DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20, 201, 207, 314, 330, 514, 515, 601, 607, 610, and 1271

[Docket No. 2005N–0403]

RIN 0910–AA49

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

AGENCY: Food and Drug Administration, HHS

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations governing drug establishment registration and drug listing. The proposed revisions would reorganize, consolidate, clarify, and modify current regulations concerning who must register establishments and list human drugs, human drugs that are also biological products (including vaccines and allergenic products), and/or human cells, tissues, and cellular and tissue-based products (HCT/Ps), and animal drugs. The proposal describes when and how to register and list and what information must be submitted for registration and listing. In addition, the proposal would make certain changes to the National Drug Code (NDC) system and would require the appropriate NDC number to appear on the labels for drugs subject to the listing requirements. The proposed regulations generally would require the electronic submission of all registration and most listing information. We (FDA) rely on establishment registration and drug listing information for administering many of our

programs, such as postmarketing surveillance (including FDA inspections), bioterrorism, drug shortages and availability, and user fee assessments. We are taking this action to use the latest technology to improve our registration and listing system, which would further our goal of protecting the public health. We also believe that the conversion to an electronic system would make the registration and listing processes more efficient and effective for industry and us. We are also taking this action to support the implementation of, for example, the electronic prescribing provisions of the Medicare Prescription Drug, Improvement, and Modernization Act, our rulemaking requiring a bar code on certain drug products, and the DailyMed initiative.

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the* **Federal Register**]. Submit written comments on the information collection requirements by [*insert date 30 days after date of publication in the* **Federal Register**] to OMB (see **ADDRESSES**). See section IX of this document for the proposed effective date and section X for the proposed compliance dates of a final rule based on this document.

ADDRESSES: You may submit comments, identified by Docket No. 2005N–0403 and/RIN 0910–AA49, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

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

Written Submissions

Submit written submissions in the following ways:

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

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

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

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Information Collection Provisions: Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB).To ensure that comments on the information collection are received, OMB recommends that written

comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-6974.

FOR FURTHER INFORMATION CONTACT: *For information concerning drugs regulated by the Center for Drug Evaluation and Research (CDER)*: Herbert Gerstenzang or John W. Gardner, 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*.

For information concerning products regulated by the Center for Biologics Evaluation and Research (CBER): Valerie A. Butler, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210, *valerie.butler@fda.hhs.gov*.

For information concerning animal drugs: Lowell Fried (HFV–212) or Isabel W. Pocurull (HFV–226), Center for Veterinary Medicine (CVM), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 301–827–7820 or 240–453–6853, *lowell.fried@fda.hhs.gov* or *isabel.pocurull@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

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I. Background

We originally published establishment registration regulations for human drugs, certain biological products, and animal drugs in the **Federal Register** of February 14, 1963 (28 FR 1457) (proposed rule) and April 3, 1963 (28 FR 3195) (final rule), and listing regulations for these drugs in the **Federal Register**

of December 12, 1972 (37 FR 26431) (proposed rule) and March 7, 1973 (38 FR 6258) (final rule).

We currently maintain a database containing the establishment registration and drug listing information submitted on paper to us. We rely on complete and accurate registration and listing information to accomplish a number of our statutory and regulatory objectives. For example, we use registration and listing information to:

- Identify the manufacturers, repackers, relabelers, and drug product salvagers of marketed drugs;[1]
- Identify the manufacturers, repackers, or relabelers of a specific drug or ingredient when that drug or ingredient is in short supply or is needed for a national emergency. This information helps us facilitate prompt drug shipment to the place where it is needed. For example, during a bioterrorism incident, we could use drug listing information to identify manufacturers, repackers, and relabelers of drugs that would be helpful in preventing or counteracting the deadly effects of biological weapons. With this information, we could facilitate prompt shipment of the drugs as needed;
- Facilitate the recall of drugs marketed by manufacturers, repackers, and relabelers;
- Identify and catalogue marketed drugs;
- Administer our postmarketing surveillance programs for drugs, including the drug surveillance sampling program that monitors the quality of the national drug supply;
- Identify drugs marketed in violation of the law;

[1] ''Drug'' or ''drugs'' refers to human drugs, including drugs that are regulated under a biologics license application, and animal drugs (including Type A medicated articles), unless otherwise specifically stated. ''Drugs'' is defined in proposed § 207.1 and discussed in section IV.A.5 of this document. Biological products subject to proposed part 207 are described in proposed § 207.9(c).

- Schedule and plan inspections of registered establishments pursuant to section 704 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 374); and

- Determine which marketed drugs are identical, related, or similar to drugs reviewed for effectiveness under the Drug Efficacy Study Implementation (DESI) program.

We also rely on registration and listing information to help us comply with several other statutory provisions. We use the information to:

- Determine which entities are subject to establishment and product user fees under the prescription drug user fee program and the animal drug user fee program (21 U.S.C.379h and 379).

- Generate accurate estimates of the number of manufacturers, repackers, relabelers, and drug product salvagers and drugs that are affected by our rulemaking. These estimates help us assess the impact of our regulations on the regulated industry, which we are required to do under the Regulatory Flexibility Act (5 U.S.C. 601–612), as amended by the Small Business Regulatory Enforcement Fairness Act (Public Law 104–121), the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*), the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520), Executive Order 12866 (September 30, 1993), and the Congressional Review Act (section 251 of Public Law 104–121).

Registration and listing information will continue to be used for all of the important public health purposes outlined above. Moreover, recent technological advances would allow us to enhance the usefulness of registration and listing information. Specifically, we are proposing that registration and listing information be submitted to us by using the electronic drug registration and listing system that we intend to develop. In addition to

making the registration and listing process more efficient for industry, the electronic submission of registration and listing information would allow us to review and use such information more quickly and effectively in carrying out all of the activities described above. Electronic submission of this information would also allow us to fully support the implementation of the provisions of the Medicare Prescription Drug, Improvement, and Modernization Act (Public Law 108–173) (Medicare Modernization Act), specifically the electronic prescribing provisions. In addition, electronic submission of registration and listing information would further the purpose of several statutes:

- The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107–188) (Bioterrorism Act) amended section 510(i) of the act (21 U.S.C. 360(i)) to require that foreign establishments submit, among other things, registration information electronically.

- The Medical Device User Fee and Modernization Act of 2002 (Public Law 107–250) also amended section 510 of the act (at section 510(p)) to explicitly give the Secretary of Health and Human Services (the Secretary) discretion to require the electronic submission of registration information, upon a finding that electronic receipt of such registration information is feasible, unless the Secretary grants a request for a waiver.

- The Government Paperwork Elimination Act of 1998 (Public Law 105–277, Title XVII) (GPEA) requires Federal agencies to give persons who are required to maintain, submit, or disclose information the option of doing so electronically when practicable as a substitute for paper, and to use electronic authentication (electronic signature) methods to verify the identity of the sender and the integrity of the electronic content.

We believe that conversion to the electronic submission of registration and listing information will further the purpose of these laws and make the registration and listing processes more efficient and effective for industry and us.

II. Summary of Current Registration and Listing Requirements

A. Summary of Section 510 of the Act

Section 510(c) of the act requires every person upon first engaging in the ''manufacture, preparation, propagation, compounding, or processing'' of a drug in any establishment that he owns or operates in any State to immediately register his name and place of business and such establishment. Under section 510(a)(1) of the act, the term ''manufacture, preparation, propagation, compounding, or processing'' must include ''repackaging or otherwise changing the container, wrapper, or labeling of any drug package * * * in furtherance of the distribution of the drug * * * from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user.'' Section 510(a)(2) of the act mandates that the term ''name'' include, among other things, the name of each partner of a partnership, and the name of each corporate officer and director of a corporation. An owner or operator of a registered establishment must also immediately register any additional establishment that he owns or operates in any State and in which he begins the ''manufacture, preparation, propagation, compounding, or processing'' of a drug (section 510(d) of the act). An owner or operator of any establishment that engages in these activities must register its establishment on or before December 31 of each year (section 510(b) of the act). Section 510(i) of the act contains certain registration requirements pertaining to foreign establishments (e.g., submission of the name of each importer of a drug in the

United States that is known to the establishment, submission of the name of each person who imports or offers for import a drug into the United States for purposes of importation). Section 510(g) of the act provides for certain exemptions from the registration requirements. In addition, section 510(p) of the act gives the Secretary discretion to require the electronic submission of registration information, upon a finding that electronic receipt of such registration information is feasible, unless the Secretary grants a request for a waiver.

Section 510(j)(1) of the act requires that every person, at the time of registration, submit a list of all drugs that are being manufactured, prepared, propagated, compounded, or processed by him for commercial distribution and that have not been previously listed by him. This information must be submitted in the form and manner prescribed by the Secretary (section 510(j)(1) of the act). This listing information must be accompanied by, among other things, a copy of certain labeling and, in some cases, advertising for certain categories of drugs. Section 510(j)(2) of the act requires certain changes in listing information to be reported every June and December, including any material changes in information previously submitted under the listing provisions.

Section 510(e) of the act permits the Secretary to assign a registration number to any person or any establishments registered under section 510 and a listing number to each drug or class of drugs listed under section 510(j) as long as the listing number is the same as that assigned pursuant to the National Drug Code. The disclosure provision in section 510(f) of the act requires the Secretary to make available for inspection any registration filed under section 510. Section 510(f) also provides that certain listing information must be

exempt from disclosure unless the Secretary finds that such exemption would be inconsistent with protection of the public health.

B. Summary of Current Registration and Listing Regulations

1. Who Must Register and List Under Current Regulations?

Under current part 207 (21 CFR part 207), with certain exceptions, owners or operators of establishments that engage in the manufacturing or processing of a drug or drugs must, in addition to other requirements, register their establishments and submit listing information for each of their drugs in commercial distribution.[2] Notwithstanding certain exceptions, foreign drug establishments that manufacture, repack, or relabel a drug that is imported or offered for import into the United States must also comply with the registration and listing requirements. As explained in section IV.E of this document, all registration and listing information must currently be submitted to us using paper forms specified by us.

2. What Are the Current Registration Requirements?

Current requirements for registration include, among other things, the following provisions:

- Owners or operators of establishments entering into the manufacturing or processing of a drug or drugs must register their establishments within 5 days after beginning the manufacturing or processing of drugs at the establishments (§ 207.21(a)).
- If owners or operators of the establishments have not previously entered into such operations, then those owners or operators must register within 5 days after the submission of a new drug application (NDA), abbreviated new

[2]''Drug or drugs'' includes drugs regulated under a BLA. For a description of biological products covered under proposed part 207, see proposed § 207.9(c).

drug application (ANDA), new animal drug application (NADA), abbreviated new animal drug application (ANADA), medicated feed mill license application, or biologics license application (BLA) (§ 207.21(a)).

- Owners or operators of establishments that are required to register must renew their registration annually in accordance with the specified schedule (§ 207.21(a)). Changes in individual ownership, corporate or partnership structure, location, or drug-handling activity must be submitted as amendments to registration within 5 days of such changes (§ 207.26).
- We assign a permanent registration number to each registered establishment (§ 207.35).
- Private label distributors that do not otherwise manufacture or process drugs are not required to register; however, they must submit specified information to us to obtain a labeler code (§ 207.20(b)). Private label distributors are owners or operators of establishments not otherwise required to register under section 510 of the act that distribute under their own label or trade name a drug manufactured or processed by a registered establishment.

3. What Are the Current Listing Requirements?

Current requirements for listing include, among other things, the following provisions:

- Owners or operators of establishments must, at the time of registration, submit a list of every drug being manufactured or processed in commercial distribution at that time (§ 207.21(a)).
- Private label distributors that do not otherwise manufacture or process drugs are not required to list, but may elect to submit listing information directly to us (§ 207.20(b)). Currently, private label distributors that elect to submit listing information directly to us assume full responsibility for

compliance with the requirements of part 207 (§ 207.20(b)). Owners or operators of establishments that are required to register and list must submit listing information to us on behalf of private label distributors that do not elect to submit listing information directly to us (§ 207.20(b)).

- Drugs that may be subject to current listing requirements include bulk drug substances; finished dosage forms, whether prescription or over-the-counter (OTC) drugs; and Type A medicated articles (§ 207.25(b)).
- The required listing information submitted to us includes, but is not limited to:

—The application number, if applicable,

—Copies of current labeling as specified in current § 207.25(b) and, in some cases, a representative sampling of advertisements,

—A quantitative listing of the active ingredient(s) (in some cases),

—The NDC number, and

—Any imprinting information (§ 207.25(b)).

- Owners or operators of establishments that are required to register must update their listing information every June and December or, at the discretion of the owner or operator, when the change occurs. Updated information must include, but is not limited to:

—A list of each drug introduced by the registrant for commercial distribution that has not been included in any previously submitted list,

—A list of all previously listed drugs for which commercial distribution has been discontinued,

—A list of all drugs for which a notice of discontinuance was submitted and for which commercial distribution has resumed, and

—Any material change, as defined under current § 207.3(a)(3), in any information previously submitted (§ 207.30(a)).

4. What Are the Current Requirements Associated With the Use of the NDC Number?

The NDC system is used, among other things, to assign a drug listing number to each drug or class of drugs.

- The NDC number currently consists of the labeler code, product code, and package code. We assign the labeler code, and, as stated in current regulations, ''establishments'' assign the product code and package code within certain parameters specified by us (§ 207.35).
- Currently, we request, but not require, that the NDC number appear on all drug labels and labeling (§ 201.2 (21 CFR 201.2), § 207.35(b)(3)). However, drug products described in current § 201.25(b) (21 CFR 201.25(b)) must have on the label a bar code that contains, at a minimum, the appropriate NDC number in a linear bar code that meets specified standards (§ 201.25).
- The current regulations specify both format and placement of the NDC number if the NDC number is included on drug labels and labeling (§ 207.35(b)(3)).

5. Who Is Exempt From Registration and Listing Under Current Regulations and Who Is Not Covered by the Current Registration and Listing Requirements in 21 CFR Part 207?

Under current regulations, certain establishments are exempt from the registration and listing requirements. For example, practitioners who are licensed by law to prescribe or administer drugs and who manufacture or process drugs solely for use in their professional practice, and persons who manufacture or process drugs not for sale but solely for use in research, teaching, or chemical analysis are exempt from registration and listing

requirements. Many of the exemptions in current § 207.10 are also listed in section 510(g) of the act.

The current regulations also describe those establishments that are not covered under part 207. Owners and operators of human blood and blood product establishments must register and list their products in accordance with part 607 (21 CFR part 607). However, such owners and operators who also manufacture or process other drug products at the same establishment must also register and list those drugs in accordance with part 207 (§ 207.7). Owners and operators of establishments that solely engage in the manufacture or processing of medical devices are not covered under part 207. However, such owners and operators must register and list their products in accordance with part 807.

6. Do Current Regulations Permit the Disclosure of Registration and Listing Information?

The current regulations specify the registration and listing information submitted to us that is available for public disclosure (§ 207.37).

III. Highlights of the Proposed Rule

This proposal would reorganize, consolidate, and modify the current registration and listing requirements. It would also assist us in promoting other important electronic health initiatives.

A. Proposed Changes to the Current Registration and Listing Requirements

We are proposing many changes to the current registration and listing requirements. In section IV of this document, we discuss in detail these changes and the reasons for the changes. The most significant proposed changes to the current requirements are as follows:

- All registration information and most listing information would be provided to us electronically using the electronic drug registration and listing system that we intend to develop. (Currently, the information is submitted to us on paper forms.)

- The appropriate NDC number would be required, with certain exceptions, to appear on drug labels. The appropriate NDC number is the NDC number belonging to the manufacturer, repacker, or relabeler, that corresponds to the particular drug; a repacker or relabeler would not be permitted to place an NDC number that corresponds to an original manufacturer on a repackaged or relabeled drug. Although the NDC number would not be required to appear on other drug labeling (that is, the prescription drug labeling or the package insert), the NDC number would need to accompany the submission of the other drug labeling. (Currently, we only request that the NDC number appear on drug labels and labeling. However, certain drug products must have on the label a bar code that contains, at a minimum, the appropriate NDC number (see § 201.25).)

- All three sections of the NDC number—that is, the labeler code, product code, and package code—would be assigned prospectively by us to drugs that have not previously been assigned NDC numbers by a manufacturer, repacker, or relabeler. (Currently, we assign the labeler code, and the registered establishment or private label distributor assigns the product code and package code within certain parameters specified by us.) The labeler code assigned prospectively by us would be the same as the labeler code (or one of the labeler codes) used by the manufacturer, repacker, or relabeler on its currently marketed drugs.

- The NDC numbers currently assigned to drugs prior to the effective date of the rule would remain unchanged, provided those NDC numbers comply with the new regulations as finalized. FDA intends to validate that current NDC numbers comply with the new regulations as finalized. Manufacturers, repackers, and relabelers should review the information that they submitted to our registration and listing database to obtain an NDC number and update the information if necessary. They should complete their reviews and updates within 9 months after a final rule's effective date. If, after the effective date of the final rule, there is a change in a drug (in accordance with proposed § 207.33(f)), we would assign a new product code and package code to the newly changed drug, but the drug would keep the labeler code. If, after the effective date of the final rule, there is a change in a drug's packaging, we would assign a new package code to the drug, but the drug would keep the labeler code and the product code. (Currently, the registered establishment or private label distributor may assign the product and package codes within certain parameters specified by us.)

- Private label distributors would not be permitted to register or list under the proposed rule. (Currently, private label distributors submit certain information to request a labeler code and may list drugs. If the private label distributor elects not to submit drug listing information directly to us and to obtain a labeler code, the registered establishment must submit the drug listing information.) Manufacturers, repackers, relabelers, or drug product salvagers must submit drug listing information for those drugs they manufacture, repack, relabel, or salvage for a private label distributor.

- Drug product salvagers would, in addition to registering, be required to list the drugs they salvage, even if they do not repack or relabel the drugs. (Currently, drug product salvagers are required to register but not list.)

- The ''content of labeling'' as defined in proposed § 207.1 would be electronically submitted at the time of listing in a format that we can process, review, and archive. (Currently, all labeling required for listing is submitted in paper form.)

B. Promotion of the Department of Health and Human Services (DHHS) Federal Health Information Technology Initiatives

The proposal would allow us to provide important support for the full implementation of the electronic prescription provisions of the Medicare Modernization Act. The proposal would also support other initiatives, described in section IV.C.2 of this document, including DHHS Federal Health Information Technology initiatives. The proposal would result in an up-to-date NDC number system, in which we assign the NDC number, providing for accurate, unique, and unambiguous NDC numbers for each drug. This would allow electronic systems to reliably and consistently link the NDC number to the appropriate drug labeling through another DHHS health information technology initiative, Structured Product Labeling (SPL). The drug labeling would supply the drug ingredient and other information necessary to support the development of the standards for medication terminology necessary for electronic prescribing. Other initiatives supported by this proposal, including bar coding for drugs, are discussed in section IV.C.2 of this document.

IV. Description of the Proposed Rule

We are proposing to reorganize, consolidate, clarify, and modify the regulations in part 207. As a result, we have revised and recodified some

provisions, added new provisions, and eliminated others. The following description of the proposed rule describes both new provisions and changes to existing regulations.

A. General

1. What Is the Purpose of Proposed Part 207?

We are proposing to add new § 207.5 to explicitly state the purpose of part 207, as set forth in the legislative history of the Drug Amendments of 1962 and the Drug Listing Act of 1972.

- Establishment registration information helps us to identify who is manufacturing, repacking, relabeling, or salvaging drugs and where those operations are being performed. As explained in Senate Report No. 1744, ''drugs should not be on the market unless [FDA] knows who is making them, and where they are being made. This will help stop illicit and substandard manufacturers who do not follow the methods or establish the controls called for by good manufacturing practice'' (1962 U.S.C.C.A.N. 2884, 2889). Knowing where drugs are being made is even more important today because it would increase the Nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies.
- Drug listing information gives us a current inventory of marketed drugs. As stated in Senate Report No. 92–924, ''[t]he effective enforcement of the drug provisions of the [a]ct requires the ready availability of a current inventory of all marketed drugs'' (1972 U.S.C.C.A.N. 2963, 2964). Moreover, the intent of drug listing is to provide us ''with an effective means of surveillance'' (Id. at 2965). Both establishment registration and drug listing information facilitate our implementation and enforcement of the act and are used for many important public health purposes. In addition, this information will help us

better respond to emergencies (for example, we will be in a better position to effectively facilitate recalls should there be such a need).

2. Who Would Part 207 Cover?

We are proposing to add new § 207.9 to explain that part 207 would apply to the following.

- Domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers, unless they are exempt under section 510(g) of the act or proposed § 207.13. The terms ''domestic manufacturers,'' ''domestic repackers,'' ''domestic relabelers,'' and ''domestic drug product salvagers'' are defined in proposed § 207.1 and are explained in section IV.A.5 of this document. Proposed § 207.9 does not change the scope of current part 207. Domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers would be covered under proposed part 207 whether or not the drugs they manufacture, repack, relabel, or salvage enter interstate commerce. Section 510(b) and (c) of the act refer to an establishment ''in any State.'' Congress's intention for section 510 of the act to apply to drugs both in interstate and intrastate commerce is stated in section 301 of Public Law 82–781, in part, as follows: ''[T]he products of all [establishments in which drugs are manufactured, prepared, propagated, compounded, or processed] are likely to enter the channels of interstate commerce and directly affect such commerce; and * * * the regulation of interstate commerce in drugs without provision for registration and inspection of establishments that may be engaged only in intrastate commerce in such drugs would discriminate against and depress interstate commerce in such drugs, and adversely burden, obstruct, and affect such interstate commerce.''[3] Accordingly, we are proposing

[3]See footnote 1 of section 510 of the act.

to add to proposed § 207.9 the clause ''regardless of whether their drugs enter interstate commerce'' to reflect this congressional finding. The phrase ''Drug products * * * must be listed whether or not the output of such establishments or any particular drug so listed enters interstate commerce'' is already included in current § 207.20(a).

- Foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers, unless they are exempt under proposed § 207.13(c) through (h). Foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers are currently required to register, and foreign manufacturers, foreign repackers, and foreign relabelers are currently required to submit listing information in accordance with section 510 of the act and § 207.40. The terms ''foreign manufacturers,'' ''foreign repackers,'' ''foreign relabelers,'' and ''foreign drug product salvagers'' are defined in proposed § 207.1 and explained in section IV.A.5 of this document.

An increased number of foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers may be required to comply with registration and/or listing requirements because we are proposing, as explained in section IV.A.4 of this document, to revoke certain provisions of current § 207.40(a) and (b). We are proposing to revoke the exemption in current § 207.40(a) relating to foreign establishments whose drugs enter a foreign trade zone and are re-exported from the foreign trade zone without having entered U.S. commerce. We are also proposing to revoke, in part, current § 207.40(b), which allows for a component of a drug imported under section 801(d)(3) of the act (21 U.S.C. 381(d)(3)) to be imported or offered for import into the United States even if the component is not listed and manufactured, prepared, propagated, compounded, or processed at a registered foreign establishment.

We are proposing to eliminate these two exemptions in current § 207.40(a) and (b) from the registration and listing requirements in light of certain statutory changes that have occurred since the publication of the final rule on foreign establishment registration and listing. Those changes include enactment of the Bioterrorism Act, which reflects Congress' desire to increase the Nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies.

- Manufacturers of drugs regulated under a BLA, as follows:

Manufacturers of drugs regulated under a BLA including, but not limited to: (1) Plasma derivatives such as albumin, Immune Globulin, Factor VIII and Factor IX, and recombinant versions of plasma derivatives or animal derived plasma derivatives; (2) vaccines; (3) allergenic products; (4) bulk product substances such as fractionation intermediates or pastes; and (5) therapeutic biological products.

Establishments solely engaged in the manufacture, as defined in § 1271.3(e) (21 CFR 1271.3(e)), of HCT/Ps, as defined in § 1271.3(d), that, under § 1271.20, are also drugs regulated under section 351 of the Public Health Service Act (PHS Act) or section 505 of the act. Proposed § 207.9(c)(2) would direct these establishments to register and list those HCT/Ps with CBER by following the procedures described in subpart B of part 1271 (21 CFR part 1271) instead of the procedures for registration and listing described in part 207. Proposed § 207.9(c)(2) is similar to current § 207.20(f), which we propose to revoke and replace with proposed § 207.9(c)(2).

