, including immediate unit-of-use container;

(v) The drug's marketing status (e.g., prescription or OTC);

(vi) The drug or drug product type (e.g., human drug or animal drug); and

(vii) For each drug product subject to the listing requirements and covered under § 206.1, including products that are exempted under § 206.7(b), manufacturers must provide the size, shape, color, and code imprint (if any).

(3) *Assigning an NDC number to a drug manufactured for a private label distributor.* We will assign a unique NDC number to a drug manufactured for a private label distributor when the manufacturer provides, in addition to the information described in paragraph (c)(1) of this section (for active pharmaceutical ingredients manufactured for a private label distributor) or paragraph (c)(2) of this section (for all other drugs manufactured for a private label distributor), the following information for the drug:

(i) The private label distributor's name, address, telephone and fax numbers, e-mail address, and labeler code; and

(ii) The drug's proprietary name, if any, assigned by the private label distributor.

(d) *What information must the repacker or relabeler submit before we will assign an NDC number to a drug?* Before we assign an NDC number to a drug, the repacker or relabeler must submit the information required under paragraphs (d)(1) or (d)(2) of this section. If that information changes, we will assign a new NDC number as described in paragraph (f) of this section.

(1) *Assigning an NDC number to a repacker's or relabeler's drug.* We will assign a unique NDC number to a drug, including an active pharmaceutical ingredient, when the repacker or relabeler of the drug provides the following information for the drug:

(i) The repacker or relabeler's name, address, telephone and fax numbers, e-mail address, and labeler code;

(ii) The NDC number assigned to the drug immediately before the drug is received by the repacker or relabeler;

(iii) The type of operation performed for the drug (that is, whether repacking or relabeling);

(iv) The drug's established name and proprietary name, if any; and

(v) For the repacker only, the package size and type, including immediate unit-of-use container, if any.

(2) *Assigning an NDC number to the drug repacked or relabeled for a private label distributor.* We will assign a unique NDC number to a drug repacked or relabeled for a private label distributor when the repacker or relabeler provides, in addition to the information described in paragraph (d)(1) of this section, the following information for the drug:

(i) The private label distributor's name, address, telephone and fax numbers, e-mail address, and labeler code; and

(ii) The drug's proprietary name, if any, assigned by the private label distributor.

(e) *How must the information be submitted to us?* The information required in paragraphs (c), (d), and (f) of this section must be provided to us in accordance with § 207.61(a)(1)(ii) and (b), unless we grant a waiver under § 207.65.

(f) *What changes in the information will require a new NDC number?* (1) Manufacturers, repackers, and relabelers must obtain a new NDC number for a drug when there is a change in any of the information for the drug required under paragraphs (c) and (d) of this section. Changes must be submitted to us in accordance with paragraphs (e) and (g) of this section. However, we will not assign a new NDC number when the change involves only the following contact information for the manufacturer, repacker, relabeler, or private label distributor: Name, address, telephone and fax numbers, and e-mail address.

(2) In addition to the requirements in paragraph (f)(1) of this section, manufacturers must obtain a new NDC number when there is a change in an inactive ingredient for each human prescription drug that the manufacturer regards as not subject to section 505 of the act and for each animal drug that the manufacturer regards as not subject to section 512 of the act.

(g) *When must a manufacturer, repacker, or relabeler provide the information for an NDC number?* A manufacturer, repacker, or relabeler must provide the information in paragraphs (c), (d), and (f) of this section to us either before or at the time drug listing information is required under § 207.45 or § 207.57.

§ 207.37 What restrictions pertain to the use of NDC numbers?

Manufacturers, repackers, and relabelers must not:

(a) Use an NDC number to represent a different drug than the drug to which the NDC number has been assigned under § 207.33.

(b) Use a different NDC number if marketing is resumed for a drug that was discontinued earlier. If marketing is resumed for a drug, and no changes have been made to the drug that would require a new NDC number under § 207.33(f), the drug must have the same NDC number that was assigned to it under § 207.33 before marketing was discontinued.

(c) Use the NDC number to denote FDA approval of that drug.

(d) Use the NDC number on products that are not subject to this part, such as dietary supplements and medical devices.