We are also explaining the relationship between the requirements for HCT/Ps in part 207 and part 1271 of this chapter. We have implemented, in part 1271, a comprehensive, risk-based regulatory approach for HCT/Ps. Under this

approach, some HCT/Ps are regulated solely under section 361 of the PHS Act (42 U.S.C. 264) and the regulations in part 1271; other HCT/Ps are also subject to regulation as drugs or devices under the act and to premarket application or notification requirements (submissions may include BLAs, NDAs, or device PMAs, product development protocols, or 510(k) applications).

Current § 207.20(f) also states that the additional listing information requirements in current § 207.31 are applicable to HCT/Ps registered in accordance with the procedures in part 1271, subpart B if they are also drugs regulated under a BLA and/or the act. We are proposing to revoke current § 207.31 and move several of its requirements to other sections of the proposed rule (see discussion in sections IV.C and IV.D of this document). Consistent with the provisions in current § 207.20(f), the requirements will continue to apply to HCT/Ps that, under § 1271.20, are also drugs regulated under a BLA or section 505 of the act.

In addition, proposed § 207.9(c)(2) would require the submission of information not currently required for HCT/Ps under part 207, although the submission of such information has been required for drug products that are not HCT/Ps. For example, proposed § 207.9(c)(2) would require establishments to submit the NDC number, as described in proposed §§ 207.49(a), 207.53(a), and 207.54(b)(1), and the route of administration, as described in proposed § 207.49(b). Under these provisions, such HCT/P establishments would not be required to register and list with both CBER and CDER. Rather, we envision that establishments will register with CBER, and then will be asked to provide additional information as required under part 207. We will manage our databases so that both CBER and CDER have use of the registration and listing information provided. The concept is that there will be a link in place when

the establishment electronically accesses the electronic registration and listing system at *http://www.fda.gov/cber/tissue/tisreg.htm* for tissue registration. This will allow access to the drug database fields to fill in the additional information such as the NDC number. If the establishment enters that it manufactures a licensed biologic, this will trigger the link. At the current time, there is only one such product.

3. Who Would Not Be Subject to Part 207?

Proposed § 207.9 also describes two categories of establishments that would not be subject to part 207:

- Owners and operators of human blood and blood product establishments. This proposed rule does not apply to owners and operators of human blood and blood product establishments unless they manufacture any of the products listed in proposed § 207.9(c)(1)(i) and (c)(1)(iv). If the owners and operators of human blood and blood product establishments manufacture any of those products, then they must register and list under part 207. Establishments that collect or process whole blood and blood products as well as establishments involved in the testing of whole blood and blood products would register and list under part 607. For purposes of this proposal, blood and blood products consist of human whole blood, plasma, or serum or any product derived from human whole blood, plasma, or serum, and the term includes biological products regulated as licensed devices. Manufacturers of licensed devices and manufacturers of licensed biological components used in a licensed device would register and list under part 607. This exclusion is consistent with current § 207.7(a) and would not apply to owners and operators of human blood and blood product establishments who also manufacture other drugs.

- Establishments that solely manufacture, prepare, propagate, compound, assemble, or process medical devices. Establishment registration and device listing regulations for such establishments and initial importers of devices, including in vitro diagnostic products, are codified in part 807. Establishments that manufacture, prepare, propagate, compound, assemble, or process medical devices, and also manufacture, prepare, propagate, compound, or process drugs, are subject to part 207 for drugs and part 807 for devices.

As a result of these proposed revisions clarifying the scope of part 207, proposed § 207.9 includes the provisions in current § 207.7 that explain the applicability of part 207 to human blood and blood products and medical devices. We are also proposing to revoke related provisions that set forth addresses in the Center for Devices and Radiological Health (CDRH) and CBER for submitting registration and listing information, and provisions that specify the appropriate forms for submitting such information.

4. Who Would Be Exempt From Registration and Listing?

Section 510(g) of the act and current § 207.10 provide for exemptions from registration and drug listing requirements. Proposed § 207.13 contains certain changes to some of the exemptions in current § 207.10, as discussed in the first part of this section. Proposed § 207.13 also incorporates without change some exemptions from current § 207.10, as discussed at the end of this section.

The introductory paragraph of proposed § 207.13, largely consistent with current § 207.10, states that, except as provided in proposed § 207.13(i), the classes of persons listed in proposed § 207.13 are exempt from registration and drug listing 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. We are proposing to add the phrase ‘‘except

as provided in proposed § 207.13(i)'' to indicate that even though the classes of persons identified in paragraphs (a) through (h) are exempt from registration and drug listing, if such persons engage in activities as set forth in paragraph (i), the exemption does not apply and they are required nonetheless to register and list. We are also proposing to include in the introductory paragraph a sentence clarifying that the exemption under proposed § 207.13 would not provide exemptions from other provisions of the act or regulations. For example, persons that do not have to register establishments and list drugs are still subject to the adulteration and misbranding provisions under sections 501 and 502 of the act (21 U.S.C. 351 and 352) and also may be subject to the new drug approval requirements under section 505 of the act (21 U.S.C. 355) or new animal drug approval requirements under section 512 of the act (21 U.S.C. 360b). We may inspect their establishments in accordance with section 704 of the act and the current good manufacturing practice requirements. We are proposing to add the clarifying sentence because in the past some manufacturers, repackers, relabelers, and drug product salvagers that were exempt from registration and listing requirements incorrectly believed these provisions provided exemptions from other provisions of the act and regulations. Accordingly, we are proposing to add this sentence to remedy any confusion on this point.

a. *Pharmacies*—The current exemption for pharmacies is codified at § 207.10(a). The proposed rule would revise and clarify the exemption, and would move it to § 207.13(a). Except as noted in the discussion below, proposed § 207.13(a) is generally consistent with current § 207.10(a).

Under proposed § 207.13(a), pharmacies would be exempt from the registration and listing requirements if they: Operate in conformance with all

applicable local laws regulating the practice of pharmacy, including all applicable local laws regulating the dispensing of prescription drugs; regularly engage in dispensing prescription drugs upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care; and do not manufacture (as defined in proposed § 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.

Additional language has been added to proposed § 207.13(a)(1)(i) and (a)(1)(ii) to more closely track the language in section 510(g)(1) of the act. In addition, proposed § 207.13(a) does not include language that is in current § 207.10(a) that provides that the supplying of prescription drugs to a practitioner licensed to administer the drugs for use in the course of the practitioner's professional practice or to other pharmacies to meet temporary inventory shortages are not acts that require pharmacies to register. We are deleting this language because it is not necessary. Pharmacies that engage in such activities would be exempt from registration if they fulfill the following requirements: Operate in conformance with all applicable local laws regulating the practice of pharmacy, including all applicable local laws regulating dispensing of prescription drugs (proposed § 207.13(a)(1)(i)); regularly engage in dispensing prescription drugs upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care (proposed § 207.13(a)(1)(ii)); and 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 (proposed § 207.13(a)(1)(iii)).

Proposed § 207.13(a)(2) clarifies that pharmacies may potentially qualify for the exemption in proposed § 207.13(a) only if they are located in any State as defined in section 201(a)(l) of the act (21 U.S.C. 321) (that is, any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico). This proposed provision is currently located in the introductory paragraph in current § 207.10. We believe it would be more clear to place this provision in proposed § 207.13(a)(2). This aspect of the proposed provision is consistent with current §§ 207.10 and 207.40.

b. *Hospitals, clinics, other health care entities, and public health agencies*—The current exemption for hospitals, clinics, and public health agencies is codified at § 207.10(b). The proposed exemption is generally consistent with current § 207.10(b), except for the addition of ''other health care entities'' and other mostly minor revisions and clarifications, as described below. The proposed exemption would move to § 207.13(b).

Hospitals, clinics, other health care entities, and public health agencies are exempt, under proposed § 207.13(b), from the registration and listing requirements if they: 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; 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 do not manufacture (as defined in proposed § 207.1), repack, or relabel drugs other than in the regular course of the practice of pharmacy, including dispensing.

The exemption in proposed § 207.13(b) would be 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. The proposed provision requiring that such facilities be located in any State is currently located in the introductory paragraph in current § 207.10. We believe it would be more clear to place this provision in proposed § 207.13(b)(2). This proposed provision (except with respect to BLA holders and the clarification with respect to positron emission tomography (PET) drugs) is generally consistent with current §§ 207.10 and 207.40.

We are proposing to add ''other health care entities'' to this exemption because we are aware that other health care entities besides hospitals, clinics, and public health agencies (such as skilled nursing facilities) lawfully provide medical care and dispense drugs and logically are similarly situated to hospitals, clinics, and public health agencies for purposes of exempting them from registration and listing, if they meet the statutory and regulatory requirements.

We are also proposing to add language to proposed § 207.13(b) to make the exemption more consistent with the pharmacy exemption in proposed § 207.13(a). For example, we are proposing to add language to proposed § 207.13(b)(1)(i) so that this exemption also specifically requires compliance with all applicable laws regulating dispensing of prescription drugs, as is required by proposed § 207.13(a)(1)(i). We are similarly proposing to add § 207.13(b)(1)(iii) to be consistent with proposed § 207.13(a)(1)(iii), although in proposed § 207.13(b)(1)(iii) we have not included the terms ''for sale'' or ''selling drugs at retail'' since this language is appropriate for retail pharmacies relying on the exemption provided by proposed § 207.13(a), but not for hospitals, clinics, other health care entities, and public health agencies relying on the exemption provided by proposed § 207.13(b).

We believe that the exemption for hospitals, clinics, other health care entities, and public health agencies provided in proposed § 207.13(b)(2) should be relied upon by pharmacies within these health care entities that dispense drugs to patients receiving care in the health care entities and that meet the requirements of the exemption, but should not be relied upon by retail pharmacies located within these health care entities. Retail pharmacies should rely upon the exemption in proposed § 207.13(a) if they meet the requirements of that proposed provision.

c. *Persons who manufacture, repack, relabel, or salvage certain medicated feeds*—Although we are proposing to reorganize and clarify the exemption for persons who manufacture, repack, relabel, or salvage certain medicated feeds, we are not proposing to change the substance of the exemption. Under proposed § 207.13(f), persons who manufacture, repack, relabel, or salvage 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, are exempt from registration. This exemption would not apply to persons who would otherwise be required to register (such as manufacturers, repackers, relabelers, or drug product salvagers of certain free-choice feeds, as defined in 21 CFR 510.455, or certain liquid feeds, as defined in 21 CFR 558.5, where the specifications and/or formulas are not published and a feed mill license is required). Proposed § 207.13(f) also clarifies that all manufacturers, repackers, relabelers, or drug product salvagers of Type B or Type C medicated feeds would be exempt from listing.

d. *The current exemptions for foreign trade zones and drugs imported under section 801(d)(3) of the act would be revoked*—In 2001, we issued a

final rule on foreign establishment registration and listing (66 FR 59138, November 27, 2001). The regulation created two exemptions in § 207.40:

- Under current § 207.40(a), a foreign establishment is not required to comply with the registration and listing requirements if its drug enters a foreign trade zone and is re-exported from that foreign trade zone without having entered U.S. commerce. We created this exemption as part of the final rule on foreign establishment registration and listing because registering such foreign establishments or listing drugs that were confined to a foreign trade zone—and were therefore not introduced into domestic commerce—was not considered necessary for the protection of the public health (see 66 FR 59138 at 59139 and 59140).

- Current § 207.40(b), which states that no drug may be imported or offered for import into the United States unless the drug is listed and manufactured, prepared, propagated, compounded, or processed at a registered foreign establishment, also states that this prohibition does not apply to components of drugs imported under section 801(d)(3) of the act. Section 801(d)(3) of the act, as it existed before June 2002, allowed persons to import unapproved or otherwise noncompliant articles (such as drug components) provided that the imported articles were further processed or incorporated into products and exported or, if not used, the imported articles were destroyed or exported. The provision in § 207.40(b) reflected the fact that, at the time, section 801(d)(3) of the act imposed very few restrictions on the admission of drug components that are imported into the United States for further processing or incorporation into a product that will be exported from the United States (66 FR 59138 at 59148).

Given the additional level of import restrictions imposed by the Bioterrorism Act, and the underlying security concerns that led to the Bioterrorism Act's adoption, we are proposing to eliminate these two exemptions in current § 207.40(a) and (b) from the registration and listing requirements. In particular, sections 321 and 322 of the Bioterrorism Act, which affected foreign establishment registration by amending sections 510 and 801 (among other provisions) of the act, suggest that Congress intended the information requirements for foreign establishments and imported products to be comprehensive, and that Congress regarded the information it was requiring to be important to its goal in increasing the Nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies. This, in turn, suggests to FDA that the exceptions from the registration and listing requirements are therefore no longer appropriate.

The Bioterrorism Act affected foreign establishment registration, in relevant part, by amending sections 510(i) and 801 of the act:

- To require, as part of an establishment's registration, the name of each importer of the drug that is known to the establishment and the name of each person who imports or offers to import the drug into the United States; and
- To provide that we may refuse admission of a product and, if the product is refused admission, that the product shall be held at the port of entry until a statement regarding the foreign establishment's registration is submitted to us.

The amendment to section 510(i) of the act reflects a determination on the part of Congress that a foreign establishment shipping drugs to the United States should provide additional information in its registration (that is, information about importers and persons who import or offer for import). FDA

is concerned that if a foreign establishment is not subject to this establishment registration requirement—either by virtue of importing into a foreign trade zone or by importing components under section 801(d)(3) of the act—it would allow some importers and persons who import or offer for import to go undetected, thereby creating an unnecessary vulnerability in Congress' system of requiring this information.

The amendment to section 801(o) of the act reflects a determination that establishment registration and drug listing information is important enough that, if it is lacking at the time the article is offered for import, the article may be refused admission (and, if refused, shall be held at the port of entry). FDA is concerned that if a foreign establishment is exempt from the registration and listing requirements—either by virtue of importing into a foreign trade zone or by importing components under section 801(d)(3) of the act—FDA would be unable to rely on amended sections 510(i) and 801 of the act to require that imported products be held at the port of entry to the United States or to prevent such product's delivery to the importer or consignee. This situation would stand in the way of implementing Congress' apparent intent that this information be a prerequisite for entry of the imported product into the United States.

We believe that removing the exception to the registration and listing requirements for products entering foreign trade zones and for products imported under section 801(d)(3) of the act is consistent with Congress' desire to increase the Nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies by requiring foreign establishments to provide more, rather than less, information for imported products.

The Bioterrorism Act also revised section 801(d)(3) of the act, in part, by:

- Requiring importers to identify the manufacturers of the imported drug component, and each processor, packer, distributor, or other entity that had possession of the article from the manufacturer to the importer;
- Requiring certificates of analysis to accompany most imported articles; and
- Giving us the ability to refuse admission to the United States if we determine there is credible evidence or information indicating that the article is not intended to be further processed by the initial owner or consignee, or incorporated by the initial owner or consignee into a drug, biological product, or other product specified in section 801(d)(3) of the act that will be exported from the United States.

These statutory changes also indicate a congressional desire to know more, rather than less, about the articles entering the United States under section 801(d)(3) of the act and to prevent potentially dangerous articles from entering the United States. The legislative history supports this belief, as the conference report for the Bioterrorism Act explained: ''Refusal of entry should not involve shipments between known shippers and known recipients unless the Secretary has received credible evidence or information that suggests such shipments may not be legitimate. The Managers intend to permit the Secretary to refuse admission of articles if the Secretary determines there is credible evidence or information that the articles may be used as instruments of terror. Such evidence might include highly toxic or otherwise exceptionally dangerous products going to recipients unknown to the Secretary or to recipients believed to lack the capability to further process such dangerous articles * * *.'' (See H. Rept. 107–481, l07th Cong. (2002), ''Joint Explanatory Statement of the

Committee of Conference,'' ''Subtitle B—Protection of Drug Supply'' (discussing section 322).) The legislative history's references to ''known'' shippers, ''known'' recipients, and recipients who may lack the ability to further process an article, combined with the new statutory provision on refusing admission even if the article is imported under section 801(d)(3) of the act, strongly support our proposal to require that all drugs imported or offered for import into the United States be listed and manufactured at a registered foreign establishment. Failure to register such foreign establishments could compromise our ability to refuse admission of a dangerous article.

Therefore, the proposed rule would eliminate the exemption from the establishment registration and drug listing requirements for foreign establishments whose drugs enter a foreign trade zone and are re-exported from that foreign trade zone without having entered U.S. commerce. In addition, the proposal would require that all drugs imported or offered for import into the United States be listed and manufactured at a registered foreign drug establishment, even if the drug is imported under section 801(d)(3) of the act.

e. *Other exemptions*—As described in current § 207.10, the following remain exempt from registration and drug listing (proposed § 207.13):

- Practitioners who are licensed by law to prescribe or administer drugs and who manufacture, repack, relabel, or salvage drugs solely for use in their professional practice (current § 207.10(c); proposed § 207.13(c)).

- Manufacturers, repackers, relabelers, or drug product salvagers of drugs solely for use in research, teaching, or chemical analysis and not for sale (current § 207.10(d); proposed § 207.13(d)). Under proposed § 207.13(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 are exempt from registration requirements. Proposed § 207.13(d) would be consistent with the exemption in section 510(g)(3) of the act, except the language would be modified to take into account the proposed rule's uses of the terms ''manufacturer,'' ''repacker,'' ''relabeler,'' ''drug product salvager,'' ''manufacture,'' ''repack,'' ''relabel,'' and ''salvage.'' We want to take the opportunity to remind interested persons that while the exemption from registration would apply to a sponsor that manufactures its own drug for use in its clinical trial of the drug, the exemption would not apply, for example, to a firm that manufactures a drug with the purpose of selling the drug to a sponsor for use in a clinical trial. In the latter situation, the manufacturer of the drug would be required to register.

- Manufacturers, repackers, relabelers, and drug product salvagers of harmless inactive ingredients (current § 207.10(e); proposed § 207.13(e)). We considered proposing to revoke this exemption because of concerns related to potential contamination of those inactive ingredients. However, we concluded that submitting and maintaining in the database all excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs could be burdensome for industry. In proposing to maintain this exemption, we note that current regulations governing the manufacture of finished drug products require all manufacturers to perform quality control testing to ensure that components meet established specifications (see generally, part 211 (21 CFR part 211)).

- Manufacturers, repackers, relabelers, and drug product salvagers of animal viruses, serums, toxins, or analogous products (current § 207.10(g); proposed § 207.13(g)).

- Carriers (current § 207.10(h); proposed § 207.13(h)).

f. *Limits on exemptions*—Proposed § 207.13(i) would clarify that any of the persons who otherwise would qualify for an exemption under § 207.13(a) through (h) are not exempt from registration or listing if they: (1) Manufacture (as defined in proposed § 207.1),[4] repack, relabel, or salvage compounded positron emission tomography (PET) drugs as defined in section 201(ii) of the act; (2) manufacture (as defined in § 600.3(u)) a biological product subject to licensing under section 351 of the Public Health Service (PHS) Act; (3) manufacture (as defined in § 1271.3(e)) an HCT/P that, under § 1271.20, are also drugs regulated under section 351 of the PHS Act or section 505 of the act; or (4) engage in activities that would otherwise require them to register under this part.

Thus, any person identified in proposed § 207.13(a) through (h), such as pharmacies, hospitals, clinics, other health care entities, public health agencies, or practitioners, if they manufacture, repack, relabel, or salvage compounded PET drugs, as defined in section 201(ii) of the act (21 U.S.C. 321(ii)), would fall outside the scope of the exemptions provided in proposed § 207.13(a) through (h). Manufacturers, repackers, relabelers, or drug product salvagers of compounded PET drugs are not included among the persons that are exempt from registration under proposed § 207.13 because exempting manufacturers of compounded PET drugs from registration would be inconsistent with section 121 of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (Public Law 105–115), which addresses the regulation of PET drug products. Section 121 of the Modernization Act directs us to develop appropriate procedures for the

[4]The term ''manufacture'' is defined in proposed § 207.1 and is used here for brevity to refer to the activities that trigger registration requirements (that is, ''manufacture, preparation, propagation, compounding, or processing'' of drugs). Although many PET facilities do not consider themselves to be ''manufacturing'' drugs, but rather preparing or compounding drugs, we are nonetheless using the term ''manufacture'' for brevity.

approval of PET drugs under section 505 of the act and appropriate CGMP requirements for such drugs. It also requires the submission of NDAs or ANDAs for PET drugs either 4 years after the date of enactment or 2 years after the date on which we establish approval procedures and CGMPs, whichever is longer. We published proposed CGMPs for PET drugs on September 20, 2005 (70 FR 55038). If Congress had intended to exempt manufacturers, repackers, relabelers, or drug product salvagers of PET drugs from registration requirements, it would have done so. Given that PET manufacturers will be expected to comply with CGMP requirements and FDA will need to inspect them to determine compliance, it is reasonable to require PET manufacturers, repackers, relabelers, or drug product salvagers to register so we can identify PET manufacturers, repackers, relabelers, or drug product salvagers and the drugs they manufacture, repack, relabel, or salvage for inspection purposes. Therefore, the proposed rule would require compounded PET drug manufacturers, repackers, relabelers, or drug product salvagers to register with us and list their drugs in accordance with section 510(j) of the act and proposed part 207.

Likewise, any person identified in § 207.13(a) through (h) who would otherwise qualify for an exemption would not qualify for an exemption if it manufactures (as defined in § 600.3(u)) a biological product subject to licensing under section 351 of the PHS Act.

We note that to the extent a person manufactures, repacks, relabels, or salvages PET drugs as set forth in proposed § 207.13(i)(1) or manufactures a biological product subject to licensing as set forth in proposed § 207.13(i)(2), the obligation to register and list would only apply to the extent that that person engages in the activities identified in proposed § 207.13(i)(1) or (i)(2).

For example, a hospital dispensing and administering drugs and that also manufactures compounded PET drugs would list only the PET drugs it manufactures, assuming none of its other activities would subject it to registration or listing requirements. Likewise, a public health agency dispensing and administering drugs that holds a biologics license application would list only the biological drugs it manufactures, assuming none of its other activities would subject it to registration or listing requirements.

Proposed paragraph (i) also states that the exemptions provided in proposed § 207.13(a) through (h) do not apply to such persons if they engage in activities that would otherwise require them to register. This concept appeared in current § 207.10(e). We are proposing to apply this concept to all the exemptions in proposed § 207.13 to reiterate that if a person qualifies for an exemption from the activities stated in proposed § 207.13(a) through (h), that person may still need to register if that person engaged in activities that would otherwise require registration.

5. What Definitions and Interpretations of Terms Would Apply to Part 207?

In proposed § 207.1, we set forth new definitions and interpretations of terms for part 207 and revise or revoke certain definitions in current § 207.3(a).

Current § 207.3(b) states that the definitions and interpretations of terms in sections 201, 502(e), and 510 of the act apply to the terms used in part 207. We are proposing to revoke this sentence because it is unnecessary and has caused confusion in the past. For purposes of proposed part 207, the following definitions and interpretations of terms would apply to proposed part 207:

Act. This term, as used in proposed § 207.1, remains the same as current § 207.3(a)(1). ''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. We are proposing to replace the term ''bulk drug substance,'' as defined in current § 207.3(a)(4), with the term ''active pharmaceutical ingredient.'' We believe that the term ''bulk drug substance'' may be confused with the term ''bulk drug.'' The term ''bulk drug,'' as commonly used in the pharmaceutical industry, means an active ingredient, inactive ingredient, or finished dosage form, packaged in a large container (for example, a drum). To prevent confusion, we are proposing to replace the term ''bulk drug substance'' with the more descriptive term ''active pharmaceutical ingredient.''

We are also proposing to revise the definition of the current term ''bulk drug substance'' (changed to ''active pharmaceutical ingredient'' in the proposal) to make it consistent with the definition of ''drug substance'' in current § 314.3 (21 CFR 314.3). Current § 207.3(a)(4) states, in part, that a ''bulk drug substance * * * becomes an active ingredient,'' but does not explain what it means for an ingredient to be ''active.'' We believe that the definition of ''drug substance'' in current § 314.3 is more descriptive; that definition explains, in part, that ''drug substance means an active ingredient 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.'' Consistent with the language of current § 314.3, we are proposing to define ''active pharmaceutical ingredient'' in proposed § 207.1 as 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. Consistent with both current § 314.3 and current § 207.3(a)(4), the term would not include intermediates used in the synthesis of the substance. As proposed, the term would include both an active pharmaceutical ingredient marketed alone and as part of a finished dosage form.

Advertising and *labeling*. We are proposing to delete current § 207.3(a)(2), which explains that the terms ''advertising'' and ''labeling,'' as used in current part 207, include the promotional material described in current § 202.1(l)(1) and (l)(2) (21 CFR 202.1(l)(1) and (l)(2)), respectively. We believe that this information is more appropriately included in the definitions of ''representative sampling of advertisements'' and ''representative sampling of any other labeling.'' As a result, we are proposing to revise the definitions of those terms accordingly and delete current § 207.3(a)(2).

Commercial distribution. We are not proposing to substantively change the definition of ''commercial distribution'' from that set forth in current § 207.3(a)(5). The term would still mean any distribution of a human drug, except for investigational use under 21 CFR part 312, and any distribution of an animal drug or an animal feed bearing or containing an animal drug for non-investigational uses. The term would 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'' would have the same meaning except that it does not include distribution of any drug that is neither

imported nor offered for import by it into the United States. We are proposing to change the term ''bulk drug substance'' in the current definition to ''active pharmaceutical ingredient'' because the proposal replaces the definition of ''bulk drug substance'' with the definition of ''active pharmaceutical ingredient.'' Defining ''commercial distribution'' is important because, under proposed part 207, listing information must be provided to us for any drug that is being manufactured, repacked, relabeled, or salvaged for commercial distribution.

Content of labeling. We are proposing to add a new term, ''content of labeling,'' to part 207. The proposed definition of the term describes the labeling material that would be required to be electronically submitted at the time of listing under proposed §§ 207.49(g) and 207.61(a)(2). The proposed requirement to electronically submit the ''content of labeling'' would be in addition to the current listing requirement that formatted copies of certain labeling be submitted. We are proposing to define ''content of labeling'' because, as explained in section IV.E.4 of this document, the electronic submission of the ''content of labeling'' would be required for drug listing to permit us to electronically review, compare, and extract data from the labeling.

- For human prescription drugs that the manufacturer regards as subject to section 505 of the act or section 351 of the PHS Act, we are proposing to define ''content of labeling'' as the content of the prescription drug labeling, as specified in §§ 201.56, 201.57, and 201.80 (21 CFR 201.56, 201.57, and 201.80), including all text, tables, and figures.[5]

This proposed definition is consistent with how the term ''content of labeling'' is used in the final rule entitled ''Requirements for Submission of

[5]The use of the language ''that the manufacturer regards as subject to section 505 of the act or section 351 of the PHS Act,'' is explained in detail in section IV.D.7 of this document.

Labeling for Human Prescription Drugs and Biologics in Electronic Format,'' (electronic labeling final rule), which published in the **Federal Register** of December 11, 2003 (68 FR 69009). Under the electronic labeling final rule, applicants are required to electronically submit, in a format that we can process, review, and archive, the ''content of labeling'' for human prescription drugs in NDAs, certain BLAs, ANDAs, supplements, and annual reports.[6] The electronic labeling final rule, including the use of the term ''content of labeling,'' only applies to this subset of drugs. Under the proposal, however, as set forth in proposed § 207.49(g), the ''content of labeling'' would be provided for drugs subject to the listing requirements of proposed part 207.

Proposed part 207 would also differ in one other respect from the way ''content of labeling'' is used in the electronic labeling final rule. The electronic labeling final rule states that the ''content of labeling'' that must be submitted electronically is commonly referred to as the content of the package insert or professional labeling. We are proposing to use the term ''prescription drug labeling'' instead of the term package insert or professional labeling. ''Prescription drug labeling'' is used in the final rule entitled ''Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,'' published in the **Federal Register** of January 24, 2006 (71 FR 3922). In that final rule, ''prescription drug labeling'' is used to mean labeling for approved prescription drug products described in §§ 201.56, 201.57, and 201.80, which is commonly described using a variety of terms including ''professional labeling,'' ''package insert,'' ''direction circular,'' or ''package

[6]For additional information, also see the guidance ''Providing Regulatory Submissions in Electronic Format—Content of Labeling'' (April 2005) (available at *http://www.fda.gov/cder/guidance/index.htm*), which discusses issues related to the submission of the content of labeling in electronic format in marketing applications for human drug and biological products. This guidance reflects our current thinking on providing in electronic format the content of labeling required in 21 CFR parts 314 and 601.

circular.'' We are proposing that the term ''content of labeling'' for human prescription drugs, as defined in proposed § 207.1 and required under proposed § 207.49(g), would be the content of the ''prescription drug labeling.''

- For human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the PHS Act, we are proposing to define ''content of labeling'' as the labeling equivalent to the content of the prescription drug labeling, as specified in §§ 201.56, 201.57, and 201.80, including all text, tables, and figures.

- For human OTC drugs, we are proposing to define ''content of labeling'' as the content of the drug facts labeling required by § 201.66 (21 CFR 201.66) (format and content requirements for OTC drug product labeling), including all text, tables, and figures. Under § 201.66(b)(10), drug facts labeling means the title, headings, subheadings, and information required under or described in § 201.66(c) (content requirements).

- For animal drugs (including, but not limited to, drugs that the manufacturer regards as subject to section 512 of the act), we are proposing to define ''content of labeling'' as the content of the labeling that accompanies the drug that is necessary to enable safe and proper administration of the drug (for example, the labeling specified in §§ 201.1 and 201.5 (21 CFR 201.1 and 201.5)), including all text, tables, and figures.

Domestic. For the purposes of registration and listing under this proposal, and when used to modify the term ''manufacturer,'' ''repacker,'' ''relabeler,'' ''drug product salvager,'' ''private label distributor,'' or ''establishment,'' we are proposing to use the term ''domestic'' to refer 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. The terms ''manufacturer,'' ''repacker,'' ''relabeler,'' ''drug product salvager,'' ''private label distributor,'' and ''establishment'' are defined in proposed § 207.1, and these definitions are discussed elsewhere in this section of the preamble. We are proposing to define the term ''domestic'' separately rather than repeat the meaning of the term under separate definitions for domestic manufacturer, domestic repacker, domestic relabeler, domestic drug product salvager, domestic private label distributor, and domestic establishment. The definition of ''foreign,'' as it would modify manufacturer, repacker, relabeler, drug product salvager, private label distributor, and establishment, is discussed elsewhere in this section of the preamble.

Drug(s). We are proposing to use the term ''drug(s),'' for purposes of proposed part 207, to mean the same as the definition of ''drug'' in section 201(g)(1) of the act. Section 201(g)(1) of the act defines ''drug'' to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, and articles (other than food) intended to affect the structure or any function of the body of man or other animals. ''Drug(s)'' under proposed § 207.1 would include drugs intended for use in humans, including the biologics described in proposed § 207.9(c), and animal drugs, including Type A medicated articles, and also includes articles ''intended for use as a component'' of any drug. The proposed term includes active pharmaceutical ingredients and finished dosage forms (prescription and OTC).

Drug product salvager, drug product salvaging. We are proposing to use the term ''drug product salvaging'' to mean applying manufacturing controls such as those required by current good manufacturing practice in parts 210

(21 CFR part 210) and part 211 to drug products and segregating out those drug products that may have been subjected to improper storage conditions (such as extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation) for the purpose of returning the products to the marketplace. We note, however, that drug product salvaging, like all manufacturing, must be conducted in accordance with current good manufacturing practice. We are proposing to use the term ''drug product salvager'' to mean a person who owns or operates an establishment that engages in drug product salvaging. When not modified by ''domestic'' or ''foreign,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, the term would include both domestic drug product salvagers and foreign drug product salvagers.

Under current § 207.3(a)(6), drug product salvaging means the act of segregating drug products that may have been subjected to improper storage conditions, such as extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation, for the purpose of returning some or all of the products to the marketplace. We are proposing to revise the current definition of drug product salvaging to include ''applying manufacturing controls such as those required by current good manufacturing practice in part 210 and part 211 to drug products.'' We are not proposing to change the meaning of drug product salvaging but to clarify the current definition by explaining that the term also includes applying manufacturing controls to drug products. Drug product salvagers apply manufacturing controls to drug products so that they can determine whether the drug products may have been subjected to improper storage conditions. As discussed further in sections IV.B.1 and IV.D.1 of this document, ''applying manufacturing controls to drug products and segregating drug products'' would be covered under the scope of manufacturing, preparing,

propagating, compounding, or processing, and repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes the final delivery or sale to the ultimate consumer or user (section 510(a)(1) of the act). This activity would trigger the requirement to register under the act. In addition, under the proposal, drug product salvagers would also be subject to the drug listing requirements in section 510(j)(1) of the act because their activities involve conducting one of the aforementioned activities with respect to a given drug for the purpose of commercial distribution. As discussed in section IV.D.1 of this document, we are requesting comments specifically on whether drug product salvagers should be subject to the drug listing requirements because the drug products are being salvaged for commercial distribution.

Establishment. We are proposing to revise the definition of ''establishment'' at current § 207.3(a)(7) to mean, for purposes of registration and drug listing, a place of business under one management at one geographic location. Under the proposed definition, 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,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, the term would include both domestic establishments and foreign establishments. We are proposing to define the term ''establishment'' because, under proposed part 207, manufacturers, repackers, relabelers, and drug product salvagers must register each establishment, providing to us such information as the name and

address of the establishment and type of operation performed at the establishment.

The proposed definition of ''establishment'' would clarify the phrase ''at one general physical location'' in the current definition by revising the phrase to read ''one geographic location'' and stating that this 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.

The proposed definition of ''establishment'' is intended to simplify the current definition. The current definition defines establishment as a place of business under one management at one general physical location, and includes, among others, independent laboratories that engage in control activities for a registered drug establishment (for example, consulting laboratories), manufacturers of medicated feeds and vitamin products that are drugs in accordance with section 201(g) of the act, human blood donor centers, animal facilities used for the production or control testing of licensed biologics, and establishments engaged in drug product salvaging. For brevity, the proposed definition of establishment does not restate the examples of establishments stated in the current definition. Some of these establishments would be covered under other definitions set forth in proposed § 207.1 and explained in section IV.A.5 of this document. For example, ''independent laboratories that engage in control activities for a registered drug establishment'' would be covered under the proposed definition of ''manufacturer.'' ''Establishments engaged in drug product salvaging'' would be covered under the proposed definition of ''drug product salvager.''

Establishment registration number. We are proposing to define ''establishment registration number'' as the number assigned by FDA to the establishment during the establishment registration process required in this part. The establishment registration number is assigned to each establishment of each manufacturer, repacker, relabeler, or drug product salvager inspected by our district office. The establishment registration number is assigned when the manufacturer, repacker, relabeler, or drug product salvager begins manufacturing, repacking, relabeling, or salvaging drugs subject to part 207. The establishment registration number would identify, among other things, where the drug is manufactured, repacked, relabeled, or salvaged. Currently, the FDA Establishment Identifier (FEI) will be the number we assign as the establishment registration number. In the future, however, we may use a different number as the establishment registration number.

Foreign. For the purposes of registration and listing under this proposal, and when used to modify the term ''manufacturer,'' ''repacker,'' ''relabeler,'' ''drug product salvager,'' or ''private label distributor,'' we are proposing to use the term ''foreign'' to refer 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. When used to modify the term ''establishment,'' we are proposing to use the term ''foreign'' to refer 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. The terms ''manufacturer,'' ''repacker,'' ''relabeler,'' ''drug product salvager,'' ''private label distributor,'' and ''establishment'' are defined in proposed § 207.1, and

these definitions are discussed elsewhere in this section of the preamble. We are proposing to define the term ''foreign'' separately rather than repeat the meaning of the term under separate definitions for foreign manufacturer, foreign repacker, foreign relabeler, foreign drug product salvager, foreign private label distributor, and foreign establishment. The definition of ''domestic,'' as it would modify manufacturer, repacker, relabeler, drug product salvager, private label distributor, and establishment, is discussed elsewhere in this section of the preamble.

Importer. We are proposing to define ''importer'' to mean a company or individual in the United States that is an owner, consignee, or recipient of the foreign establishment's drug that is imported into the United States. We recognize that a foreign establishment may have more than one ''importer'' and we are proposing to include in this term any 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. Under this proposal, the recipient of the drug would 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. As described in section IV.B.3 of this document, this proposal would require foreign establishments to provide, for drugs manufactured, repacked, relabeled, or salvaged at the establishment, the name of each importer known to the establishment of such drug into the United States. Therefore, the establishment would need to provide the name of each owner, consignee, or recipient of the foreign establishment's drug imported into the United States that was known to the establishment. We describe more fully what we mean by ''known to the establishment'' in section IV.B.3 of this document. We invite comments

on our definition of importer, including the scope of the entities included in the definition.

Manufacture, manufacturer. We are proposing to use the term ''manufacture'' for purposes of this part to mean 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.

We are proposing to use the term ''manufacturer'' for purposes of this part to mean a person who owns or operates an establishment that manufactures a drug. When not modified by ''domestic'' or ''foreign,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, ''manufacturer'' would include both domestic manufacturers and foreign manufacturers.

Under section 510(a)(1) of the act, the term ''manufacture, preparation, propagation, compounding, or processing'' includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user. Accordingly, section 510(a)(1) of the act sets up a shorthand way of referring to all the activities that trigger registration requirements by using the specified phrase ''manufacture, preparation, propagation, compounding, or processing'' throughout section 510 of the act. However, for purposes of proposed part 207, the term ''manufacture'' would refer to the manufacture, preparation,

propagation, compounding, or processing of a drug, as set forth in the proposed definition.

The term ''manufacturer'' would include, among others, control laboratories, contract laboratories, contract manufacturers, contract packers, contract labelers, and other entities that manufacture a drug, as defined in proposed § 207.1 and discussed in section IV.A.5 of this document. A ''control laboratory'' and a ''contract laboratory'' include independent establishments that manipulate, sample, test, or perform other quality control functions for another registered establishment's drug, including, for example, analytical testing of drugs. A ''contract manufacturer'' is sometimes employed by other manufacturers to manufacture the drug. Similarly, a manufacturer may sometimes subcontract part of the manufacturing process such as packing or labeling to a ''contract packer'' or a ''contract labeler.'' The term ''manufacturer'' would include control laboratories, contract laboratories, contract manufacturers, and other entities that manufacture a drug because their activities include the making of drugs by chemical, physical, biological, or other procedures, including the manipulation, sampling, testing, or control procedures applied to the final drug product or to a part of the process. Such activities would fall under the scope of activities (that is, manufacture, prepare, propagate, compound, or process) in section 510(a)(1) of the act that trigger registration requirements.

The proposed definition of ''manufacture'' also explains that, for purposes of proposed part 207, the term manufacture is defined and used separately from the terms relabel, repack, and drug product salvage. Although we explain that repacking, relabeling, and drug product salvaging are activities that trigger registration (because the term ''manufacture, preparation, propagation,

compounding, or processing,'' under section 510 of the act includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes the final delivery or sale to the ultimate consumer or user), we believe that it is clearer to use four separate terms for the different activities for purposes of proposed part 207. We use separate terms so that we can clarify and differentiate the responsibilities of the four types of parties engaged in the separate activities of: ((1) Manufacturing that does not include repacking, relabeling, or drug product salvaging; (2) repacking; (3) relabeling; and (4) drug product salvaging).

Similarly, the proposed definition of ''manufacturer'' explains that the term manufacturer is defined and used separately from the terms relabeler, repacker, and drug product salvager. We explain that repackers, relabelers, and drug product salvagers are ''manufacturers'' (as that entity is contemplated in section 510 of the act), but we believe that, for purposes of proposed part 207, it is clearer to use four separate terms for the different entities: (1) Manufacturers (that are not also repackers, relabelers, or drug product salvagers); (2) repackers; (3) relabelers; and (4) drug product salvagers. Repackers, relabelers, and drug product salvagers would be subject to the provisions of part 207 that are applicable to repackers, relabelers, and drug product salvagers, respectively, but would not be subject to the provisions of part 207 that are applicable to ''manufacturers,'' as that term is defined in this proposal. For example, if a repacker, relabeler, or a drug product salvager supplies us with the manufacturer's NDC number, we would not require the repacker, relabeler, or drug product salvager to provide all of the information that the manufacturer provides to list a drug or, for the repacker or relabeler,

to obtain an NDC number. We would already have much of the information in the database linked to the manufacturer's NDC number, and it would be an unnecessary burden to require that the information be provided again.

We are proposing to delete the definition of ''manufacturing or processing'' at current § 207.3(a)(8) and incorporate parts of the definition elsewhere in the proposed definitions. For example, the phrase ''control procedures applied to the final product or to any part of the process'' in the proposed definition of ''manufacture'' is part of the current definition of ''manufacturing or processing.''

Material change. We are proposing to revise the definition of ''any material change'' in current § 207.3(a)(3). The current definition includes, but is not limited to: (1) Any change in the name of the drug; (2) any change in the identity or quantity of the active ingredient(s); (3) any change in the identity or quantity of the inactive ingredient(s) where quantitative listing of all ingredients is required by current § 207.31(a)(2); (4) any significant change in the labeling of a prescription drug; and (5) any significant change in the label or package insert of an OTC drug. Changes that are not significant currently include changes in arrangement or printing or changes of an editorial nature. The proposed definition would continue to exclude labeling changes in arrangement or printing or labeling changes of an editorial nature. The inclusion of a bar code or NDC number on the label would not be considered a material change because it would be too burdensome to require the resubmission of labeling if the only change was to include a bar code or an NDC number. We are, however, proposing to rename the term ''material change'' and to more precisely identify all of the changes that would be considered ''material'' in the current definition. With respect to manufacturers,

repackers, and relabelers, and drug product salvagers, a change in any information provided under proposed §§ 207.49, 207.53, 207.54, 207.55, or 207.57 would be considered a material change.

All listing information required under the proposal is needed to identify the drug. Under the broader definition of material change, as proposed, we would be better informed of changes to marketed drugs. This would result in more accurate and up-to-date drug listing information. Under proposed § 207.57 and section 510(j)(2)(D) of the act, the June and December updates of listing information must include reports of ''material changes'' in listing information previously submitted. The proposed definition of ''material change'' has been revised to more precisely identify which changes must be reported under proposed § 207.57.

Person who imports or offers for import. We are proposing to define a ''person who imports or offers for import'' as an agent, broker, or other entity that the foreign establishment uses to facilitate the import of its drug into the United States. As described in section IV.B.3 of this document, this proposal would require foreign establishments to provide, for drugs manufactured, repacked, relabeled, or salvaged at the establishment, the name of each person known to the establishment who imports or offers for import such drug into the United States. Therefore, the establishment would need to provide the name of each agent, broker, or other entity that the foreign registrant uses to facilitate the import of its drug into the United States. We describe more fully what we mean by ''known to the establishment'' in section IV.B.3 of this document. The term ''person who imports or offers to import'' would not include carriers, consistent with the legislative history of the Bioterrorism Act. The legislative history shows that although the House provision originally

would have required registration information for importers and carriers, the conference substitute changed the language. The conference substitute deleted the term ''carriers,'' replacing it with ''persons who import or offer for import,'' clarifying that foreign manufacturers are not required to include information on carriers with annual registration. (See H. Rept. 107–481, 107th Cong., 2d sess., p. 140, 2002, Conf. Rept. to accompany H.R. 3448) We invite comments on our proposed definition of ''persons who import or offer for import.''

We also invite comment on our use of the word ''facilitate'' in the proposed definition. We recognize that the term could be interpreted to include middlemen or other entities that may be viewed as assisting with or promoting the importation of a drug into the United States. For example, we are aware that ''buyer's clubs'' could be captured in the definition if ''facilitate'' were to be interpreted broadly. Buyer's clubs are groups that consolidate orders for drugs purchased from foreign establishments and then, once those drugs are imported into the United States, send them to the individuals or other entities who ordered the drugs through the clubs. It is also possible that ''facilitate'' could be interpreted to include organizations that may promote the awareness and sale of products through advertisements on the internet, for example. We recognize that, under this proposal, foreign establishments would only be required to give us information for persons who import or offer for import that are known to the establishments. Although the knowledge requirement in this proposed rule would include information that the foreign establishment, and persons in the foreign establishment, has reason to know of, we believe it is likely that foreign establishments generally would not know about most of the ''middlemen'' described previously. Therefore, even though the term ''facilitate'' in the proposed definition would be interpreted broadly to include

middlemen, if the foreign establishment did not know of, or have reason to know of, the middlemen, the foreign establishment would not be required to report information about the middlemen under this proposal.

We also note that the terms ''broker'' or ''agent'' include ''customhouse brokers'' who facilitate importation by filing documents with the U.S. Customs Service, as well as FDA and other Federal agencies responsible for the regulation of imported products. We specifically invite comment on our use of the term ''facilitate'' in this proposal. We invite comment on whether we should interpret the term ''facilitate'' broadly to include middlemen as described previously. We also invite comment on whether foreign establishments would know about such middlemen and, if so, what effect a requirement to report information about those middlemen would have on foreign establishments. We also invite comment on whether there are benefits associated with such a reporting requirement, and, if so, what they are.

Private label distributor. We are proposing to define ''private label distributor'' to mean 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,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, the term would include both domestic private label distributors and foreign private label distributors.

Private label distributors are not considered to be manufacturers, repackers, relabelers, or drug product salvagers because they do not conduct any of the activities covered in section 510(a)(1) of the act with respect to the products they commercially distribute. Private label distributors only distribute drugs under their own label or trade name. The proposed definition is

consistent with current § 207.20(b) and the description of private label distributors set forth in the 1973 final rule on drug listing requirements (38 FR 6258 at 6259). We are proposing to define this term to clarify its meaning and to distinguish private label distributors from manufacturers, repackers, relabelers, and drug product salvagers. Under the proposed definition, a private label distributor does not engage in any activities performed by a manufacturer, repacker, relabeler, or drug product salvager for the drug it distributes. As discussed in section IV.D.1 of this document, private label distributors currently may elect to submit listing information to us for the drugs they distribute. Under the proposal, private label distributors would not be permitted to list, and manufacturers, repackers, relabelers, and drug product salvagers would be required to provide listing information to us for drugs being manufactured, repacked, relabeled, or salvaged for private label distributors. However, if a private label distributor is a manufacturer with respect to a particular drug or drugs, for example, the private label distributor is subject to the registration and listing requirements for manufacturers in proposed part 207 with respect to that drug or drugs.

Relabel, relabeler. We are proposing to use the term ''relabel'' to mean changing the label or labels on a drug or drug package, or adding to the labeling for a drug or drug package, without repacking the drug or drug package. We remind interested persons that those activities must be conducted in accordance with the act and FDA regulations. We are proposing to use the term ''relabeler'' to mean a person who owns or operates an establishment that relabels a drug. When not modified by ''domestic'' or ''foreign,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, the term would include both domestic relabelers and foreign relabelers.

Under the proposal, relabelers must provide registration and listing information. Under section 510(a)(1) of the act, the term ''manufacture, preparation, propagation, compounding, or processing'' includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user. As discussed previously, we use the term ''relabeler'' separately from the term ''manufacturer'' because, although the relabeler's registration and listing responsibilities in general are the same as those for manufacturers under the act, the proposal would modify some of these requirements. For example, as described under the definition of ''manufacturer'' in section IV.A.5 of this document, if a relabeler supplies us with the manufacturer's NDC number, we would not require the relabeler to provide all of the information that the manufacturer provides to obtain an NDC number and to list a drug. We would already have much of the information in the database linked to the manufacturer's NDC number, and it would be an unnecessary burden to require that the information be provided again. Under the proposed definition, a relabeler does not engage in any other activity performed by a manufacturer for the drugs they relabel.

Repack, repacker. We are proposing to use the term ''repack'' to mean repack or repackage or otherwise change the container or wrapper of a drug or drug package. We are proposing to use both the terms ''repack'' and ''repackage'' in the definition because these terms are often used interchangeably with respect to drugs and, whether such activities are characterized as repacking or repackaging, they are subject to the requirements of this part. Although the term ''repackaging'' is used in section 510(a)(1) of

the act, the terms ''repacking,'' ''repack,'' and ''repacker'' are more commonly used by industry when referring to this activity, and, therefore, we are using these terms throughout the proposal. We are proposing to use the term ''repacker'' to mean a person who owns or operates an establishment that repacks a drug or drug package. When not modified by ''domestic'' or ''foreign,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, the term would include both domestic repackers and foreign repackers.