SUBPART D—LISTING

§ 207.41 Who must list drugs?

(a) Manufacturers, repackers, relabelers, and drug product salvagers who are subject to the registration requirements under § 207.17 must list their drugs being manufactured, repacked, relabeled, or salvaged for commercial distribution. Domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers who are subject to the registration requirements under § 207.17 must list such drugs regardless of whether the drugs enter interstate commerce. When operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments, listing information may be submitted by the parent, subsidiary, and/or affiliate company for drugs at all establishments.

(b) Manufacturers, repackers, relabelers, and drug product salvagers who engage in more than one activity for drugs must list each drug in accordance with the requirements for the activity engaged in for that drug. For example, a company may manufacture Drug X and relabel Drug Y. The company must provide the information described in § 207.49 for Drug X and the information described in § 207.53 for Drug Y.

(c) Manufacturers, repackers, relabelers, and drug product salvagers must provide all listing information to us for drugs that they manufacture, repack, relabel, or salvage for private label distributors. Private label distributors must not list drugs that they do not manufacture, repack, relabel, or salvage for commercial distribution.

§ 207.45 When must initial listing information be provided?

At the time of initial registration of an establishment, manufacturers, repackers, relabelers, and drug product salvagers must list any drug being manufactured, repacked, relabeled, and salvaged for commercial distribution at that establishment.

§ 207.49 What listing information is required for manufacturers?

Manufacturers must provide all of the following listing information to us for each drug they list, including a drug manufactured for a private label distributor:

(a) The NDC number, assigned by us under § 207.33, for each drug; the NDC number must be provided for the drug to be considered listed;

(b) The route of administration of the drug;

(c) The approved U.S. application number or approved U.S. BLA number, if any;

(d) The registration number of each establishment where the manufacturing is performed for the drug;

(e) The schedule of the drug under section 202 of the Controlled Substances Act, if applicable;

(f) With respect to foreign establishments only, unless previously provided under § 207.25(h), the name, address, telephone and fax numbers, and e-mail address of each importer of such drug in the United States that is known to

the establishment, and of each person who imports or offers for import such drug to the United States;

(g) *Labeling*—(1) *Human prescription drugs*. Unless the approved U.S. application number is provided under paragraph (c) of this section, a copy of all current labeling (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code), including the content of labeling for each human prescription drug;

(2) *Human OTC drugs*—(i) *Manufacturer regards as subject to section 505 of the act or section 351 of the Public Health Service Act*. A copy of all current labeling (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code), including the content of labeling for each human OTC drug that the manufacturer regards as subject to section 505 of the act or section 351 of the Public Health Service Act, unless the approved U.S. application number is provided under paragraph (c) of this section;

(ii) *Manufacturer regards as not subject to section 505 of the act or section 351 of the Public Health Service Act*. A copy of the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code), the content of labeling, the package insert (if any), and a representative sampling of any other labeling for each human OTC drug that the manufacturer regards as not subject to section 505 of the act or section 351 of the Public Health Service Act;

(3) *Animal drugs*—(i) *Manufacturer regards as subject to section 512 of the act*. A copy of all current labeling (except that only one representative

container or carton label need be submitted where differences exist only in the quantity of contents statement), including the content of labeling, for each animal drug that the manufacturer regards as subject to section 512 of the act;

(ii) *Manufacturer regards as not subject to section 512 of the act.* For all other animal drugs, a copy of the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), the package insert, the content of labeling, and a representative sampling of any other labeling, for each drug that the manufacturer regards as not subject to section 512 of the act;

(h) *Advertisements.* (1) A representative sampling of advertisements for human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the Public Health Service Act;

(2) If we request it, for good cause, a copy of all advertisements for a particular drug described in paragraph (h)(1) of this section, including those described in § 202.1(l)(1) of this chapter. Such advertisements must be submitted within 30 calendar days after our request; and

(i) If the drug is manufactured for a private label distributor, the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor.

§ 207.53 What listing information is required for repackers and relabelers?