Under the proposal, repackers must provide registration and listing information. Under section 510(a)(1) of the act, the term ''manufacture, preparation, propagation, compounding, or processing'' includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user. We use the term ''repacker'' separately from the term ''manufacturer'' because, although the repacker's registration and listing responsibilities in general are the same as those for manufacturers under the act, the proposal would modify some of these requirements. For example, as described under the definition of ''manufacturer'' in section IV.A.5 of this document, if a repacker supplies us with the manufacturer's NDC number, we would not require the repacker to provide all of the information that the manufacturer provides to obtain an NDC number and to list a drug. We would already have much of the information in the database linked to the manufacturer's NDC number, and it would be an unnecessary burden to require that the information be provided again. Under the proposed definition, a

repacker does not engage in any other activity performed by a manufacturer for the drugs they repack.

Representative sampling of advertisements. We are proposing to revise the definition of ''representative sampling of advertisements.'' Currently, § 207.3(a)(2) explains that the term ''advertising'' as used in part 207 includes the promotional material described in § 202.1(l). However, current § 207.3(a)(9) expressly excludes such material from the definition of ''representative sampling of advertisements.'' We believe that the inconsistency between the two provisions was an unintended result of certain editorial amendments made to part 207. We are proposing to revise the definition of ''representative sampling of advertisements'' to resolve the inconsistency. Specifically, we believe that the content of current § 207.3(a)(2) should be incorporated into the definition of ''representative sampling of advertisements'' to clarify that the term includes the promotional material described in § 202.1(l)(1).

We are proposing to define ''representative sampling of advertisements'' as typical advertising material (including the promotional material described in § 202.1(l)(1), but excluding labeling as determined in § 202.1(l)(2)), that gives a balanced picture of the promotional claims used for the drug. In addition to resolving the inconsistency described previously, the proposed definition would delete the example currently provided in § 207.3(a)(9) (that is, if more than one medical journal advertisement is used but the promotional content is essentially identical, only one needs to be submitted). We believe that this example is unnecessary and are proposing to simplify the definition by deleting it.

Representative sampling of any other labeling. We are proposing to revise the definition of ''representative sampling of any other labeling.'' We are

proposing to delete current § 207.3(a)(2), which explains that the term ''labeling'' as used in part 207 includes the promotional material described in § 202.1(l)(2). We believe that this information would be more appropriately included in the definition of ''representative sampling of any other labeling.''

We are proposing to define ''representative sampling of any other labeling'' as typical labeling material (including the promotional material described in § 202.1(l)(2), but excluding labels and package inserts) that gives a balanced picture of the promotional claims used for the drug. In addition to incorporating the relevant content of current § 207.3(a)(2), the proposed definition would delete the example currently provided in current § 207.3(a)(10) (that is, if more than one brochure is used but the promotional content is essentially identical, only one needs to be submitted). We believe that this example is unnecessary and are proposing to simplify the definition by deleting it.

United States agent. We are proposing to remove the definition of ''United States agent'' in current § 207.3(a)(11). Proposed § 207.69 would incorporate many of the provisions of the current definition of United States agent and current § 207.40 (registration and listing requirements for foreign establishments). The same requirements in the current definition appear at proposed § 207.69(b)(1), (b)(2), and (b)(3).

B. Registration

1. Who Would Be Required to Register?

Proposed § 207.17(a) would require manufacturers, repackers, relabelers, and drug product salvagers to register each establishment. This provision would replace the requirement at current § 207.20(a) that owners or operators of all drug establishments that engage in the manufacture, preparation,

propagation, compounding, or processing of a drug must register. The terms ''manufacturer,'' ''repacker,'' ''relabeler,'' and ''drug product salvager,'' as defined in proposed § 207.1 and discussed in section IV.A.5 of this document, more clearly indicate who must register.

Manufacturers, repackers, relabelers, and drug product salvagers would be required to register because the activities they perform fall within the scope of activities that trigger registration requirements in section 510(a)(1) of the act. Section 510(a)(1) states that the phrase ''manufacture, preparation, propagation, compounding, or processing'' includes repacking or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user.

We are proposing to use the terms ''repacker,'' ''relabeler,'' and ''drug product salvager'' separately from the term ''manufacturer'' in the proposal because, although the repacker, relabeler, and drug product salvager's listing responsibilities in general are similar to those for manufacturers under the act, the proposal would modify some of these requirements. In particular, if a repacker, relabeler, or drug product salvager supplies us with the manufacturer's NDC number, we would not require the repacker, relabeler, or drug product salvager to provide all of the information that the manufacturer provides to list a drug. Similarly, we would not require repackers and relabelers to submit all of the information that the manufacturer submits to obtain an NDC number.

Proposed § 207.17(a) would enable us to identify who is making drugs and where they are being made. Being able to accurately identify who makes drugs and where they are made is very important. Certain marketed drugs may need

to be quickly identified and used to help counteract the effects of a bioterrorism attack. Registration information also assists us in scheduling and planning inspections of registered establishments pursuant to section 704 of the act.

Proposed § 207.17(a) also provides that registration information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments. This provision would also apply when operations are conducted at both domestic and foreign establishments and there exists joint ownership and control among all the establishments. This provision is consistent with current § 207.20(a).

We are proposing to revoke the requirement in current § 207.20(a) that no owner or operator may register an establishment if any part of that establishment is registered by another owner or operator. The requirement has caused uncertainty about who must register and which establishment must be registered. Under proposed § 207.17(a), manufacturers, repackers, relabelers, and drug product salvagers must register each establishment unless they are otherwise exempt under section 510(g) of the act or proposed § 207.13.

Under proposed § 207.17(b), private label distributors would not register with us unless they also manufacture, repack, relabel, or salvage drugs and are required to register under the act or proposed § 207.17(a). Private label distributors are not considered to be manufacturers, repackers, relabelers, or drug product salvagers because they do not conduct any of the activities covered under section 510(a)(1) of the act with respect to the drugs they commercially distribute. Private label distributors only distribute drugs under their own label or trade name. Proposed § 207.17(b) would revise the provision

in current § 207.20(b) that owners or operators of establishments that distribute under their own label or trade name a drug manufactured or processed (as defined in current § 207.3(a)(8)) by a registered establishment may elect to obtain a labeler code from us and submit listing information directly to us. Under current regulations, if a private label distributor does not elect to submit drug listing information to us, the registered establishment must submit the drug listing information. As explained in section IV.D.1 of this document, we are proposing to revise current § 207.20(b) and not permit private label distributors to register or list. Manufacturers, repackers, relabelers, and drug product salvagers must submit drug listing information for those drugs they manufacture, repack, relabel, or salvage for commercial distribution for a private label distributor.

2. When Would Initial Registration Information Be Provided?

Under proposed § 207.21, a domestic manufacturer, domestic repacker, domestic relabeler, and domestic drug product salvager must register each establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug. The proposed timeframe ''no later than 5 calendar days'' is consistent with current § 207.21(a) in that the current registration requirement also provides for a 5-day registration timeframe for owners or operators of establishments entering into the ''manufacturing or processing'' of a drug (as defined in current § 207.3(a)(8)). The proposed timeframe is also consistent with the requirement in section 510(c) of the act to register each establishment ''immediately'' and ''upon first engaging in the manufacture, preparation, propagation, compounding, or processing'' of a drug.

Under proposed § 207.21, a foreign manufacturer, foreign repacker, foreign relabeler, and foreign drug product salvager 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. This is consistent with current § 207.40(b), which states that no drug may be imported or offered for import into the United States unless it is listed and manufactured, prepared, propagated, compounded, or processed at a registered foreign drug establishment. In addition, section 510(i) of the act states that any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or device that is imported or offered for import into the United States shall register with the Secretary.

Proposed § 207.21 uses the term ''each establishment'' to emphasize that the requirement to register would apply even if the manufacturer, repacker, relabeler, or drug product salvager has previously registered one or more other establishments. This proposed requirement is consistent with two provisions of section 510 of the act. Section 510(d) of the act requires registration of any additional establishment immediately upon beginning the manufacture, preparation, propagation, compounding, or processing of a drug at that establishment. Section 510(i)(1) of the act states that any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States must register with the Secretary.

We are proposing to specify ''calendar'' days to be consistent with the terminology and timeframes used in the international pharmaceutical regulatory guidances of the International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (*http://www.ich.org*) and the World Health Organization's Council for

International Organizations of Medical Sciences (CIOMS) (*http://www.cioms.ch*).

We are proposing to revoke the requirement in current § 207.21(a) to register within 5 days after submitting certain marketing applications if the owner or operator has not previously entered into the manufacture or processing of a drug (as defined in current § 207.3(a)(8)). We are also proposing to revoke the requirement in current § 207.20(c) that, before beginning the manufacture or processing of a drug subject to certain marketing applications, an owner or operator of an establishment must register before the application is approved. We are proposing to revoke these requirements because, under proposed § 207.21 and consistent with section 510(c) and (d) of the act, registration of each establishment must occur no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug at the establishment. This provision would govern when to register an establishment rather than the date a marketing application is submitted or approved. We believe that this proposed requirement would provide us with sufficient notice as to who is manufacturing, repacking, relabeling, or salvaging drugs and where those activities are taking place. In addition, marketing application approval is linked to registration elsewhere in our regulations. Under current § 314.125(b)(11) (21 CFR 314.125(b)(11)), we may refuse to approve an application if the drug will be manufactured or processed in an establishment that is not registered. For consistency with current § 314.125(b)(11), we are proposing to revise § 514.111(a)(12) (21 CFR 514.111(a)(12)) for NADAs to state that we will refuse to approve an application if ''the drug will be manufactured in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and part 207.'' For licensed

human biological products, current 21 CFR 601.4(b) includes a provision that we must deny a BLA if the establishment or product does not meet ''requirements established in Title 21, Chapter I'' (this would include the registration and listing provisions).

3. What Information Would Be Required for Registration?

Under proposed § 207.25, all manufacturers, repackers, relabelers, and drug product salvagers must provide the following information to register each of their establishments:

- Name of the owner or operator of each establishment; if a partnership, the name of each partner would be submitted; if a corporation, the name of each corporate officer and director and the place of incorporation would be submitted (proposed § 207.25(a)). This provision is consistent with section 510(a)(2) of the act, which states that ''the term 'name' shall include in the case of a partnership the name of each partner and, in the case of a corporation, the name of each corporate officer and director, and the State of incorporation.'' The proposal would replace ''State of incorporation'' with ''place of incorporation'' to include foreign corporations. Proposed § 207.25(a) is also consistent with section 510(c) of the act, which states that ''Every person * * * shall immediately register with the Secretary his name, place of business, and such establishment.'' The proposal would use ''owner or operator'' for consistency with current § 207.25(a), which provides that the information required for registration includes the name of the owner or operator of the establishment. Current § 207.25(a) provides that the term ''name of the owner or operator'' includes, in the case of a partnership, the name of each partner and, in the case of a corporation, the name and title of each corporate officer and director and the name of the State of incorporation. The

proposal would revoke the requirement to include the title of each corporate officer and director because we have determined that it is not necessary for registration purposes. Current § 207.25(a) also requires the submission of the ''kind of ownership or operation (that is, individually owned, partnership, or corporation).'' The proposal would replace this requirement because the kind of ownership or operation would be captured under the requirement to provide, if applicable, the name of each partner, and corporate officer and director, and the place of incorporation in proposed § 207.25(a).

- Name, trade name(s), and address of each establishment (proposed § 207.25(b), (c), and (d)). This provision is consistent with section 510(c) of the act and current § 207.25(a). The proposal would continue the requirement in current § 207.25(a) to submit all trade names used by the establishment, but rephrase current § 207.25(a) to clarify that, for purposes of this subsection, we want the trade name(s) of the establishment, names under which the establishment conducts business, and additional names by which the establishment is known. We are not seeking under this section the trade name(s) of the drugs of the establishment. Although we are interested in the trade names of the drugs, we can obtain that information through the drug listing requirements.

- Registration number of each establishment, if previously assigned to the establishment by us (proposed § 207.25(e)). If not previously assigned by us, we would assign a registration number after we receive the registration information (proposed § 207.25(e)). Under section 510(e) of the act, we may assign a registration number to any person or establishment registered and, under current § 207.35(a), we will assign a permanent registration number to each establishment that registers. The ''establishment registration number'' is

defined in proposed § 207.1 to mean the number assigned by FDA to the establishment during the establishment registration process. (Currently, the FEI will be the number we assign as the establishment registration number.) We are proposing to require the submission of the registration number because each establishment is identified by its registration number for registration and inspection purposes and to enable us to identify all registered establishments. The registration number is currently submitted on Form FDA 2656.

- Type of operations(s) performed at each establishment—for example, manufacturing, repacking, relabeling, or salvaging (proposed §207.25(f)). We are proposing to require this information because it is important for identifying, prior to an inspection, which operation the establishment engages in so that our investigators can be better prepared before inspection. Currently, the ''business type'' (for example, manufacturer, repacker, relabeler) must be submitted on Form FDA 2656.

- Name, address, telephone and fax numbers, and e-mail address of the official contact, as provided in proposed § 207.69(a), for each establishment (proposed § 207.25(g)). We are proposing to require this information because we need a contact person to facilitate discussion with the manufacturer, repacker, relabeler, and drug product salvager. This information needs to be current and, under proposed § 207.29(a)(3), any change in this information must be provided to us within 30 calendar days. This information is not required under current part 207. The requirements for the official contact are discussed in section IV.F.1 of this document.

- Information for foreign establishments only (proposed § 207.25(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 proposed § 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. The requirements for the United States agent are discussed in section IV.F.1 of this document. The name, address, and phone number of the United States agent is required to be submitted under current § 207.40(c). The information on importers and persons who import is not required to be submitted under current part 207. We are proposing to require the submission of the information on importers and persons who import because the Bioterrorism Act requires foreign establishments to submit, among other things, the name of each importer of each drug that is known to the manufacturer, repacker, relabeler, and drug product salvager and the name of each person who imports or offers for import each drug to the United States for purposes of importation. We want to make clear that the term ''known to'' would include any importer that is known to the foreign establishment as well as any importer that the foreign establishment has reason to know of. We therefore expect that the person responsible for completing the required registration forms on behalf of the foreign establishment would undertake appropriate due diligence in completing those forms, including to find out and report importers that others in his or her establishment know of or have reason to know of. In addition to the name, the proposal would require that the address, telephone and fax numbers, and e-mail address of each importer and of each person who imports or offers for import be provided to enable us to contact these persons.

All information required under proposed § 207.25 must be submitted for the establishment to be considered registered. As explained in section IV.B.l

of this document, establishment registration would enable us to identify who is making drugs and where they are being made. Being able to accurately identify who makes drugs and where they are made is very important for protecting the public health. Among other things, registration information would enable us to become aware of and take action to stop manufacturers, repackers, relabelers, and drug product salvagers who do not follow the requirements set forth in the act and in our regulations.

4. What Are the Proposed Requirements for Reviewing and Updating Registration Information?

The proposal would modify and streamline the requirements associated with updating registration information. Currently, manufacturers, repackers, relabelers, and drug product salvagers must enter new or revised registration information on Form FDA 2656 and return the form to us annually. Under the proposal, manufacturers, repackers, relabelers, and drug product salvagers would access the electronic drug registration and listing system and review their current registration information online, making any changes where needed. Updating registration information would be less time consuming under the proposal because the manufacturer's, repacker's, relabeler's, and drug product salvager's information would be easily accessible at any time and only changes to the information already in the system would need to be entered in the fields provided.

The following sections provide a description of the proposed requirements for reviewing and updating registration information and how they modify or reduce the burden of the current requirements.

a. *Expedited updates of registration information*. Manufacturers, repackers, relabelers, and drug product salvagers would report, under proposed

§ 207.29(a), the following changes as expedited updates no later than 30 calendar days after the change:

- The close or sale of an establishment;
- Any change in the name or address of an establishment; and
- Any change in the name, address, telephone and fax numbers, or e-mail address of the official contact or the United States agent.

We are proposing to require that these changes be reported as expedited updates because we need to know as soon as possible when a business has closed or has been sold and when the establishment's name or address has changed. This information is especially important for scheduling inspections. We also need current information for contacting the official contact or United States agent. As previously mentioned, it is increasingly important for us to be able to identify where drugs are being made and when drugs are no longer available. The expedited receipt of this information will help promote the efficient enforcement of the act.

Manufacturers, repackers, relabelers, and drug product salvagers are encouraged to provide expedited updates as soon as possible but no later than 30 calendar days after the change occurs. Our electronic drug registration and listing system will be easily accessible all the time to make changes.

The close or sale of an establishment, and a change in the name or address of an establishment, are currently reported annually on Form FDA 2656.

Proposed § 207.29(a) would revise current §§ 207.26 and 207.40(c)(3). Current § 207.26 requires the submission of certain amendments to registration information within 5 days of the change, and as noted previously, § 207.40(c)(3) requires the submission of any changes to the United States agent's name, address, or phone number within 10 business days of the change.

As explained below, the proposal would lengthen the time period for reporting the changes in current § 207.40(c)(3). The proposal also would lengthen the time period for reporting some of the changes in current § 207.26 and revoke some of the reporting requirements in current § 207.26:

- A change in location would no longer be submitted as an amendment to registration within 5 days of the change, but would be reported under proposed § 207.29(a)(2) as an expedited update no later than 30 calendar days after the change (''address'' of an establishment is used in the proposal instead of location). We have determined that notification no later than 30 calendar days would be sufficient and would be consistent with the proposed timeframe for the other expedited updates.

- A change in ''drug-handling activity'' would no longer be submitted as an amendment to registration within 5 days of the change. A change in this information would only be reported during the annual review and update under proposed § 207.29(b). (The term ''type of operations'' is used in proposed § 207.25(f) instead of ''drug-handling activity.'') We have determined that annual notification of this change would be sufficient.

- Changes in ''individual ownership'' and ''corporate or partnership structure,'' in current § 207.26, would no longer be reported as amendments to registration because the proposal would revoke the corresponding provision for registration in current § 207.25(a) (the ''kind of ownership or operation (that is, individually owned, partnership or corporation)''). As explained in section IV.B.3 of this document, the kind of ownership or operation would no longer be submitted for registration because the information would be captured under the requirement to provide, if applicable, the name of the partner, corporate officer and director, and the place of incorporation in proposed § 207.25(a).

This information would be reviewed and updated annually under proposed § 207.29(b). This proposed requirement is consistent with current § 207.26, which specifies that changes in the names of officers and directors of the corporation do not require an amendment and must be submitted at the time of annual registration.

- Under current § 207.26, a change in a registered establishment's firm name within 6 months of the registration of the establishment must be supported by a signed statement of the establishment's owner or operator that the change was not made for the purpose of changing the name of the manufacturer of a drug product under current § 201.1. This verification would no longer be required to be submitted as an amendment to registration. A change in the name of an establishment would be reported under proposed § 207.29(a)(2) no later than 30 calendar days after the change.

Proposed § 207.29(a)(3) would revise current § 207.40(c)(3), which provides that a foreign drug establishment or United States agent must report to us, within 10 business days, any changes to the United States agent's name, address, or phone number. The proposal would make the following revisions:

- The changes to the information about the United States agent would be revised to include not only the name, address, and telephone number, but also the fax number and e-mail address. This provision would be consistent with the information required to be submitted for the United States agent for registration under proposed § 207.25(h).

- The time period for reporting the changes would be lengthened to no later than 30 calendar days for consistency with the time period for the other expedited reports in proposed § 207.29(a).

- Changes in the name, address, telephone and fax numbers, and e-mail address of the official contact would also be reported under proposed § 207.29(a)(3) within 30 calendar days. This provision would be consistent with the information required to be submitted for the official contact for registration under proposed § 207.25(g).

- Under proposed § 207.29(a)(3), the 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. This provision would make the updates easier than the requirement in current § 207.40(c)(3) because it would enable the official contact and the United States agent (in addition to the manufacturer, repacker, relabeler, and drug product salvager) to update their own or each other's registration information.

- Under proposed § 207.29(a)(3), only a manufacturer, repacker, relabeler, or drug product salvager may designate a new official contact or United States agent. This proposed requirement is necessary because the manufacturer, repacker, relabeler, and drug product salvager is ultimately responsible for the actions of the official contact and the United States agent.

The requirements for the official contact and the United States agent are discussed in section IV.F.1 of this document.

b. *Annual review and update of registration information*. Proposed § 207.29(b) would require that the registration information provided under proposed § 207.25 be reviewed and updated annually. This timeframe is consistent with the requirement in section 510(b) of the act that owners or operators register on or before December 31 of each year and with the requirement in current § 207.21(a) that owners or operators renew their

registration information annually. Proposed § 207.29(b) uses the term ‘‘review and update’’ to stress the importance of first reviewing all registration information to determine if any changes have occurred and then updating the information where needed. Proposed § 207.29(b)(1) specifies that the first review and update must occur no later than 1 year after the date of the initial registration of each establishment and that subsequent reviews and updates must occur no later than annually thereafter from the date of initial registration. Proposed § 207.29(b)(2) provides that the updates must reflect all changes that have occurred since the last annual review and update.

The proposal would add a new requirement for updating registration information. Under proposed § 207.29(b)(3), if none of the registration information has changed since the last annual registration (accomplished through the review and update of registration information), manufacturers, repackers, relabelers, and drug product salvagers must certify electronically that no changes have occurred. This is consistent with section 510(b) of the act, which requires manufacturers to register on or before December 31 of each year. If manufacturers, repackers, relabelers, and drug product salvagers certify that no changes have occurred, this certification would be the equivalent of resubmitting registration information, thereby satisfying the annual registration requirement. We are proposing to require that manufacturers, repackers, relabelers, and drug product salvagers certify annually that no changes have occurred because many manufacturers, repackers, relabelers, and drug product salvagers have not reviewed or updated this information on a regular basis. It has been difficult for us to determine whether failure to register annually is the result of no changes in information or noncompliance. The proposed requirement is intended to reduce these instances and improve the accuracy

of our registration database. To increase the nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies, it is increasingly important for manufacturers, repackers, relabelers, and drug product salvagers to comply with registration requirements. With accurate information, we can identify where drugs are being made and better ensure that drugs are promptly available when needed. Furthermore, taking steps to increase compliance is consistent with section 301(p) of the act (21 U.S.C 331(p)), which makes it a prohibited act to fail to register under section 510 of act.

C. The National Drug Code (NDC) Number: What is It? How is It Used? What Changes Are We Proposing?

1. What Is the NDC Number?

The NDC number is a widely used identifier for drugs. It is a unique 10-digit number consisting of 3 segments: The labeler code, the product code, and the package code. Currently, the labeler code consists of four or five digits, the product code consists of either three or four digits, and the package code consists of either one or two digits. We assign the labeler code to the manufacturer, repacker, or relabeler after it has registered with us. For private label distributors, currently we provide a labeler code to the private label distributor if the private label distributor submits the required information to us. Alternatively, we provide a labeler code for a private label distributor to the manufacturer, repacker, or relabeler who is manufacturing, repacking, or relabeling the drug for the private label distributor after the manufacturer, repacker, or relabeler provides the required registration information pertaining to the private label distributor. The manufacturer, repacker, relabeler, or

private label distributor then assigns the product code and package code to each drug within certain parameters that we have established.

2. How Did NDC Numbers Originate? How Are They Used?

Created in 1969, NDC numbers were originally intended to ''provide an identification system in computer language to permit automated processing of drug data by Government agencies, drug manufacturers and distributors, hospitals, and insurance companies'' (see 34 FR 11157, July 2, 1969). Participation in the NDC system was voluntary initially, and the program covered ''firms which manufacture and label or which repackage and label drugs'' (id.). In 1971, the NDC system expanded to include ''distributors who are marketing drug products in interstate commerce, under their own name (label), and through multiple wholesale outlets and/or five or more retail outlets'' (see 36 FR 27, January 1, 1971).

The enactment of the Drug Listing Act of 1972 (Public Law 92–387, 86 Stat. 559) changed the NDC number system even further. The Drug Listing Act required registered establishments to list all drugs that the establishment manufactures, prepares, propagates, compounds, or processes for commercial distribution and authorized us to assign a ''listing number'' to each drug or class of drugs that was listed. The Drug Listing Act declared that, ''Any number assigned * * * shall be the same as that assigned pursuant to the National Drug Code.'' Thus, by linking drug listings to the NDC numbers, the Drug Listing Act, in essence, authorized us to make participation in the NDC number system mandatory. In addition, by referring to the word, ''drug,'' the Drug Listing Act extended the NDC number system to over-the-counter drugs and animal drugs (because both are ''drugs'' under the act and are listed under section 510(j) of the act).

Today, NDC numbers continue to be an important, standardized, identification system for drug products used in data or claims processing, as well as in applications other than data or claims processing. For example, consumers may use NDC numbers to identify drugs that are the subject of a recall. Health care professionals submitting MedWatch reports (concerning possible adverse drug events) use NDC numbers to identify the drug at issue. Our investigators sometimes use NDC numbers to determine a drug's compliance status by linking the NDC number to our registration and listing database to verify whether the manufacturer has registered and listed a particular drug. We compile the NDC numbers in the National Drug Code Directory, and the directory is accessible online at *http://www.fda.gov/cder/ndc/database*.

In addition, several new or future public health programs or initiatives rely or will rely on NDC numbers. For example:

- On February 26, 2004 (69 FR 9120), we published in the **Federal Register** a final rule to require certain human drug and biological products to have bar codes (see 69 FR 9120). The bar code must contain, at a minimum, the drug's NDC number. This rule is designed to reduce the number of medication errors in hospitals and other health care settings by allowing health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is being administered to the right patient at the right time.

- The electronic prescription drug program 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 (see 42 U.S.C.

1860D–4(e)(3)(C)(iii)). 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. As we stated previously in this document, drug listing numbers are, under the Drug Listing Act of 1972, to be the same as NDC numbers.

- The Health Insurance Portability and Accountability Act (Public Law 104–191) required, among other things, adoption of code set standards to facilitate electronic transactions. The standard code set for drugs is the NDC (see final rule on ''Health Insurance Reform: Standards for Electronic Transactions'' (65 FR 50312, August 17, 2000), 45 CFR 162.1002(c); amended February 20, 2003: ''Health Insurance Reform: Modifications to Electronic Data Transaction Standards and Code Sets'' (68 FR 8381), 45 CFR 162.1002(a)(3) and (b)(2)).

- We are working with the National Library of Medicine, manufacturers, repackers, relabelers, and health care information suppliers to improve patient safety by better access to medication information through the DailyMed initiative. The DailyMed is an up-to-date, computerized repository of medication information including product labeling. The changes we are proposing to the NDC number would complement the DailyMed initiative by providing a link to product labeling made available through the DailyMed. The product labeling in this repository would be in the form of SPL. SPL is a standardized computer readable product labeling that links the NDC number to the product information.

To illustrate how this would work, someone could simply scan a bar code encoded with the NDC number or type into the DailyMed search program the NDC number on the carton label to access the most current information in the

product labeling available from the DailyMed. This capability would enable DailyMed users to have the most up-to-date information for a drug, which could be an important public health benefit for consumers and health care professionals. For example, assume that a manufacturer modified its labeling to reflect a new adverse drug experience. If a consumer, pharmacist, or health care provider received a drug whose labeling had been printed earlier, the consumer, pharmacist, or health care provider would not be alerted to the new adverse drug experience. By using the DailyMed, the consumer, pharmacist, or health care provider would be able to access the new drug labeling and would, therefore, learn about the new adverse drug experience and possibly be able to avoid it. The consumer, pharmacist, or health care provider would also be better able to assess the risks and benefits of the drug and, therefore, would be able to make more informed decisions about using the drug. The DailyMed would be a publicly accessible repository of drug information that could be used in many ways by various parties, such as by those who could add value to the information, such as pricing information, and make it available to other parties.

Unfortunately, despite the widespread and growing use and reliance on NDC numbers, the existing NDC number system has several shortcomings. For example, manufacturers, repackers, and relabelers can assign NDC numbers, and the current regulations at § 207.35(b)(4)(ii) permit them to re-use the product codes under certain circumstances (such as taking the NDC number assigned to drug X and then, after drug X has been discontinued, later assign the same NDC number to drug Z). Also, under current regulations, it is difficult for FDA to control the practice of a manufacturer, repacker, or relabeler making

changes to a drug but continuing to use the same NDC number despite those changes.

The manufacturer, repacker, and relabeler's ability to assign the product code and package code themselves has also resulted in problems that affect the National Drug Code Directory and its reliability. Product and package codes are not always assigned appropriately, and industry practices for assigning codes are inconsistent. In addition, manufacturers, repackers, and relabelers currently do not tell us what codes they have assigned until they list drugs with us; this means that the National Drug Code Directory is not always complete or comprehensive. Moreover, manufacturers, repackers, and relabelers may never list a product or may sometimes omit information or submit incorrect information to us; this often prevents us from including the correct information in the National Drug Code Directory and forces us to devote resources to obtaining, sometimes unsuccessfully, the correct information.

Furthermore, because NDC code segments can vary in length (such as a NDC having a four-digit labeler code, a four-digit product code, and a two-digit package code while another NDC has a five-digit labeler code, a three-digit product code, and a two-digit package code), electronic systems that view the NDC as a single number might interpret two different NDC numbers as being the same number. For example, one manufacturer, repacker, or relabeler's drug might have a NDC number that reads as 12345–678–90 while another could have a drug whose NDC number reads as 1234–5678–90. If a database omits the hyphens, the result would be a misleading impression that both drugs have identical NDC numbers (i.e., 1234567890), although they are made by different manufacturers and may be entirely different products.

We have also found that some manufacturers, repackers, and relabelers have assigned NDC numbers to products that are not drugs, such as dietary supplements and medical devices; such actions can confuse drug databases or lead to inappropriate reimbursements.

Consequently, to address these shortcomings and to create an accurate, up-to-date NDC number system, we propose to revise the NDC number system. In brief, we believe that to ensure that the numbers are unique and unambiguous, we need to take on the responsibility of assigning the NDC numbers prospectively to drugs that have not previously been assigned NDC numbers by a manufacturer, repacker, or relabeler. The NDC numbers currently assigned to drugs prior to the effective date of the rule would remain unchanged, provided those NDC numbers comply with the new regulations as finalized. FDA intends to validate that current NDC numbers comply with the new regulations as finalized. We believe that the NDC number structure can remain very similar to what exists today, as we describe below, and still allow for unique and unambiguous NDC numbers if we assign the NDC numbers.

The proposal would also delete obsolete or unnecessary requirements. For example, current § 207.35 refers to the National Health Related Items Code (NHRIC) system as another code system; the proposal would omit references to the NHRIC system because we no longer maintain the NHRIC database (see 42 FR 52808 at 52810, September 30, 1977)).

We describe the proposed changes in more detail in the next section.

3. What Changes Are We Proposing?

a. *Proposed § 201.2—Drugs; National Drug Code (NDC) Number*. Currently, § 201.2 states that NDC numbers are requested, but not required, to appear on

all drug labels and in all drug labeling, ''including the label of any prescription drug container furnished to a consumer.'' Section 201.2 also states that if the NDC number appears on the drug label, it must be displayed as required by current § 207.35(b)(3).

The proposal would revise § 201.2 to explain:

- What drugs must have an NDC number, in human-readable form, on the label;
- What an appropriate NDC number is;
- Whether any other NDC number may appear on a label;
- What prefix must be used to identify the NDC number on the label; and
- Where the NDC number goes on the label.

Specifically, proposed § 201.2(a) would require the appropriate NDC number, in human-readable form, to appear on the labels of drugs subject to the drug listing requirements. In this case, the word ''drugs'' should be interpreted in light of proposed § 207.1 and encompasses human drugs, including the drugs regulated under a BLA, as described in proposed § 207.9(c), and animal drugs, including Type A medicated articles. These drugs may be active pharmaceutical ingredients or finished dosage forms, whether prescription or OTC. The drugs regulated under a BLA, as described in proposed § 207.9(c) include, but are not limited to: (1) Plasma derivatives such as albumin, Immune Globulin, Factor VIII and Factor IX, and recombinant versions of plasma derivatives or animal derived plasma derivatives; (2) Vaccines; (3) Allergenic products; (4) Bulk product substances such as fractionation intermediates or pastes; and (5) Therapeutic biological products.

We propose to require human-readable NDC numbers to appear on drug labels because various individuals and databases use and rely on NDC numbers, and those individuals or databases might not have the technology

or means to read an automatic identification technology such as a bar code that is required under § 201.25. In addition, for those who are able to read bar codes, a human-readable NDC number may serve as a ''backup'' in case the bar code is damaged, cannot be read, or is otherwise illegible.

Proposed § 201.2(b) would explain that an ''appropriate NDC number'' is the NDC number that we have assigned (under proposed §§ 207.33 or 207.37, which we discuss later in this part) to the last manufacturer, repacker or relabeler (including a drug product salvager who repacks or relabels the drug), or private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer. For example, assume that a manufacturer makes a drug and sells that drug to a wholesaler or retailer. Under proposed § 201.2(b), the manufacturer is the last person responsible for the drug immediately before it reached the wholesaler or retailer, so the appropriate NDC number would be the manufacturer's NDC number that we have assigned to that drug. If, however, the manufacturer sold the drug to a repacker, who then repackages the drug and sells the repackaged drug to a retailer, the repacker is the last person responsible for the drug immediately before it reached the retailer, so the appropriate NDC number would be the repacker's NDC number that we have assigned and not the manufacturer's NDC number.

Identifying the last person responsible for a drug may be important in situations where the drug's quality, purity, labeling, or packaging may be at issue; for example, if a drug appeared to be contaminated, knowing who the last person was who manufactured, repacked, or relabeled the drug could help focus an investigation to determine how the contamination occurred. It also allows linking to the correct product information in the DailyMed. In addition, requiring the NDC number of the last manufacturer, repacker, relabeler, or

private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer would enable us to accurately and quickly identify the original manufacturer by connecting the NDC number on the label to the information in the electronic drug registration and listing system.

The proposed approach of assigning NDC numbers would mean that repackers, for example, would have to use their own NDC number, rather than using the manufacturer's NDC number on drug labels. We recognize that some, but not all, repackers have been using the manufacturer's NDC number rather than their own on drug labels. We are aware that some repackers' practice of using the manufacturers' NDC numbers has led to some confusion among FDA, the Centers for Medicare & Medicaid Services (CMS), other Federal agencies, State agencies, and private insurance organizations that rely on NDC numbers for many purposes, including to identify a drug and a drug's source and for purposes of reimbursement and dispensing systems. It also has led to some confusion by practitioners and patients. There may be other reasons that this practice has posed difficulties or is cause for concern.

We are aware that the use of manufacturer's NDC numbers by some repackers may lead to inaccurate or improper reimbursement by Medicaid, Medicare, and private insurers. It also may result in misunderstanding as to which rebate agreement a particular drug is covered by or whether a particular drug is covered by any rebate agreement at all.

We are also aware that the use of manufacturer's NDC numbers by repackers may not always be accurate or consistent. For example, a repacker might use a manufacturer's NDC number for a particular drug and then continue to use that manufacturer's NDC number for generic equivalents to

that drug. This may lead to confusion for caregivers and patients who may be dispensed medication based on the original manufacturer's NDC number, but receive a drug that is different in size, shape and/or color than the drug they are accustomed to using. Additionally, there could be reimbursement differences between one firm's product and another firm's product. Further, the NDC number of the wrong manufacturer on the drug's label (even if the drugs of both manufacturers are generic equivalents) may also be a problem when pharmacies rely on verification systems that include exact color images of drugs based on NDC numbers.

Recently, the National Association of Chain Drug Stores (NACDS) and the Healthcare Distribution Management Association (HDMA) asked us to exercise enforcement discretion concerning our recent bar code rule (see 21 CFR 201.25 (69 FR 9170, February 26, 2004)) so that repackers could continue using manufacturers' NDC numbers on retail-based repackaged drug products (Ref. 1). In brief, NACDS and HDMA assert that FDA has ''historically allowed the use of original manufacturer NDC numbers by repackagers on the product labels of retail-based repackaged drug products'' and that this practice is standard among repackers (Ref. 1, p. 2). NACDS and HDMA also stated that use of the repackers' NDC numbers ''is not necessary or desirable'' because repackers identify themselves on the drug labels and that procedures exist to allow recall of particular lots of repacked drugs (rather than all drugs made by a manufacturer). They also stated that mandatory use of the repackers' NDC numbers might affect patient safety adversely and create additional, excessive costs to patients, health care providers, and payers because databases use the manufacturers' NDC numbers and cannot be modified to accommodate repackers' NDC numbers (Ref. 1, pp. 4 through 9). For example, NACDS and

HDMA said that requiring repackers to use their own NDC numbers could ''greatly increase the potential for medication errors'' because pharmacists would: ''be required to inefficiently and manually choose between multiple options of the same product, e.g., Motrin 800mg by [one manufacturer] or Motrin 800mg repackaged by 5 different repackagers. The more NDC numbers in use for the same product across the country, the greater the chance that data entry errors will occur across the many pharmacies that use repackaged products.'' (Ref. 1, p. 7.) In addition, NACDS and HDMA said that requiring repackers to use their own NDC numbers would oblige them to pay substantial rebate fees under Medicaid when Congress intended drug manufacturers, not repackers, to pay those rebates and would complicate Medicaid billing; they further stated that requiring repackers to use their own NDC numbers would lead to a ''sharp reduction or elimination of this type of repackaging'' (Ref. 1, p. 8).

On March 28, 2005, we issued a response to the letter from NACDS and HDMA. The response stated, among other things, that we intend to temporarily exercise our enforcement discretion and permit repackers to use manufacturers' NDC numbers in bar codes placed on their products. We said that there will be an opportunity to directly consider this issue when we issue our proposed rule on establishment registration and drug listing. The response stated that we will consider all information provided that documents the impact on repackers.

We lack sufficient information to assess whether requiring repackers to use their own NDC numbers would be as problematic and expensive as NACDS and HDMA suggest. We also do not know the extent to which databases that use NDC numbers cannot be modified to accommodate repackers' NDC

numbers or to associate more than one NDC number with drugs made by the same manufacturer. Moreover, although repackers currently assign their own NDC numbers and report those numbers to us, we do not know whether databases ignore or omit repackers' NDC numbers that we make available through the National Drug Code Directory.

We believe that allowing repackers to use the manufacturers' NDC numbers would be contrary to the proposal's goal of making the NDC number unique and the system more accurate and reliable.

We are requesting additional information on this issue. We specifically invite comments on the proposed approach of requiring on the drug's label the NDC number of the last manufacturer, repacker or relabeler (including the drug product salvager who repacks or relabels the drug), or private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer, which would result in prohibiting the use of manufacturer's NDC numbers by repackers. We are especially interested in: (1) Examples and discussions of dispensing errors or difficulties, confusion, reimbursement problems, or other difficulties that may have been caused or contributed to by the practice of some repackers using the manufacturer's NDC number; (2) The magnitude of the problems that may be attributed to the use of manufacturer's NDC numbers by repackers and of the problems that NACDS and HDMA have articulated that may result from mandating the use of repacker's NDC numbers by repackers; (3) the extent to which such problems do or are likely to occur; and (4) whether there are technological (that is, software) solutions or alternatives that could address the issues presented in the NACDS and HDMA letter, other issues identified in this preamble, or those raised in comments to this proposed rule.

By inviting comment, we are specifically giving NACDS and HDMA, and any other interested parties, the opportunity to comment on whether repackers should be able to use the manufacturers' NDC numbers on the repacked drugs' label.

Proposed § 201.2(c) states that only the appropriate NDC number required by proposed § 201.2(b) may appear on the label. This provision would complement proposed § 201.2(b) by requiring the drug's label to bear the appropriate NDC number.

Proposed § 201.2(d) would require the human-readable NDC number to be immediately preceded by the letters ''NDC.'' This provision would modify the current requirement at § 207.35(b)(3)(ii), which states that the NDC number must be preceded by the prefix ''NDC'' or ''N'' when used on a label or labeling. We decided to limit the prefix to ''NDC'' because, when compared to ''N'' alone, ''NDC'' is a clearer signal that the number following ''NDC'' is the NDC number.

Proposed § 201.2(e) would require that the appropriate NDC number appear clearly on the drug's label as defined by section 201(k) of the act. Section 201(k) of the act defines ''label'' as ''a display of written, printed, or graphic matter upon the immediate container of any article.'' Section 201(k) also states that ''a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.'' This proposed requirement would be a change from current § 207.35(b)(3)(i), which requires the NDC number to appear

''prominently in the top third of the principal display panel.'' We decided to remove the restriction on the NDC number's location because our bar code rule, which requires the bar code to encode the drug's NDC number, allows the bar code to appear anywhere on the drug's label. Consequently, some establishments may wish to place the human-readable NDC number next to the bar code, so we have decided against specifying the location of the human-readable NDC number.

We are also proposing to revise current § 201.25 because, as discussed in section IV.A.5 of this document (definition of ''drug(s)'') and in the February 26, 2004, bar code final rule, certain drugs that would be subject to proposed part 207 are not subject to current § 201.25. Under proposed § 201.25(e), a drug product that is subject to the drug listing requirements of proposed part 207 but is not subject to current § 201.25 may display a bar code on the label only if the bar code meets the requirements of § 201.25(c). We are proposing this revision to help ensure consistency in the appearance, content, and placement of bar codes on drug labels. We are also proposing to revise current § 201.25 to further clarify what ''appropriate'' NDC number must appear in the bar code. Current § 201.25(c)(1) states that each drug product subject to current § 201.25 must have a bar code that contains, at a minimum, the appropriate NDC number. To clarify this requirement, we are proposing to amend current § 201.25(c)(1) to state that the ''appropriate NDC number,'' as used in current § 201.25(c)(1), is described in proposed § 201.2(b).

We note that when there is a change in the NDC number on a drug product 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.

b. *Proposed § 207.33—What is the National Drug Code Number, who must obtain it, and what information must be submitted?* Proposed § 207.33 would describe the NDC number and the process for obtaining NDC numbers. The proposal would differ from the pre-existing NDC number system by having us assign the NDC number for newly listed drugs, by describing the changes that would require a manufacturer, repacker, or relabeler to obtain a new NDC number, and by describing when information must be submitted to us to obtain an NDC number. Under the proposal, all three sections of the NDC number would be assigned prospectively by us to drugs that have not previously been assigned NDC numbers by a manufacturer, repacker, or relabeler. The NDC numbers currently assigned to drugs prior to the effective date of the rule would remain unchanged, provided those NDC numbers comply with the new regulations as finalized. FDA intends to validate that current NDC numbers comply with the new regulations as finalized.

Currently, § 207.35(a) states that we will provide a validated copy of an establishment's registration form and assign a permanent registration number to each drug establishment in accordance with our regulations. Current § 207.35(b)(1) and (b)(2) state that we will assign a drug listing number to each drug or class of drugs and that the number of characters in that number may differ depending on whether the drug is already listed in the NDC system or the NHRIC system. For example, current § 207.35(b)(1) states that if a drug is already listed in the NDC system or NHRIC system, the drug listing number is the same as that assigned under those codes and that we will add a lead zero to the first three characters to create a four-character labeler code. Current

§ 207.35(b)(1) also states that manufacturers or distributors may retain alphanumeric characters that they already use in the product and package code segments and must inform us if they convert those code segments into numeric digits. Current § 207.35(b)(2) also explains how many characters may be in a labeler code, product code, and package code.

Given that this proposal would designate the responsibility of assigning the NDC number to FDA, the proposal would eliminate many of the provisions in current § 207.35, such as our need to provide to sponsors validated copies of registration forms as well as information on how to assign the product code and package code. Proposed § 207.33(a) explains that the NDC number is a unique 10-digit number composed of a labeler code, product code, and package code. Proposed § 207.33(a) also states that we would assign the complete NDC number (that would include the existing labeler code, if any) to each drug that is subject to the listing requirements in part 207. We would use the same configuration when assigning each segment of the NDC number: The labeler code would be either five or four digits, the product code would be either four or three digits, and the package code would be either two digits or one digit. When we assign a NDC number to a drug, we intend to leave a space between the segments of the NDC number so that the separate codes are distinguishable. Manufacturers, repackers, and relabelers may add symbols, such as hyphens or asterisks, between the segments of the human-readable NDC number if they want to visually distinguish the codes in such a manner. Under the proposal, manufacturers, repackers, and relabelers would keep the same labeler code that they use for currently marketed drugs. However, if more than one labeler code is currently used by a manufacturer, repacker, or relabeler, only one labeler code would be used for any new NDC numbers that we would assign under

this rule prospectively. Also, as described below, the proposal would allow currently marketed drugs to keep the same NDC numbers in most cases.

Proposed § 207.33(b)(1) and (b)(2) would require that manufacturers, repackers, relabelers, and, in certain circumstances, drug product salvagers, obtain NDC numbers from us for each drug that is subject to the drug listing requirements. In the case of drug product salvagers, they would obtain an NDC number for each drug that is subject to the drug listing requirements only if they repack or relabel the salvaged drug. For private label distributors, proposed § 207.33(b)(3) states that the manufacturer, repacker, or relabeler who manufactures, repacks, or relabels the drug for the private label distributor is responsible for obtaining the NDC number from us for each drug that is subject to the drug listing requirements.

Proposed § 207.33(b) is intended to clarify who must obtain NDC numbers. For example, drug product salvagers ordinarily would not need to obtain NDC numbers because they merely salvage drugs. If a drug product salvager simply recovers the drug and sells it without repacking or relabeling the product, the drug product salvager would not need to obtain an NDC number for the salvaged drug. However, if the drug product salvager repacks or relabels the salvaged drug, then the drug product salvager is similar to a repacker or relabeler, and proposed § 207.33(b) would require the drug product salvager to obtain an NDC number from us for the repacked or relabeled drug. As another example, under the proposal, private label distributors would not be permitted to register or list and, consequently, they would not obtain NDC numbers for the drugs they distribute. Instead, the manufacturer, repacker, or relabeler who manufactures, repacks, or relabels the drug for the private label distributor would be responsible for obtaining the NDC number, including a

labeler code appropriate for the private label distributor. This change ensures that more accurate information is provided to FDA about the drug distributed by the private label distributor because the manufacturer supplies the necessary drug information to FDA.

Under current § 207.35, manufacturers, repackers, and relabelers assign NDC numbers to the drugs they manufacture, repack, or relabel, and private label distributors assign NDC numbers to the drugs they distribute if they opt to list the drugs themselves. Drug product salvagers currently do not receive NDC numbers for the drugs they salvage, and under current § 207.20(a), they are not required to list the drugs they salvage.

As noted previously, even though we would assign NDC numbers under the proposal, an establishment's labeler code would remain the same in most cases. For example, if a manufacturer's labeler code were 12345, we would assign NDC numbers for the manufacturer's drugs and still use 12345 as the manufacturer's labeler code. However, under the proposal, if a manufacturer, repacker, or relabeler uses more than one labeler code, we would prospectively assign NDC numbers that use only one labeler code for that manufacturer, repacker, or relabeler.

Note, too, that other components in an NDC number may remain unchanged under the proposal. For example, assume that a drug is already listed in the National Drug Code Directory and its manufacturer later decides to change its package size. In this situation, the labeler code and the product code would ordinarily remain the same, and, generally, we would assign a new package code for the changed drug.

Furthermore, if a drug already has an NDC number at the time of the effective date of a final rule, the drug would retain that NDC number provided

that the manufacturer, repacker, or relabeler, within 9 months after the effective date of a final rule, reviews and updates, in accordance with proposed §§ 201.2, 207.33, 207.37, 610.60, and 610.61, the information in our database for the NDC number (see sections IV.C.4, IX, and X of this document for information on the proposed implementation and effective and compliance dates of this rulemaking). We also will work with manufacturers, repackers, and relabelers to address any problems with existing NDC numbers (such as duplicate or potentially duplicate NDC numbers) that might arise after a final rule becomes effective.

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.

The proposal would also omit the references to Form FDA–2656 in current § 207.35(a) and (b)(2) because the proposal's electronic submission of

registration and listing information would make it unnecessary for us to provide validated copies of forms. In addition, because we would assign NDC numbers, the proposal would eliminate the provision in current § 207.35(b)(1) that allows manufacturers and distributors to convert alphanumeric product codes and package codes they may have and report such changes to us. (If any establishment still has alphanumeric product or package codes for a drug, we will work with them to assign new NDC numbers.) The proposal would also omit references in current § 207.35(b)(1) and (b)(2) to the NHRIC system because we do not maintain a NHRIC database (see 42 FR 52808 at 52810).

Proposed § 207.33(c) and (d) describes the information that a manufacturer, repacker, or relabeler would be required to submit before we assign an NDC number to a drug. As discussed earlier in this section, if a drug product salvager simply recovers the drug and sells it without repacking or relabeling the drug, the drug product salvager would not need to obtain an NDC number for the salvaged drug. However, if the drug product salvager repacks or relabels the salvaged drug, then the drug product salvager is similar to a repacker or relabeler, and proposed § 207.33(b) would require the drug product salvager to obtain an NDC number from us for the repacked or relabeled drug. The following table illustrates the proposed requirements.