Repackers and relabelers must provide all of the following listing information to us for each drug they list, including a drug repacked or relabeled for a private label distributor:

(a) The NDC number, assigned by us under § 207.33, for each drug; the NDC number must be provided for the drug to be considered listed;

(b) The registration number of each establishment where the repacking or relabeling is performed for the drug;

(c) With respect to foreign establishments only, unless previously provided under § 207.25(h), the name address, telephone and fax numbers, and e-mail address of each importer of such drug in the United States that is known to the establishments, and of each person who imports or offers for import such drug to the United States;

(d) *Labeling*—(1) *Human prescription drugs*. If any change in labeling is made to the drug repacked or relabeled, a copy of all changed labeling for each human prescription drug that is repacked or relabeled;

(2) *Human OTC drugs*—(i) *Manufacturer regards as subject to section 505 of the act or section 351 of the Public Health Service Act*. If any change in labeling is made to the drug repacked or relabeled, a copy of all changed labeling for each human OTC drug that is repacked or relabeled;

(ii) *Manufacturer regards as not subject to section 505 of the act or section 351 of the Public Health Service Act*. A copy of the current label, a copy of any changes made to the package insert, if there is one, and a representative sampling of any other labeling for each human OTC drug that the manufacturer of the drug regards as not subject to section 505 of the act or section 351 of the Public Health Service Act;

(3) *Animal drugs*. A copy of the current label, a copy of changes made to each animal drug labeling, and a representative sampling of any other labeling for each animal drug;

(e) *Advertisements*. (1) A representative sampling of advertisements for human prescription drugs that the repacker or relabeler regards as not subject to section 505 of the act or section 351 of the Public Health Service Act;

(2) If we request it for good cause, a copy of all advertisements for a particular drug described in paragraph (e)(1) of this section, including those

described in § 202.1(l)(1) of this chapter. Such advertisements must be submitted within 30 calendar days after our request; and

(f) If the drug is repacked or relabeled for a private label distributor, the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor.

§ 207.54 What listing information is required for drug product salvagers who are not repackers or relabelers?

(a) Drug product salvagers who also repack and relabel the drugs they salvage must list those drugs as a repacker or relabeler in accordance with § 207.53.

(b) Drug product salvagers who do not otherwise repack or relabel drugs they salvage must provide all of the following listing information to us for each drug they list, including a drug salvaged for a private label distributor:

(1) The NDC number assigned to the drug immediately before the drug is received by the drug product salvager; the NDC number must be provided for the drug to be considered listed;

(2) The lot number and expiration date of the salvaged drug product;

(3) The registration number of each establishment where the drug product salvager salvages the drug;

(4) With respect to foreign establishments only, unless previously provided under § 207.25(h), the name address, telephone and fax numbers, and e-mail address of each importer of such drug in the United States that is known to the establishment, and of each person who imports or offers for import such drug to the United States; and

(5) If the drug is salvaged for a private label distributor, the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor.

§ 207.55 What additional drug listing information may be required?

For a particular drug product, upon our request, the manufacturer, repacker, relabeler, or drug product salvager must briefly state the basis for its belief that the drug product is not subject to section 505 or 512 of the act or section 351 of the Public Health Service Act.

§ 207.57 What are the requirements for reviewing and updating listing information?

Manufacturers, repackers, relabelers, and drug product salvagers must review and update their drug listing information required under §§ 207.49, 207.53, 207.54, and 207.55.

(a) Manufacturers, repackers, relabelers, and drug product salvagers must provide listing information, during the annual review and update of registration information, for any drug that has not been previously listed.

(b) Manufacturers, repackers, relabelers, and drug product salvagers must review and update their listing information each June and December of every year. They must:

(1) Provide listing information, in accordance with §§ 207.49, 207.53, 207.54, and 207.55, for any drug manufactured, repacked, relabeled, or salvaged for commercial distribution that has not been previously listed;

(2) Submit the date that they discontinued the manufacture, repacking, relabeling, or salvaging for commercial distribution of a listed drug and provide the expiration date of the last lot manufactured, repacked, relabeled, or salvaged;

(3) Submit the date that they resumed the manufacture, repacking, or relabeling for commercial distribution of a drug previously discontinued and provide any other listing information not previously required or submitted;