TABLE 1.—INFORMATION TO BE SUBMITTED TO OBTAIN AN NDC NUMBER, ARRANGED BY MANUFACTURER, REPACKER, OR RELABELER AND DRUG

Proposed Section	Type of Drug	Information to be Submitted
§ 207.33(c)(1) (Manufacturer)	Active pharmaceutical ingredient	• Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code • Drug's established name and proprietary name (if any) • Package size and type • Drug Master File number or Veterinary Master File number, if any, assigned to the active pharmaceutical ingredient
§ 207.33(c)(2) (Manufacturer)	Drug other than an active pharmaceutical ingredient	• Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code • Drug's established name and proprietary name (if any) • Name and quantity of each active pharmaceutical ingredient or the approved U.S. application number • Name of each inactive ingredient (or approved U.S. application number) for certain drugs, and whether you consider the name of the inactive ingredient to fall under § 20.61 (21 CFR 20.61) of this chapter or to be otherwise prohibited from disclosure and, if so, why • Dosage form • Package size and type, including immediate unit-of-use container • Marketing status (e.g., prescription or OTC) • Drug or drug product type (human drug or animal drug) • Imprinting information

TABLE 1.—INFORMATION TO BE SUBMITTED TO OBTAIN AN NDC NUMBER, ARRANGED BY MANUFACTURER, REPACKER, OR RELABELER AND DRUG—Continued

Proposed Section	Type of Drug	Information to be Submitted
§ 207.33(c)(3) (Manufacturer)	Active pharmaceutical ingredient for a private label distributor	• Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code • Drug's established name and proprietary name (if any) • Package size and type • Drug Master File number or Veterinary Master File number, if any, assigned to the active pharmaceutical ingredient • Private label distributor's name, address, telephone number, fax number, e-mail address, labeler code • Drug's proprietary name (if any) as assigned by the private label distributor
§ 207.33(c)(3) (Manufacturer)	Drug other than an active pharmaceutical ingredient for a private label distributor	• Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code • Drug's established name and proprietary name (if any) • Name and quantity of each active pharmaceutical ingredient or the approved U.S. application number • Name of each inactive ingredient (or approved U.S. application number) for certain drugs, and whether you consider the name of the inactive ingredient to fall under § 20.61 of this chapter or to be otherwise prohibited from disclosure and, if so, why • Dosage form • Package size and type, including immediate unit-of-use container • Marketing status (e.g., prescription or OTC) • Drug or drug product type (human drug or animal drug) • Imprinting information • Private label distributor's name, address, telephone number, fax number, e-mail address, and labeler code • Drug's proprietary name (if any) as assigned by the private label distributor
§ 207.33(d)(1) (Repacker or relabeler)	Drug that is repacked or relabeled	• Repacker's or relabeler's name, address, telephone number, fax number, e-mail address, and labeler code • NDC number assigned to the drug immediately before its receipt by the repacker or relabeler • Type of operation performed for the drug (repacking or relabeling) • Drug's established name and proprietary name (if any) • Package size and type, including immediate unit-of-use container, if any (required for repackers only)
§ 207.33(d)(2) (Repacker or relabeler)	Drug that is repacked or relabeled for a private label distributor	• Repacker's or relabeler's name, address, telephone number, fax number, e-mail address, and labeler code • NDC number assigned to the drug immediately before its receipt by the repacker or relabeler • Type of operation performed for the drug (repacking or relabeling) • Drug's established name and proprietary name (if any) • Package size and type, including immediate unit-of-use container, if any (required for repackers only) • Private label distributor's name, address, telephone number, fax number, e-mail address, and labeler code • Drug's proprietary name (if any) assigned by the private label distributor

Proposed § 207.33(c) and (d) are intended to accomplish several goals:

1. The proposal would reduce redundant data submission and improve the accuracy of information that we receive. For example, under the current system, a manufacturer and a repacker may submit the same drug listing information for the same type of drug. However, the repacker might not have adequate information from the manufacturer or might describe the drug differently than the manufacturer; this would lead to data discrepancies and omissions. So, by requiring only manufacturers to provide descriptive information about the drugs they make, we would eliminate potential duplicate submissions, data discrepancies, and data omissions. Instead, the repacker, under the proposal, would simply tell us the NDC number of the drug that

the repacker receives, and we could use the NDC number to link the drug back to its manufacturer.

2. By having manufacturers, repackers, relabelers, and drug product salvagers submit information on behalf of private label distributors, the proposal would eliminate the potential for redundant, incomplete, or inconsistent submissions by private label distributors. For example, under the current system, some manufacturers have submitted information for drugs that they manufactured for private label distributors, and the private label distributors also submitted information for the same drugs; if the manufacturers and private label distributors described the drugs differently to us, we then had different information for the same drugs.

3. By linking a repacker's or relabeler's drug to an NDC number, the proposal would eliminate a problem that some repackers and relabelers have encountered in the past. Under the current listing system, repackers and relabelers have sometimes found it difficult to obtain necessary information from manufacturers. This difficulty has resulted in data errors and omissions and an incomplete or inaccurate National Drug Code Directory.

4. By separating the NDC number process from drug listing and creating an electronic drug registration and listing system, the proposal should make it easier for manufacturers, repackers, and relabelers (and drug product salvagers who obtain NDC numbers for private label distributors) to obtain their NDC numbers quickly and, as a result, prepare product labels and marketing plans earlier.

5. Under the proposal, the information submitted about the drug to obtain an NDC number would be retained in the electronic drug registration and listing system. Thus, when the manufacturer, repacker, or relabeler later lists

the drug, they would need to provide only the additional information required for listing.

6. By assigning a unique NDC number to each drug, the proposal would ensure that the drug has an accurate identifier, allowing us to support the implementation of the electronic prescribing provisions of the Medicare Modernization Act. We would link the accurate NDC number to the product labeling that would be made available through the DailyMed initiative.

i. *Information to be submitted to receive an NDC number*. We describe the information that proposed § 207.33(c) and (d) would require and our reasons for proposing to require the information, as follows:

- Name, address, telephone and fax numbers, e-mail address, and labeler code. Proposed § 207.33(c) and (d) would require manufacturers, repackers, and relabelers to provide this information to enable us to identify and contact (if necessary) the appropriate manufacturer, repacker, or relabeler and identify their labeler code. In situations where a manufacturer, repacker, or relabeler manufactures, repacks, or relabels a drug for a private label distributor, the proposal would also require the manufacturer, repacker, or relabeler to provide comparable information for the private label distributor. This information would enable us to associate the manufacturer's, repacker's, or relabeler's drugs with a particular private label distributor and to contact that private label distributor if necessary.

- The drug's or active pharmaceutical ingredient's established name and proprietary name (if any). The established name (sometimes referred to as generic name) is ordinarily either the drug's compendial name or, if there is no compendial name, the drug's common or usual name. The proprietary name (sometimes referred to as trade name) is generally the drug's marketed or

advertised name as designated by the manufacturer, repacker, relabeler, or private label distributor. Most consumers recognize a drug by its proprietary name rather than its established name. Proposed § 207.33(c) and (d) would require submission of these names because knowing a drug's established name would let us determine, for example, which companies market identical drugs and which drugs can be substituted in the event of drug shortages or recalls. Knowing a drug's proprietary name would enable us to identify a drug to the public during a recall or consumer alert. This information is currently required under § 207.25(b)(1) and is submitted on Form FDA 2657.

- The Drug Master File (DMF) number or Veterinary Master File (VMF) number, if any, assigned to the active pharmaceutical ingredient. Under proposed § 207.33(c)(1)(iv) (and, if applicable, proposed § 207.33(c)(3)), if a DMF number or VMF number is assigned to the active pharmaceutical ingredient, the manufacturer would identify for us the DMF number or the VMF number. The DMF or VMF may contain additional information about the active pharmaceutical ingredient that our electronic drug registration and listing system could associate with the active pharmaceutical ingredient at other points in the registration and listing process. This could reduce the burden on the manufacturer of submitting to us the information already contained in the DMF or VMF. This information is not currently provided to us under current part 207 or Form FDA 2657 or Form FDA 2658.

- Name and quantity of each active pharmaceutical ingredient in a drug. Proposed § 207.33(c)(2) and, if applicable, proposed § 207.33(c)(3), would require manufacturers to submit this information to us (unless the approved U.S. application number is provided). Knowing the name and quantity of a drug's active pharmaceutical ingredients would help us assign unique product

codes and help ensure that the assigned NDC numbers are unique to different products. For example, assume that a manufacturer makes a drug in two different strengths, 100 milligrams (mg) and 500 mg. If we only required the manufacturer to identify the active pharmaceutical ingredient, we might assume, incorrectly, that the manufacturer made two versions of the same drug in the same strength and then assign the same product code to both drugs. Instead, by proposing to require information about the quantity of the drug's active pharmaceutical ingredient, we would be able to assign one product code to the 100 mg product and a different product code to the 500 mg product. As an alternative to providing the name and quantity of the drug's active pharmaceutical ingredient, proposed § 207.33(c)(2) would allow a manufacturer to give us the drug's approved U.S. application number; the approved U.S. application number would allow us to link the drug to a particular application and determine the name and quantity of the active pharmaceutical ingredients in that drug.

The proposed requirement is similar to the requirement regarding quantitative listing of active ingredients in current § 207.25(b). Current § 207.25(b)(6) requires a quantitative listing of a drug's active ingredient(s) for drugs that a registrant regards as not being subject to sections 505 or 512 of the act or section 351 of the PHS Act. Current 207.25(b)(2) requires, for each drug listed that the registrant regards as subject to section 505 or 512 of the act, the application number. The act, for purposes of certain drug listing requirements, appears to treat drugs differently depending on whether those drugs are subject to sections 505 or 512 of the act or not. Section 510(j)(1)(A) of the act mandates that the drug list be prepared in the form and manner prescribed by us. That drug list, for drugs subject to sections 505 or 512 of

the act, must be accompanied by ''the authority for the marketing of such drug''. In contrast, section 510(j)(1)(C) of the act states that the drug list, for drugs that are not subject to either section 505 or 512 of the act, must be accompanied by a ''quantitative listing'' of the drug's active ingredient or ingredients and that we may require a quantitative listing of all ingredients with respect to a particular product if we find such submission is necessary to carry out the act's purposes.

We believe that these provisions, and others, give us sufficient authority to require the submission of active ingredient information for all drugs as part of the NDC number assignment process. We already have such information for drugs approved under sections 505 and 512 of the act because information concerning active ingredients is an essential part of the drug's marketing application. Thus, when a manufacturer gives us the approved U.S. application number (as proposed § 207.33(c)(2)(i) would require and as current § 207.25(b)(2) (pertaining to required drug listing information) requires), the manufacturer is, in essence, giving us a link to information about the drug's active ingredients. As noted previously, section 510(j)(1)(A) of the act, for drugs subject to sections 505 or 512 of the act, requires the ''reference to the authority for the marketing of such drug.'' This reference would be the approved U.S. application number. The act, for drugs not subject to section 505 or 512, explicitly requires a quantitative listing of active ingredients. Proposed § 207.33(c)(2)(i) would, therefore, enable us to input the active ingredient information into an electronic database. This would enable us to link to certain information in the application, and would be more efficient than having to review individual marketing applications, identify each drug's active ingredients, and then enter that data into the database ourselves.

- Name of the inactive ingredient(s). Proposed § 207.33(c)(2), and, if applicable, (c)(3) would require manufacturers to give us the drug's approved U.S. application number or, in the alternative, 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 PHS Act, and for each human OTC drug that the manufacturer regards as not subject to section 505 of the act, and whether the name of an inactive ingredient falls under § 20.61 or is otherwise prohibited from disclosure and, if so, why. Proposed § 207.33(c)(3) describes the requirements of the manufacturer who is manufacturing a drug for a private label distributor. Such manufacturers would be required to give us the name of each inactive ingredient for certain drugs, as described previously, or the drug's U.S. approved application number for the drug it manufactures for a private label distributor. Proposed § 207.33(c)(2) and (c)(3) are authorized under section 510 of the act as well as other provisions. We are considering whether to require the name of each inactive ingredient to be submitted for other categories of drugs as well.

- Dosage form. Proposed § 207.33(c)(2) and (c)(3) would require manufacturers to identify a drug's dosage form. This information will also help us distinguish between drug products that contain the same active ingredient and, consequently, assign unique product codes to such drugs. For example, assume that a manufacturer makes drug X, in a 100 mg strength, in a tablet form and also in a gelatin capsule. If we did not know there were two dosage forms of drug X, we might mistakenly assign the same product code to the tablet and gelatin capsule. Thus, information about dosage forms will help us create an NDC system that ties unique NDC numbers to unique products. The drug's dosage form is currently submitted on Form FDA 2657.

- Package size and type. Proposed § 207.33(c)(1), (c)(2), (c)(3) (if applicable), (d)(1), and (d)(2) would require manufacturers and repackers respectively to provide information about package size and type. This information would obviously be relevant in helping us assign package codes to a particular drug. For example, a drug packaged in a glass container would have a different NDC number from the same drug packaged in a plastic container. The proposal would require that information about the drug's package size and type be provided for each package, including the immediate unit-of-use container. For example, a drug packaged in a box containing a card of 12 unit-of-use blisters would have a different NDC number than each individual blister (unit-of-use). In the latter example, the different NDC numbers would have a practical impact with respect to our bar code requirements. A database system computer reading the bar code for the individual unit-of-use blister would see that the health care professional is administering a single dose of a particular drug to a patient; if the NDC number for the box were the same as that used for each unit-of-use blister, then the computer might mistakenly believe that the health care professional was administering 12 doses to the patient. In these scenarios, distinct NDC numbers for each package level would enhance the bar code's accuracy and value. The drug's package size and type is currently submitted on Form FDA 2657.

- Marketing status. Proposed § 207.33(c)(2) and, if applicable, (c)(3), would require manufacturers to tell us whether the drug is available only by prescription or is available OTC. Having such information in our electronic database would enable us to determine quickly which drugs are available by prescription and which are OTC. In addition, some entities that rely on NDC numbers, such as CMS and health care insurance companies, might treat

prescription drugs differently from OTC drugs. For example, an insurer might reimburse consumers for prescription drug expenses, but not for OTC drug expenses. The drug's marketing status—whether prescription or OTC—is currently submitted on Form FDA 2657.

- Drug or drug product type. Under proposed § 207.33(c)(2) and, if applicable, (c)(3), manufacturers would identify whether a drug is a human drug or animal drug. This information would enable us to refine our databases to distinguish quickly between human and animal drugs. Having such information readily available could help us determine the regulatory obligations for a particular drug. For example, the bar code requirement applies to human drugs only. Thus, if we could differentiate quickly between human and animal drugs based on NDC numbers alone and we received a report that a particular drug failed to have a bar code on its label, we would be able to determine, based on the NDC number alone, whether that drug was subject to the bar code requirement. This information is currently submitted under ''product type'' on Form FDA 2657.

- Imprinting information. 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) (proposed § 207.33(c)(2)(vii) and, if applicable, proposed § 207.33(c)(3)). This provision is similar to current § 207.25(c), except the current provision also requires that the name of the drug product, its active ingredient(s), dosage strength, NDC number, and the name of its manufacturer or distributor be submitted. Under the proposal, the name of the drug product, its active ingredient(s) (proposed § 207.33(c)(2) uses the term ''active pharmaceutical ingredient''), and dosage strength (proposed § 207.33(c)(2) uses

the term ''dosage form'') would be submitted to us under proposed § 207.33(c) along with the imprinting information. The NDC number would be submitted under proposed § 207.49 for listing, the name of the private label distributor would be submitted under proposed §§ 207.33 and 207.49 for listing, and the name of the manufacturer would be submitted under proposed § 207.25 for registration. All of this information would be accessible via our electronic drug registration and listing system. The proposal would also delete the requirement in current § 207.25(c) that ''any other characteristic that identifies the drug product as unique'' must be submitted. We need to know the drug's size, shape, color, and code imprint, as well as the other information required under proposed § 207.33(c), to assign an NDC number to the manufacturer's drug. Imprinting information would enable us to investigate reports of medication errors and counterfeiting and to assist poison control centers in identifying drugs in overdose and accidental poisoning situations.

- NDC number assigned to the drug immediately before the repacker or relabeler received that drug. Proposed § 207.33(d) would require repackers and relabelers to give us the NDC number of the drug that they receive. This information would enable us to link that drug to a particular source and, as we said earlier in this part, eliminate the need for repackers and relabelers to obtain certain drug information from those sources to obtain an NDC number. For example, assume that relabeler Alpha received drug X from manufacturer Beta. If Alpha gives us the NDC number for drug X, we will then be able to link Alpha's relabeled drug to Beta. We would also eliminate any need for Alpha to ask Beta for information about drug X for purposes of getting an NDC number and eliminate the possibility that Alpha might report incorrect

or contradictory information about drug X compared to the information given to us by Beta.

- Type of operation. Proposed § 207.33(d) would require repackers and relabelers to report the type of operation (that is, repacking or relabeling) performed for a drug. This information is comparable to the information we currently receive about an establishment's ''type of business'' on Form FDA 2657, except that proposed § 207.33(d) is limited to repackers and relabelers.

- Information regarding private label distributors. Proposed § 207.33(c)(3) and 207.33(d)(2) would require manufacturers, repackers, and relabelers who manufacture, repack, or relabel drugs for a private label distributor to tell us the private label distributor's name, address, telephone number, fax number, e-mail address, labeler code, and any proprietary name assigned by the private label distributor to the drug. This information will help us link the manufacturer's, repacker's, or relabeler's drug to a particular private label distributor and, as we stated earlier in this part, eliminate potential data duplication, omissions, and inaccuracies that would otherwise result if private label distributors were able to seek NDC numbers from us. Manufacturers, repackers, and relabelers should be able to obtain the necessary information from private label distributors. Listing information for private label distributors is currently submitted on Form FDA 2658.

ii. *How the information would be submitted*. Proposed § 207.33(e) would require manufacturers, repackers, and relabelers to submit information to us electronically, in accordance with proposed § 207.61 unless we grant a waiver under proposed § 207.65. We discuss proposed §§ 207.61 and 207.65 later in this document.

iii. *Types of changes that would require a new NDC number*. Proposed § 207.33(f) would describe the types of changes in information that would require a new NDC number. In brief, proposed § 207.33(f)(1) would require a new NDC number for any change of information that would be required under proposed § 207.33(c) and (d), except for the following contact information: Name; address; telephone and fax numbers; and e-mail address for the manufacturer, repacker, relabeler, or private label distributor. In addition, § 207.33(f)(2) requires manufacturers to 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. Although we are not proposing to require, at this time, that manufacturers submit the name of each inactive ingredient to us when they obtain an NDC number for these drugs, we are proposing to require that manufacturers notify us only of the fact that there has been a change in an inactive ingredient for these drugs. This would ensure that a unique NDC number is assigned to these drugs when the drug's inactive ingredient(s) has changed. It is important that marketed drugs have unique NDC numbers that are accurate because, as discussed in section IV.C.2 of this document, NDC numbers are an important, standardized, identification system for drug products and are used for many purposes. In addition, identifying marketed drugs in our electronic database for which inactive ingredients have changed would help us investigate, as discussed in section IV.C.3 of this document, incidents of allergic reactions in patients as well as possible drug contamination, counterfeiting, or adulteration. Although we are not proposing it at this time, we are considering requiring in the future that manufacturers submit the name of each inactive

ingredient to obtain an NDC number for categories of drugs beyond those referenced in proposed § 207.33(c)(2)(ii) and 207.33(c)(3). We are specifically requesting comments on the feasibility of submitting these inactive ingredients. The proposed rule would be similar to current § 207.35(b)(4)(i), which requires a registrant to assign a new NDC number if any change occurs in a product's characteristics that clearly distinguishes one drug product version from another. However, proposed § 207.33(f) would differ from the current requirement in several important respects. First, proposed § 207.33(f) would require changes to be reported to us in accordance with proposed § 207.33(e) (which would require electronic submission of information) and § 207.33(g) (which describes timing requirements discussed later in this part). The current regulation has no comparable electronic reporting requirement. Second, proposed § 207.33(f) would not require us to publish a notice in the **Federal Register** announcing our determination as to whether a change requires assignment of a new product code. Because the proposed rule would create an electronic drug registration and listing system and have us assign NDC numbers quickly that would be accessible in the registration and listing database, we find it unnecessary and impractical to publish **Federal Register** notices regarding product code changes. Third, although current § 207.35(b)(4)(i) allows registrants to assign their own package codes for changes involving trade packages, proposed § 207.33(f) would eliminate this provision because we would assign the new NDC number ourselves to ensure that the NDC number is unique and that our NDC number database is accurate and up-to-date. Fourth, proposed § 207.33(f), in conjunction with proposed § 207.33(c) and (d), gives a more complete description of which changes would require a new NDC number, compared with current § 207.25(b)(4)(i) (which

currently lists examples of changes). Because manufacturers, repackers, and relabelers currently have different practices with respect to assigning NDC numbers, this change would eliminate inconsistency and would introduce an element of certainty with respect to the assignment of new NDC numbers.

iv. *When the information would be provided*. Proposed § 207.33(g) would explain when a manufacturer, repacker, or relabeler must provide the information to obtain an NDC number. In brief, the proposal would require a manufacturer, repacker, or relabeler to provide the information described in proposed § 207.33(c), (d), and (f) either before or at the time drug listing information is required under proposed §§ 207.45 or 207.57. (We discuss proposed §§ 207.45 and 207.57 later in this document.) The proposed requirement differs slightly from current §§ 207.21(b), 207.22(b), and 207.25(b)(8), which allows manufacturers, repackers, and relabelers to give us NDC numbers as part of their drug listing information, because the proposal would allow companies to give us information earlier than the drug listing process would be completed. This ability to seek NDC numbers throughout the year should help us keep the National Drug Code Directory current and, as a result, provide more accurate and useful NDC number information to entities that rely on or use NDC numbers. In addition, the proposed scheme would give manufacturers, repackers, and relabelers more flexibility to obtain an NDC number earlier for their own planning purposes. Furthermore, we will know which NDC number corresponds to a drug immediately because we will assign it, rather than the current system where manufacturers, repackers, and relabelers assign their own NDC numbers and only report those numbers to us as part of their drug listing information.

We considered assigning the NDC number as part of the drug listing process, but believe that allowing for earlier assignment would provide optimal flexibility for manufacturers, repackers, and relabelers. We note that the information submitted to have an NDC number assigned is a subset of the information submitted to list a drug. Therefore, if a manufacturer, repacker, or relabeler provides us the information early to get an NDC number, they will only need to provide the additional information needed when they later list the drug.

c. *Proposed § 207.37—What restrictions pertain to the use of NDC numbers?* Proposed § 207.37 would establish four restrictions on the use of NDC numbers insofar as FDA-regulated products or activities are concerned. The proposed restrictions reflect practical problems or difficulties that we have encountered when manufacturers, repackers, or relabelers assign their own NDC numbers.

Proposed § 207.37(a) would state that an NDC number must not be used to represent a different drug than the drug to which it was assigned. This restriction would prevent manufacturers, for example, from using the same NDC number for different drugs and thus prevent potential discrepancies among databases that rely on or use NDC numbers to distinguish between drugs. The restriction would prevent two different drugs from having the same NDC number and avoid medication errors that could result if the NDC number encoded in a bar code represented more than one drug. Use of an NDC number not assigned to a drug would also cause a drug to be misbranded under section 502(a) of the act because the drug's label would be misleading.

Proposed § 207.37(b) would state that a different NDC number must not be used 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 earlier before marketing was discontinued. This would prevent two NDC numbers from being assigned to or used for the same drug. Consistent with this rationale, proposed § 207.37(b) would revoke current § 207.35(b)(4)(ii), which states that the product code of a discontinued product may be reassigned to another product 5 years after the expiration date of the discontinued product or, if there is no expiration date, 5 years after the last shipment of the discontinued product into commercial distribution.

Proposed § 207.37(c) would state that NDC numbers must not be used to denote FDA approval. This is similar to current § 207.39, which states, in part, that assignment of an NDC number does not in any way denote approval of a product. For drugs subject to sections 505 or 512 of the act, those drugs must be shown to be safe and effective for their intended uses to obtain FDA approval. Mere assignment of an NDC number by us is not equivalent to our determining whether a drug is safe and effective for its intended uses.

Proposed § 207.37(d) would state that NDC numbers must not be used on products that are not subject to the drug listing requirements of part 207, such as dietary supplements and medical devices. We are proposing this requirement because the fundamental purpose behind NDC numbers was to establish an identification system to help in the automated processing of drug data and claims. Use of NDC numbers on non-drug products could introduce misleading information in databases, lead to inappropriate claims processing, and undermine the accuracy and reliability of an NDC system. For example, some human dietary supplements bear an NDC number on their labels. FDA

considers a human dietary supplement that bears an NDC number misbranded under 21 U.S.C. 343(a)(1), which provides that a food is misbranded if its labeling is false or misleading in any particular. A product labeled and marketed as a human dietary supplement is not a drug listed with FDA; thus, the presence of an NDC number on the label is a false representation about the nature of the product.

d. *Proposed §§ 610.60(a)(2) and 610.61(b)—Where would the NDC number be required for biological products?* Under proposed § 201.2(a), all drugs, including human biological drugs, subject to the drug listing requirements of part 207 must have labels that bear the appropriate NDC number in human-readable form, in accordance with the provisions in proposed § 201.2. Current § 610.60(a) (21 CFR 610.60(a)) specifies which items must appear on the label affixed to each container of a biological product capable of bearing a full label and current § 610.61 specifies which items must appear on the label affixed to each package containing a biological product. We are proposing to amend §§ 610.60(a)(2) and 610.61(b) (21 CFR 610.60(b)) to require that the NDC number appear, in accordance with proposed part 207, on these biological product labels. Many individuals and companies use NDC numbers and they may not have the technology or ability to read an automatic identification technology such as a bar code that is required under current § 207.25 or § 610.67. In addition, a human-readable NDC number may serve as a ''backup'' in case the bar code is damaged, cannot be read, or is otherwise illegible.

4. How Do We Intend to Implement the NDC Number Changes?

a. *When would we expect compliance with the NDC number requirements?* We are proposing that our electronic drug registration and listing system be used to enter and update all NDC number information, as well as all

registration and listing information, no later than 9 months after the effective date of a final rule. If a drug already has an NDC number at the time of the effective date of a final rule, the drug would retain that NDC number provided that the manufacturer, repacker, or relabeler, within 9 months after the effective date of a final rule, reviews and updates, in accordance with proposed §§ 201.2, 207.33, 207.37, 610.60, and 610.61, the information in our database for the NDC number. To retain the NDC number, new information about the drug's characteristics may need to be provided to us. We will, if necessary, assign a new product code and/or package code, creating a new NDC number for the drug. If a manufacturer, repacker, or relabeler does not review or update its information within 9 months after a final rule's effective date, we may assign a new NDC number to the drug or take other appropriate steps.

As discussed in section IV.E.6 of this document, we intend to make available guidance on how to provide to us in electronic format information required to receive an NDC number, as well as registration and listing information. We can assist manufacturers, repackers, and relabelers in determining whether their NDC numbers are accurate and address any problems with existing NDC numbers (such as duplicate or potentially duplicate NDC numbers). We are available to work with manufacturers, repackers, and relabelers to resolve issues that might arise after a final rule becomes effective. Information on how to contact us for assistance will be specified in the guidance.

b. *When would we expect NDC numbers to appear on drug labels?* Although current regulations do not require NDC numbers on drug labels (other than NDC numbers encoded in a bar code, where such bar codes are required under current § 201.25), almost all human and animal prescription

drugs already have NDC numbers on their labels because government agencies and third-party payers rely on NDC numbers for reimbursement and other purposes. Thus, when we issue a final rule requiring NDC numbers to appear on drug labels, such a requirement should have little impact on human and animal prescription drug labels.

We intend to phase-in the requirements for NDC number placement and appearance on human and animal prescription drug labels over a 3-year period, starting from the effective date of a final rule. This implementation scheme should lessen the impact on prescription drug labels (which might stem from changing the NDC number on the label or adding an NDC number, for example, for unit-of-use blisters).

As for human and animal OTC drugs, we estimate that approximately 30 percent of these drug labels currently have NDC numbers. (We discuss this issue further in section VI of this document.) We intend to phase-in the requirements for NDC number placement and appearance on OTC drug labels over a 7-year period, starting from the effective date of a final rule.

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. We invite comment on whether a shorter implementation period would be preferable.

These implementation periods would permit manufacturers, repackers, and relabelers to incorporate the appropriate NDC number at minimal additional cost when redesigning their labels in the course of the normal relabeling cycle. We should note, however, that manufacturers, repackers,

relabelers, and private label distributors who are subject to the bar code requirements at current § 201.25 might find it easier to put human-readable NDC numbers on their labels when they revise those labels to accommodate the bar code. We remind readers that the bar code requirement became effective on April 26, 2004, and the compliance dates varied depending on when we approved a drug relative to the April 26, 2004, date. For example, for drugs approved on or after April 26, 2004, we expected compliance within 60 days of the drug's approval date. For drugs approved before April 26, 2004, we expect compliance within 2 years. So, for example, a manufacturer whose prescription drug is subject to the bar code requirement might find it easier to redesign its label once to add a human-readable NDC number and a bar code, rather than redesign its label twice.

We invite comments on the implementation scheme described here.

D. Listing

1. Who Would Be Required To List Drugs?

Proposed § 207.41(a) would require manufacturers, repackers, relabelers, and drug product salvagers who are subject to the registration requirements under proposed § 207.17 (and not exempt under proposed § 207.13) to list drugs being manufactured, repacked, relabeled, or salvaged by them for commercial distribution. Proposed § 207.41(a) is consistent with current § 207.20(a), which states that owners or operators of all drug establishments, not exempt under section 510(g) of the act or current § 207.10, that engage in the manufacture, preparation, propagation, compounding, or processing of a drug submit a list of every drug in commercial distribution. Section 510(j)(1) of the act requires, among other things, that every person who registers with

the Secretary must list drugs that are being manufactured, prepared, propagated, compounded, or processed for commercial distribution.

Under current § 207.20(a), such drugs must be listed whether or not they enter interstate commerce. This is consistent with Congress's intention for section 510 of the act to apply to drugs both in interstate and intrastate commerce as stated in section 301 of Public Law 82–781, in part, as follows: ''[T]he products of all [establishments in which drugs are manufactured, prepared, propagated, compounded, or processed] are likely to enter the channels of interstate commerce and directly affect such commerce; and * * * the regulation of interstate commerce in drugs without provision for registration and inspection of establishments that may be engaged only in intrastate commerce in such drugs would discriminate against and depress interstate commerce in such drugs, and adversely burden, obstruct, and affect such interstate commerce.''

Proposed § 207.41(a) also provides that 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. This provision would also apply when operations are conducted at both domestic and foreign establishments and there exists joint ownership and control among all the establishments. This provision is consistent with current § 207.20(a).

Under proposed § 207.41(a), drug product salvagers would be required to list. As discussed in sections IV.A.5 and IV.B.1 of this document, and consistent with current § 207.20(a), drug product salvagers would continue to be required to register because their activities include applying manufacturing

controls to drug products and segregating drug products. This activity would be covered under the scope of manufacturing, preparing, propagating, compounding, or processing, and would trigger the requirement to register under the act. Because drug product salvagers are conducting one of these activities with respect to a given drug for the purpose of commercial distribution, this activity would also trigger the requirement to list under the act (section 510(j)(1) of the act). (Drug product salvagers sometimes repack/relabel drug products and would also have to register because of those activities.) Under current § 207.20(a), drug product salvagers are not required to list. Because drug product salvagers place the salvaged drug in commercial distribution, we are proposing to require that drug product salvagers submit listing information to us. We specifically invite comments on the scope of activities of drug product salvagers, that is, whether drug product salvagers salvage drug products for commercial distribution and whether these activities should trigger listing under the act.

Under proposed § 207.41(b), manufacturers, repackers, relabelers, and drug product salvagers who engage in more than one activity for drugs would list each drug in accordance with the requirements for the activity engaged in for that drug. An example of a company that engages in more than one activity for drugs would be a company that manufactures Drug X and relabels Drug Y. The company would provide the listing information described in proposed § 207.49 for Drug X and the listing information described in proposed § 207.53 for Drug Y. We are proposing this requirement to clarify which listing information would be provided by manufacturers, repackers, relabelers, and drug product salvagers who engage in more than one activity for drugs. As discussed below, manufacturers, repackers and relabelers, and drug product

salvagers would provide similar listing information to us (although some information would be provided by reference).

Under proposed § 207.41(c), manufacturers, repackers, relabelers, and drug product salvagers would, in addition to listing their own drugs, provide all listing information to us for drugs they manufacture, repack, relabel, or salvage for private label distributors. In general, private label distributors would not list drugs with us. However, private label distributors would be required to list a drug with us if they manufacture, repack, relabel, or salvage the drug for commercial distribution. Proposed § 207.41(c) would revise current § 207.20(b), which states that owners or operators of establishments, not otherwise required to register, that distribute under their own label or trade name a drug manufactured or processed (as defined in current § 207.3(a)(8)) by a registered establishment may elect to submit listing information directly to us and obtain a labeler code. Under current part 207, if a private label distributor does not elect to submit drug listing information to us, the registered establishment must submit the drug listing information. Currently, private label distributors that elect to submit listing information must include the registration number of the establishment that manufactured or processed (as defined in current § 207.3(a)(8)) each drug listed and must assume full responsibility for compliance with all the requirements of part 207. Private label distributors must currently certify to the registered establishment that the submission has been made by providing a signed copy of Form FDA 2656 to the registered establishment. Private label distributors must submit to us the original Form FDA 2656 showing this certification. A list showing the NDC number assigned to each drug must accompany the certification.

We are proposing to alter the arrangement permitted under current § 207.20(b). Although we recognize that this proposed shift in responsibility may alter current business practices, we believe that proposed § 207.41(c) will help to ensure that listing information is more accurate and complete. The current scheme has caused confusion and resulted in inaccurate and incomplete listing information. Some private label distributors that have elected to list their drugs have not had access to all the information needed to list the drugs accurately. Some private label distributors have claimed that manufacturers, repackers, and relabelers have been reluctant to provide certain information to them. In addition, in some instances, the parties have been uncertain about who is responsible for listing.

As discussed in section IV.B.1 of this document and previously, manufacturers, repackers, relabelers, and drug product salvagers would be required to register and list the drugs they manufacture, repack, relabel, or salvage. They would be required to do so even if they conduct such activities on behalf of private label distributors. This proposed requirement would be consistent with section 510(j)(1) of the act which requires every person who registers to submit listing information for drugs ''which are being manufactured, prepared, propagated, compounded, or processed by him for commercial distribution'' (emphasis added). In addition, private label distributors would not be required (nor permitted) to register because their activities are not covered under the scope of manufacturing, preparing, propagating, compounding, or processing. Nor do private label distributors conduct one of these activities with respect to a given drug for the purpose of commercial distribution and, thus, would not be required (nor permitted) to list. Private label distributors only commercially distribute drugs under their

own label or trade name. Manufacturers, repackers, relabelers, and drug product salvagers often manufacture, repack, relabel, or salvage drugs that are distributed by a private label distributor, and they have all the information about the drug that is necessary to list the drug distributed by the private label distributor. Under the proposal, to list a drug that is manufactured, repacked, relabeled, or salvaged for a private label distributor, manufacturers, repackers, relabelers, and drug product salvagers would have to obtain any existing NDC number from the private label distributor or would have to obtain the NDC number from FDA for a drug distributed by a private label distributor. Manufacturers, repackers, relabelers, and drug product salvagers would have to place the NDC number assigned to the private label distributor's drug on the label. We specifically invite comments on this proposed change in the listing responsibilities of manufacturers, repackers, relabelers, drug product salvagers, and private label distributors and its potential effect on business practices.

2. When Would Initial Listing Information Be Provided?

Under proposed § 207.45, manufacturers, repackers, relabelers, and drug product salvagers would 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 provision is consistent with section 510(j)(1) of the act, which requires, among other things, that every person who registers with the Secretary under sections 510(b), (c), (d), or (i) of the act must list drugs that are being manufactured, prepared, propagated, compounded, or processed for commercial distribution. Proposed § 207.45 pertains to the submission of listing information for drugs at the time of the initial registration of an establishment. Reviewing and updating information

for drugs already listed and providing listing information for drugs not previously listed are covered under proposed § 207.57. Proposed § 207.57 is discussed in section IV.D.8 of this document.

3. What Listing Information Would Be Required?

To list a drug, manufacturers would be required to provide the information in proposed § 207.49, repackers and relabelers would be required to provide the information in proposed § 207.53, and drug product salvagers who are not repackers or relabelers would be required to provide the information in proposed § 207.54. We are proposing different listing requirements for manufacturers, repackers and relabelers, and drug product salvagers because much of the information about a drug is submitted to us by the manufacturer to obtain an NDC number and to list the drug. When the repacker, relabeler, and drug product salvager provide, during listing, the required NDC number for the drug, we can incorporate by reference the information already submitted about the drug by the manufacturer. The information required to obtain an NDC number is explained in section IV.C of this document, and the requirements for providing the NDC number during listing are explained in section IV.D.4.a of this document.

The following paragraphs summarize the information that would be required for listing from manufacturers, repackers, relabelers, and drug product salvagers. These summaries are followed by descriptions of each of the listing requirements (see section IV.D.4 of this document).

a. *Summary of proposed listing information for manufacturers.* Manufacturers would be required to submit to us the following listing information (if applicable to the drug being listed) under proposed § 207.49:

- NDC number;

- Route of administration;
- Approved U.S. application number or approved U.S. BLA number, if any;
- Registration number of each establishment where the manufacturing is performed for the drug;
- Schedule of the drug under section 202 of the Controlled Substances Act (21 U.S.C. 812);
- With respect to foreign establishments only, the name and contact information of each importer of the drug and of each person who imports or offers for import the drug;
- Labeling;
- Advertisements; and
- Information about the private label distributor, if any.

b. *Summary of proposed listing information for repackers and relabelers.* Repackers and relabelers would be required to submit to us the following listing information (if applicable to the drug being listed) under proposed § 207.53:

- NDC number;
- Registration number of each establishment where the repacking or relabeling is performed for the drug;
- With respect to foreign establishments only, the name and contact information of each importer of the drug and of each person who imports or offers for import the drug;
- Labeling;
- Advertisements; and
- Information about the private label distributor, if any.

c. *Summary of proposed listing information for drug product salvagers who are not repackers or relabelers*. Drug product salvagers who do not otherwise repack or relabel the drugs they salvage would be required to submit to us the following listing information (if applicable to the drug being listed) under proposed § 207.54:

- NDC number assigned to the drug immediately before the drug is received by the drug product salvager;
- Lot number and expiration date of the salvaged drug;
- Registration number of each establishment where the drug product salvager salvages the drug;
- With respect to foreign establishments only, the name and contact information of each importer and of each person who imports or offers for import the drug; and
- Information about the private label distributor, if any.

4. What Listing Information Would Be Required for Manufacturers?

Under proposed § 207.49, manufacturers would be required to provide to us the following listing information for each drug they list, including a drug manufactured for a private label distributor.

a. *NDC number*. For a drug to be considered listed, manufacturers and, as discussed below, repackers, relabelers, and drug product salvagers, must submit the NDC number for the drug as part of the drug's listing information.[7] The NDC number, including the information that would be submitted to us to obtain an NDC number, is explained under proposed § 207.33. Knowing the

[7]The drug product salvager (that does not repack or relabel) would submit the NDC number assigned to the drug immediately before the drug is received by the drug product salvager; the manufacturer, repacker, and relabeler (and the drug product salvager that repacks or relabels) would submit the NDC number assigned to their drug under proposed § 207.33(c) and (d).

NDC number of the drug would enable us to incorporate by reference information about the drug submitted by the manufacturer, repacker, or relabeler to obtain an NDC number under proposed § 207.33(c) and (d), as well as information submitted by the manufacturer, repacker, or relabeler to list the drug. This would reduce the amount of information that must be provided to us by manufacturers, repackers, relabelers, and drug product salvagers for listing. Current § 207.25(b)(8) requires the submission of the NDC number for each drug listed, and this information is currently submitted on Form FDA 2657.

b. *Route of administration*. The route of administration would enable us to identify a specific formulation of a drug. For example, drugs having the same active ingredient may have different routes of administration. The route of administration is currently submitted on Form FDA 2657.

c. *Approved U.S. application number*. The approved U.S. application number or the approved U.S. BLA number,[8] if any, would enable us to link to the information about the drug that was already submitted to us for marketing approval. Section 510(j)(1)(A) of the act requires the submission of a reference to the authority for marketing a drug subject to section 505 or 512 of the act. In addition, current § 207.25(b)(2) requires the submission of the application number for each drug listed that the registrant regards as subject to section 505 or 512 of the act. The drug's application number is currently submitted on Form FDA 2657. As discussed in section IV.D.4.g of this document, if the approved U.S. application number is provided to us when a human prescription or OTC drug is listed, the manufacturer would not be required to re-submit the labeling for the approved drug. The application

[8]Human drugs are approved by FDA under an NDA, ANDA, or a BLA. Part 314 (21 CFR part 314) for human drugs and part 601 (21 CFR part 601) for biologics set forth the approval requirements.

number would incorporate by reference the labeling for approved drugs. This would eliminate unnecessary duplication of effort and cost to industry. The application number may have already been provided under § 207.33(c)(2)(i) and (c)(2)(ii) instead of providing the names of the active pharmaceutical ingredient and the inactive ingredient. If so, it will already be in our database and would not need to be resubmitted.

d. *Registration number of each establishment*. The registration number of each establishment where the manufacturing is performed for the drug would enable us to identify the establishment where the drug is manufactured. This would help our investigators better prepare for inspections and collect postmarketing surveillance samples. Although this information would already be submitted for registration under proposed § 207.25(e), submitting it at listing would enable us to link this information to the drug being listed. Current § 207.25(b)(7) requires, for each drug listed, the submission of the registration number of each drug establishment at which the drug is manufactured or processed (within the meaning of current § 207.3(a)(8)). Current § 207.25(b)(3) requires the submission of the license number of the manufacturer of drugs subject to section 351 of the PHS Act. The ''establishment registration number'' is defined in proposed § 207.1 to mean the number assigned by FDA to the establishment during the establishment registration process. Currently, we plan to assign the FEI number as the establishment registration number. In the future, however, we may use a different number as the establishment registration number. The establishment registration number is currently submitted on Form FDA 2657.

e. *Schedule of the drug*. The schedule of the drug under section 202 of the Controlled Substances Act would enable us to provide yearly estimates

of medical, scientific, and reserve stock needs for Schedule I and II substances (21 CFR part 1303, 21 U.S.C. 826). Under section 302(a) of the PHS Act (42 U.S.C. 242(a)), the Secretary is responsible for providing to the Drug Enforcement Administration estimates of the quantities of controlled substances for which production quotas must be established that will be required to meet the legitimate medical, scientific, and reserve stock needs of the United States for the following calendar year. The schedule of the drug is currently submitted on Form FDA 2657.

f. *Information about each importer of the drug and each person who imports or offers for import the drug to the United States*. Foreign establishments only must provide 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. As discussed under section IV.B.3 of this document, the term ''known to'' would mean any importer that is known to the foreign establishment as well as any importer that the foreign establishment has reason to know of. We therefore expect that the person responsible for completing the required registration forms on behalf of the foreign establishment would undertake appropriate due diligence in completing those forms, including to find out and report importers that others in his or her establishment know of or have reason to know of. Foreign establishments would provide this information for listing unless previously provided under proposed § 207.25(h) for registration. The Bioterrorism Act requires foreign establishments to submit, among other things, the name of each importer of each drug that is known to the establishment, and the name of each person who imports or offers for import each drug to the United States

for purposes of importation. The Bioterrorism Act requires submission of such information as part of registration information and also specifically requires listing information to be submitted for each drug being manufactured for commercial distribution (see section IV.A.4.d of this document). We are proposing, under this part, to make the submission of information concerning importers of drugs and persons who import or offer for import drugs to the United States both a registration and a listing requirement. However, if the information has been previously provided by the foreign establishment at registration, the foreign establishment would not be required to re-enter that information into the database at listing. Our listing database will be populated automatically with the required information. This would reduce the amount of information that must be provided to us by the foreign establishment at listing. The information about each importer of the establishment's drug that is known to the establishment and each person who imports or offers for import the drug to the United States is not currently required to be submitted under current part 207 or on Form FDA 2656 or Form FDA 2657.

g. *Labeling*. Under proposed § 207.49(g), the following labeling would be provided to us for each drug listed:

- Human prescription drugs. If the manufacturer has not provided the drug's approved U.S. application number as part of the listing information under proposed § 207.49(c), the manufacturer would submit a copy of all current labeling, including the content of labeling, for each human prescription drug (proposed § 207.49(g)(1)).

Under proposed § 207.49(g)(1) and, as discussed below under proposed §§ 207.49(g)(2) and 207.49(g)(3), only one representative container or carton label would be submitted where differences exist only in the quantity of

contents statement or the bar code. This proposed provision is consistent with current § 207.25(b)(2), although the proposal would add differences in the bar code to the provision. This provision would reduce the number of labels that must be submitted to us by the manufacturer.

If the manufacturer provides the drug's approved U.S. application number as part of the drug's listing information, the labeling required under proposed § 207.49(g)(1) and, as discussed below under proposed § 207.49(g)(2), would be deemed to accompany the listing information. Incorporating the labeling, including the content of labeling, by reference to the application number would eliminate unnecessary duplication of effort and cost to industry. This proposed exception would not apply to animal drugs approved under section 512 of the act because currently these application holders are not required to provide the content of labeling electronically with the application for those drugs.

The ''content of labeling'' would be provided to FDA under proposed § 207.49(g)(1) and, as discussed below, under proposed § 207.49(g)(2) and (g)(3). The ''content of labeling'' is defined in proposed § 207.1 and discussed in sections IV.A.5 and IV.E.4 of this document and would mean, for human prescription drugs that the manufacturer regards as subject to section 505 of the act or section 351 of the PHS Act, the content of the prescription drug labeling, including all text, tables, and figures. For human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the PHS Act, the ''content of labeling'' would mean the labeling equivalent to the content of the prescription drug labeling, including all text, tables, and figures. For human OTC drugs, the ''content of labeling'' would mean the content of the drug facts labeling required by § 201.66, including all

text, tables, and figures. For animal drugs, the ''content of labeling'' would mean the content of the labeling that accompanies the drug that is necessary to enable the safe and proper administration of the drug, including all text, tables, and figures.

The labeling submission requirements in proposed § 207.49(g) are almost identical in substance to the labeling submission requirements of current § 207.25(b)(2) through (b)(5), except that manufacturers would also be required, as discussed previously, to submit electronically the ''content of labeling.'' In addition, the labeling submission requirements in proposed § 207.49(g) conform to the statutory requirements of section 510(j) of the act. The proposed requirement to submit labeling, including the content of labeling, for human prescription drugs and, as discussed below, for human OTC drugs and animal drugs, whether or not the drugs are subject to the pre-approval provisions of the act or the PHS Act, is consistent with the statutory requirements of section 510(j)(1)(A), 510(j)(1)(B)(i), and 510(j)(1)(B)(ii) of the act. Section 510(j)(1)(A) of the act requires, among other things, the submission of a copy of all labeling for drugs subject to section 505 or 512 of the act. Section 510(j)(1)(B)(i) requires, among other things, the submission of a copy of all labeling for prescription drugs not subject to section 505 or 512 of the act, and section 510(j)(1)(B)(ii) requires, among other things, the submission of the label, package insert, and representative sampling of any other labeling for OTC drugs not subject to section 505 or 512 of the act. We also have the authority to require that labeling be submitted in this format under other sections of the act (e.g., sections 201, 301, 501, 502, 503, 505, 506, 506A, 506B, 506C, 513–516, 518–520, 701, 704, 721, 801 of the act) and the PHS Act.

- Human OTC drugs that manufacturers regard as subject to section 505 of the act or section 351 of the PHS Act. If the manufacturer has not provided the drug's approved U.S. application number as part of the listing information under proposed § 207.49(c), the manufacturer would submit a copy of all current labeling, 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 PHS Act (proposed § 207.49(g)(2)(i)).

Drugs subject to section 505 of the act or section 351 of the PHS Act must be approved by FDA under an NDA, ANDA, or a BLA. Part 314 for human drugs and part 601 for biological products set forth the approval requirements.

- Human OTC drugs that manufacturers regard as not subject to section 505 of the act or section 351 of the PHS Act. The manufacturer would submit a copy of the current label, 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 PHS Act (proposed § 207.49(g)(2)(ii)).

The term ''label'' means the container label as defined at section 201(k) of the act. ''Content of labeling'' is defined at proposed § 207.1 (as discussed in section IV.A.5 of this document) and for OTC drugs refers to the content of the drug facts labeling as specified at § 201.66. Most OTC drugs do not have a package insert. However, for those that do, it is currently required to be submitted for drug listing under section 510(j)(1)(A) and (j)(1)(B)(ii) of the act and current § 207.25(b)(4) and (b)(5). We are proposing to retain that requirement in proposed § 207.49(g)(2)(i) and (g)(2)(ii). For OTC drugs marketed pursuant to an approved application, any package insert would be included within the requirement to submit ''all current labeling.'' The term

''representative sampling of any other labeling,'' as used in proposed § 207.49(g)(2)(ii) and, as discussed below, in proposed § 207.49(g)(3)(ii), is defined in proposed § 207.1 and discussed in section IV.A.5 of this document. Examples of OTC drugs that a manufacturer may regard as not subject to section 505 of the act or section 351 of the PHS Act would include human OTC drugs marketed under an OTC monograph and deemed generally recognized as safe and effective (see part 330 (21 CFR part 330)).

- Animal drugs that manufacturers regard as subject to section 512 of the act. The manufacturer would submit a copy of all current labeling, including the content of labeling, for each animal drug that the manufacturer regards as subject to section 512 of the act (proposed § 207.49(g)(3)(i)).

- Animal drugs that manufacturers regard as not subject to section 512 of the act. For all other animal drugs, the manufacturer would submit a copy of the current label, the package insert, the content of labeling, and a representative sampling of any other labeling, for each animal drug that the manufacturer regards as not subject to section 512 of the act (proposed § 207.49(g)(3)(ii)).

h. *Advertisements*. Under proposed § 207.49(h), and in accordance with section 505(j)(1)(B)(i) of the act, the following advertisements would be provided by the manufacturer for each drug listed:

- 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 PHS Act. Proposed § 207.49(h)(1) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.25(b)(4). The term ''representative sampling of advertisements'' is defined in proposed § 207.1 and discussed in section IV.A.5 of this document.

- If we request it, for good cause, a copy of all advertisements for human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the PHS Act, including those advertisements described in § 202.1(l)(1), would be required to be submitted to FDA within 30 calendar days after our request. Proposed § 207.49(h)(2) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.31(a)(1). Section 510(j)(1)(B)(i) of the act requires, among other things, the submission of a representative sampling of advertisements and, upon request for good cause, a copy of all advertisements for prescription drugs not subject to section 505 of the act. Current § 207.31(a)(1) requires, upon request, the submission of a copy of all advertisements for prescription drugs that the manufacturer regards as not subject to section 505 of the act.

i. *Private label distributor*. If the drug is manufactured for a private label distributor, the manufacturer would submit the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor. The manufacturer may obtain this information from the private label distributor or other sources. This information would indicate whose drug (the manufacturer's or the private label distributor's) is being listed and would identify and enable us, if needed, to contact the private label distributor. The information for a private label distributor is currently submitted on Form FDA 2658.

5. What Listing Information Would Be Required for Repackers and Relabelers?

Under proposed § 207.53, repackers and relabelers would be required to provide to us all of the following listing information for each drug they list, including a drug repacked or relabeled for a private label distributor.

a. *NDC number*. For a drug to be considered listed, repackers and relabelers would submit the NDC number for the drug being repacked or relabeled as part of the drug's listing information. This requirement is explained in section IV.D.4.a of this document.

b. *Registration number of each establishment*. The registration number of each establishment where the repacking or relabeling is performed for the drug would enable us to identify the establishment where the drug is repacked or relabeled. This requirement is explained in section IV.D.4.d of this document.

c. *Information about each importer of the drug and each person who imports, or offers for import, the drug to the United States*. This requirement is explained in section IV.D.4.f of this document.

d. *Labeling*. Under proposed § 207.53(d), the following labeling must be provided for each drug listed:

- Human prescription drugs. If the repacker or relabeler makes any change in the labeling of the drug repacked or relabeled, the repacker or relabeler would submit a copy of all changed labeling for each human prescription drug that is repacked or relabeled (proposed § 207.53(d)(1)). We would already have, as required under proposed § 207.49(g), the labeling for the drug provided by the manufacturer during listing, and the repacker or relabeler would not need to resubmit it to us unless they make changes to the labeling. Proposed § 207.53(d)(1) is consistent with section 510(j)(1)(A) and (j)(1)(B)(i) of the act and current § 207.25(b)(2) and (b)(4), except that repackers and relabelers would not need to resubmit labeling when no changes have been made.

- Human OTC drugs that manufacturers regard as subject to section 505 of the act or section 351 of the PHS Act. If the repacker or relabeler makes any changes, in accordance with the act and FDA regulations, in the labeling

of the drug repacked or relabeled, the repacker or relabeler would submit a copy of all changed labeling for each human OTC drug that the manufacturer of the drug regards as subject to section 505 of the act or section 351 of the PHS Act (proposed § 207.53(d)(2)(i)). As stated previously, we would not need a copy of the unchanged labeling because we would already have the labeling for the drug provided by the manufacturer during listing. Proposed § 207.53(d)(2)(i) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.25(b)(2), except that some of the information required under current § 207.25(b)(2) would not need to be provided by the repacker or relabeler under proposed § 207.53(d)(2)(i) if the repacker or relabeler provides the manufacturer's NDC number. The NDC number would provide a link to that information.

- Human OTC drugs that manufacturers regard as not subject to section 505 of the act or section 351 of the PHS Act. The repacker or relabeler would submit 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 PHS Act (proposed § 207.53(d)(2)(ii)). The term ''representative sampling of any other labeling,'' as used in proposed § 207.53(d)(2)(ii) and, as discussed below, in § 207.53(d)(3), is defined in proposed § 207.1 and discussed in section IV.A.5 of this document. Examples of OTC drugs that a manufacturer may regard as not subject to section 505 of the act or section 351 of the PHS Act would include human OTC drugs marketed under an OTC monograph and deemed generally recognized as safe and effective (see part 330). Proposed

§ 207.53(d)(2)(ii) is consistent with section 510(j)(1)(B)(ii) of the act and current § 207.25(b)(5), except redundant information would not be submitted.

- Animal drugs. The repacker or relabeler would submit a copy of the current label, a copy of any changes made to each animal drug labeling, and a representative sampling of any other labeling for each animal drug (proposed §§ 207.53(d)(3)). Proposed § 207.53(d)(3) is consistent with section 510(j)(1)(B)(ii) of the act and current § 207.25(b)(2) and (b)(5), except redundant information would not be submitted.

e. *Advertisements*. Under proposed § 207.53(e), and in accordance with section 505(j)(1)(B)(i) of the act, the following advertisements would be provided by the repacker or relabeler for each drug listed:

- 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 PHS Act. Proposed § 207.53(e)(1) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.25(b)(4).

- If we request it, for good cause, a copy of all 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 PHS Act, including those advertisements described in § 202.1(l)(1), would be required within 30 calendar days after our request. Proposed § 207.53(e)(2) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.31(a)(1).

f. *Private label distributor*. If the drug is repacked or relabeled for a private label distributor, the repacker or relabeler would submit the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor. The repacker or relabeler may obtain this information from the private label distributor or other sources. This information would indicate

whose drug (the repacker's, relabeler's, or private label distributor's) is being listed and would identify and enable us, if needed, to contact the private label distributor. The information for a private label distributor is currently submitted on Form FDA 2658.

6. What Listing Information Would Be Required for Drug Product Salvagers Who Are Not Repackers or Relabelers?

Drug product salvagers who do not otherwise repack or relabel the drugs they salvage would be required to provide all of the following listing information to us for each drug they list, including a drug salvaged for a private label distributor. 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.

a. *NDC number*. For a drug to be considered listed, the drug product salvager would be required to provide the NDC number assigned to the drug immediately before the drug is received by the drug product salvager. Under the proposal, we would assign an NDC number to a manufacturer's, repacker's, or relabeler's drug (or to a drug manufactured, repacked, or relabeled for a private label distributor) after the information required under proposed § 207.33(c) or (d) is provided (see discussion in section IV.D.4.a of this document). The drug product salvager who is not also a repacker or a relabeler for the drug would provide to us the NDC number that is already on the salvaged drug's label (that is, the NDC number of the manufacturer, repacker, relabeler, or private label distributor). Knowing the NDC number of the drug would enable us to incorporate by reference information about the drug submitted by the manufacturer, repacker, or relabeler to obtain an NDC number

under proposed § 207.33(c) and (d), as well as information submitted by the manufacturer, repacker, or relabeler to list the drug.

b. *Lot number and expiration date*. We need to know the lot number and expiration date to properly identify the drug because the drug product salvager who is not a repacker or relabeler for the drug would not be assigned an NDC number for the drug. The salvaged drug's lot number would enable us to specifically identify the salvaged drug and determine which batch of a manufacturer's drug has been processed by the drug product salvager. Lot number (or control number or batch number) is defined at current § 210.3(b)(11) as any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined. Knowing the drug's expiration date would indicate approximately how long the salvaged drug may be available for use by consumers. The expiration date would also allow us to identify the approximate date that the salvaged drug would no longer be marketed.

c. *Registration number of each establishment*. The registration number of each establishment where the drug product salvager salvages the drug would enable us to connect the salvaging activity to a particular drug and identify the specific location where the drug product salvaging is performed for the drug. This information would also be used in conducting our establishment inspections and for collecting postmarketing surveillance samples. Current § 207.25(b)(7) requires, for each drug listed, the submission of the registration number of each drug establishment at which the drug is manufactured or processed (within the meaning of current § 207.3(a)(8)), and current

§ 207.25(b)(3) requires the submission of the license number of the manufacturer of drugs subject to section 351 of the PHS Act. The establishment registration number is currently submitted on Form FDA 2657.

d. *Information about each importer of the drug and each person who imports, or offers for import, the drug to the United States*. This requirement is explained under section IV.D.4.f of this document.

e. *Private label distributor*. If the drug is salvaged for a private label distributor, the drug product salvager would be required to submit the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor. The drug product salvager may obtain this information from the private label distributor or other sources. This information would identify the private label distributor and enable us, if needed, to contact the private label distributor. The information for a private label distributor is currently submitted on Form FDA 2658.

7. What Additional Drug Listing Information May Be Required?

Under proposed § 207.55, if we request it, the manufacturer, repacker, relabeler, or drug product salvager would be required to briefly state the basis for its belief that a particular drug product is not subject to section 505 or 512 of the act or section 351 of the PHS Act. This proposed provision, which is consistent with section 510(j)(1)(D) of the act and current § 207.31(a)(3), is needed because some manufacturers, repackers, and relabelers have mistakenly considered a drug not to be subject to section 505 or 512 of the act or section 351 of the PHS Act. Although in some cases manufacturers, repackers, and relabelers have correctly concluded that a drug is not subject to section 505 or 512 of the act or section 351 of the PHS Act, in other cases we may consider the drug to be subject to section 505 or 512 despite that conclusion.

The brief statement that would be requested under proposed § 207.55 may include, for example, the **Federal Register** citation for the applicable OTC monograph. We anticipate that our electronic drug registration and listing system will provide some options for brief statements, including **Federal Register** citations as described in the example above, from which manufacturers, repackers, relabelers, and drug product salvagers may select as the basis for their belief that a particular drug product is not subject to section 505 or 512 of the act or section 351 of the PHS Act.

We are also considering whether to require establishments to provide the number of batches and batch size for each drug subject to the listing requirements that they manufactured, repacked, or relabeled since the establishment last provided listing information. Typically, this information would be provided every 6 months, based on the obligation to review and update listing information in June and December of each year. We would consider ''batch size'' to mean, as a general matter, the batch size included in the master production and control records for each drug, as required by the regulations governing current good manufacturing practice for finished pharmaceuticals in part 211, including § 211.186(a) (master production and control records). Typically, ''batch size'' would be the number of unit dosage forms (such as for tablets) or, if the unit dosage form is not defined before primary packaging (such as for liquids), the total batch weight or volume before primary packaging.

We are considering this requirement because it would provide us with important data regarding a product's volume in the U.S. marketplace to assess the potential impact the product has on the public health, which, in turn, will enable us to use our limited resources more efficiently, particularly with regard

to inspectional oversight. For example, we currently use data collected as a surrogate for production volume, among many other factors, in our risk-based model to prioritize routine inspections. This model is a systematic, objective, data-driven method to prioritize inspections. (See ''Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model'' at *http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm*.) However, better estimates of manufacturing volume would improve our ability to implement a more risk-based approach to manufacturing quality oversight activities. By requiring establishments to provide the number of batches and batch size for each drug subject to the listing requirements, we would have objective data regarding production volume and be better able to find and address CGMP violations that may have the most impact on public health. Actual production data would also give us the ability to more efficiently allocate our resources in other areas.

We specifically invite comments on whether we should require manufacturers, repackers, relabelers, and drug product salvagers to provide the number of batches and batch size for each drug subject to the listing requirements.

8. What Are the Proposed Requirements for Reviewing and Updating Listing Information?

Currently, manufacturers, repackers, and relabelers must enter new or revised listing information on Form FDA 2657 (Form FDA 2658 is used when manufacturers, repackers, and relabelers enter new or revised information for a private label distributor's drug) and return the form to FDA. Under the proposal, manufacturers, repackers, relabelers, and drug product salvagers would access our electronic drug registration and listing system and review

their current listing information online, making any changes where needed. Updating listing information would be less time consuming under the proposal because the manufacturer, repacker, relabeler, and drug product salvager would be able to easily access their information at any time, and only changes to the information already in the system would need to be entered in the fields provided.

Under proposed § 207.57, manufacturers who are required to list under proposed § 207.41 would review and update all listing information provided under proposed §§ 207.49, 207.55, and 207.57; repackers and relabelers (including drug product salvagers who repack and/or relabel) who are required to list under proposed § 207.41 would review and update all listing information provided under proposed §§ 207.53, 207.55, and 207.57; and drug product salvagers (who are not repackers and/or relabelers) who are required to list under proposed § 207.41 would review and update all listing information provided under proposed §§ 207.54, 207.55, and 207.57. Proposed § 207.57 uses the term ''review and update'' to stress the importance of first reviewing all listing information to determine if any changes have occurred and then updating the information.

Under proposed § 207.57(a), during the annual review and update of registration information, manufacturers, repackers, relabelers, and drug product salvagers would provide listing information for any drug that has not been previously listed. Proposed § 207.57(a) is consistent with section 510(j)(1) of the act, which requires, among other things, that a list of all drugs must be provided at the time of annual registration.

Under proposed § 207.57(b), manufacturers, repackers, relabelers, and drug product salvagers would review and update their listing information each June

and December of every year. Proposed § 207.57(b) is consistent with the timeframes set forth in section 510(j)(2) of the act, which requires, among other things, that each person who registers must report certain listing information ''once during the month of June of each year and once during the month of December of each year.'' Under current § 207.21(b), an update of listing information must occur each June and December.

Under proposed § 207.57(b)(1) through (b)(5), manufacturers, repackers, relabelers, and drug product salvagers would, during the review and update, submit the following information:

- Listing information would be provided for any drug manufactured, repacked, relabeled, or salvaged for commercial distribution that has not been previously listed (proposed § 207.57(b)(1)). The information would be provided in accordance with proposed §§ 207.49, 207.53, 207.54, and 207.55. This information is currently required under section 510(j)(2)(A) of the act and current § 207.30(a)(1).

- The date that the manufacture, repacking, relabeling, or salvaging for commercial distribution of a listed drug has been discontinued would be provided (proposed § 207.57(b)(2)). The date of discontinuation is currently required under section 510(j)(2)(B) of the act and current § 207.30(a)(2). Section 510(j)(2)(B) of the act requires submission of a ''notice of discontinuance.'' We are proposing to also require that the expiration date of the last lot manufactured, repacked, relabeled, or salvaged be part of proposed § 207.57(b)(2). This information would enable us to know when a drug is no longer marketed and approximately how long the discontinued drug may be available for use by consumers.

We recognize that because of their business practices, drug product salvagers may discontinue commercial distribution of a listed drug almost immediately after they salvage the drug. Drug product salvagers may salvage a drug, put the drug into commercial distribution by selling it to a retailer or other party, and then discontinue salvaging the drug. In that case, we intend to minimize the reporting burden on drug product salvagers by allowing the drug product salvager to provide notice of discontinuation of the drug at the same time the drug product salvager lists the drug. We would not expect under proposed § 207.57(b)(2) that the drug product salvager inform us again, during the review and update of listing information in either June or December of the year, that the salvaged drug is discontinued. Under this proposal, we expect that our electronic drug registration and listing system would provide the opportunity for drug product salvagers to first list a drug, as required by proposed § 207.54, and then indicate that they are discontinuing the drug, as required by proposed § 207.57(b)(2). Because the drug product salvager would have provided the lot number and expiration date for the drug under proposed § 207.54(b)(2), we would not require that same information be submitted again under proposed § 207.57(b)(2).

- The date that the manufacture, repacking, or relabeling for commercial distribution of a previously discontinued drug has resumed and any other listing information not previously required or submitted for the drug would be provided (proposed § 207.57(b)(3)). This proposed provision is consistent with section 510(j)(2)(C) of the act, which requires, among other things, that if a registrant has resumed the manufacture, preparation, propagation, compounding, or processing of a discontinued drug for commercial distribution, the registrant must provide notice and the date of such

resumption, the established name and proprietary name of the drug, and other listing information required under section 510(j)(1) of the act not previously provided. The established name and proprietary name would have previously been submitted at the time of listing. Because we would be able to reference that information in our listing database, manufacturers, repackers, and relabelers would not need to resubmit the established name and proprietary name. Current § 207.30(a)(3) requires, in addition to the date of resumption of commercial distribution, that the NDC number, the established name and proprietary name, and any other listing information not previously submitted must be provided. Under the proposal, this information would not need to be provided at this time because we would have access to it from the listing database.

We anticipate that drug product salvagers would not report information under proposed § 207.57(b)(3) because we are unaware of instances when drug product salvagers resume salvaging a drug that they have already salvaged and returned to the marketplace. Drug product salvagers salvage a drug and then put the drug into commercial distribution by selling it to a retailer or other party. This activity ends the drug product salvager's association with that drug. In contrast, manufacturers, repackers, and relabelers may resume the manufacture, repacking, or relabeling of a drug (usually a different lot of the drug) that they had previously listed but are currently not manufacturing, repacking, or relabeling. Thus, we anticipate that proposed § 207.57(b)(3) would not be applicable to drug product salvagers. We invite comment on whether drug product salvagers resume salvaging a drug that they have already salvaged and returned to the marketplace.

- The June and December review and update of listing information would include the submission of all material changes in any information previously submitted under § 207.49, § 207.53, § 207.54, § 207.55, or § 207.57 (proposed § 207.57(b)(4)). Current § 207.30(a)(4) requires that any material change in any information previously submitted must be reported every June and December or, at the discretion of the registrant, when the change occurs. Material changes are listed in the definition of ''any material change'' in current § 207.3(a)(3). As discussed in section IV.A.5 of this document, we are proposing to broaden this definition to mean any change in any listing information provided under proposed §§ 207.49, 207.53, 207.54, 207.55, and 207.57 (except for labeling changes in arrangement or printing or of an editorial nature, or the inclusion of a bar code or NDC number on the label). Under the proposed definition of ''material change,'' the number of changes in listing information that are considered ''material'' would include more than the five types of changes considered ''material'' in the current definition. We are proposing a broader definition of material change because, for the reasons explained in section IV.D of this document, the accuracy of all listing information is essential for us to maintain a reliable and current drug listing database. Proposed § 207.57(b)(4) is consistent with section 510(j)(2)(D) of the act, which requires that each person who registers shall report once during the month of June of each year and once during the month of December of each year any material change in any information previously submitted pursuant to section 510(j)(1) or section 510(j)(2) of the act. Section 510 of the act does not define ''material change.''

- If no changes have occurred since the last review and update of listing information, manufacturers, repackers, relabelers, and drug product salvagers would certify that no changes have occurred (proposed § 207.57(b)(5)).

Proposed § 207.57(b)(5) also provides that if a drug is discontinued and we have received the information required under proposed § 207.57(b)(2) concerning the discontinuation of a listed drug, no further certifications would be necessary for the discontinued drug. We are proposing to revoke current § 207.30(b), which states that no report is required when no changes have occurred since the previously submitted list.

FDA is proposing this certification to ensure that manufacturers, repackers, relabelers, and drug product salvagers have reviewed their listing information and have determined that there have been no changes. There have been many instances where manufacturers, repackers, and relabelers have not updated their listing information on a regular basis. It has been difficult for us to determine whether failure to update listing information is the result of no changes in information or noncompliance. The proposed requirement is intended to reduce these instances and improve the accuracy of our drug listing database. Furthermore, under section 301(p) of the act, it is a prohibited act to fail to submit drug listing information under section 510(j) of the act. Failure to submit drug listing information would also render a drug misbranded under section 502(o) of the act. In addition, the proposed requirement to certify is supported by the statutory provision in section 701(a) of the act (21 U.S.C. 371(a)) that the Secretary has the authority to promulgate regulations for the efficient enforcement of the act.

We specifically request comment on any burden that may result from this proposed requirement that manufacturers, repackers, relabelers, and drug product salvagers certify that no changes have occurred.

Current § 207.30(a) provides that the updates to listing information must be submitted during each June and December or, at the discretion of the

registrant, when the change occurs. Although proposed § 207.57(b) would require that listing information be reviewed and updated only every June and December, we are requesting that manufacturers, repackers, relabelers, and drug product salvagers provide all updates to listing information within 30 calendar days of a change. We are requesting that this information be provided on an expedited basis because our listing database will be more accurate if listing information is submitted sooner.

E. Electronic Format

1. How Would Registration and Listing Information Be Provided To FDA?

Under proposed § 207.61(a)(1), the following information required under proposed part 207 would be provided to us using our electronic drug registration and listing system:

- Establishment registration information required in proposed §§ 207.25 and 207.29 (proposed § 207.61(a)(1)(i));
- Information required for an NDC number in proposed § 207.33 (proposed § 207.61(a)(1)(ii)); and
- Drug listing information required in proposed § 207.49 (except for labeling and advertising information in proposed § 207.49(g) and (h)), 207.53 (except proposed §§ 207.53(d) and (e)), 207.54, 207.55, and 207.57 (proposed § 207.61(a)(1)(iii)). As explained in section IV.E.7 of this document, the submission of establishment registration and drug listing information and information required for an NDC number would be made in accordance with 21 CFR part 11, except for the requirements under § 11.10(b), (c), and (e), and the corresponding requirements in § 11.30.

Proposed § 207.61(a)(2) would require that the content of labeling defined in proposed § 207.1 and required under proposed § 207.49(g)(1) through (g)(3)

be provided to us in electronic format. The NDC number would also be provided with[9] the content of labeling for each drug. As explained in section IV.E.7 of this document, the submission of the content of labeling would be made in accordance with 21 CFR part 11, except for the requirements under § 11.10(a), (c) through (h), and (k), and the corresponding requirements under § 11.30. As explained in section IV.E.4 of this document and stated in proposed § 207.49(g), the labeling, including the content of labeling, would not be required if the approved U.S. application number is provided by the manufacturer when the drug is listed.

In addition to the electronic submission of information under proposed § 207.61(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(2)), advertisements and labeling (other than the content of labeling) required under §§ 207.49(g) and (h) and 207.53(d) and (e) would be provided to us in either paper or electronic format (proposed § 207.61(a)(3)). The NDC number would also be provided with[10] the advertisements and labeling. As explained in section IV.E.7 of this document, the electronic submission of advertisements and labeling, other than the content of labeling, would be made in accordance with part 11 (21 CFR part 11), except for the requirements under § 11.10(a), (c) through (h), and (k), and the corresponding requirements under § 11.30.

Under proposed § 207.61(a)(4), electronic format submissions must be in a form that we can process, review, and archive. As explained in section IV.E.6 of this document, we may periodically issue guidance on how to provide registration and listing information in electronic format (for example, method of transmission, media, file formats, preparation and organization of files).

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[9] As explained in section IV.E.4 of this document, the NDC number may accompany the content of labeling; it does not need to be in the content of labeling.

[10] See footnote 9.

The electronic submission of the information covered under proposed § 207.61(a) would provide a number of advantages over the current submission of FDA paper forms:

- We would receive a greater quantity of accurate information in less time than it takes to receive information from paper submissions. The information received would also be more accurate because our electronic drug registration and listing system would eliminate errors associated with inputting paper-based data into an electronic system.

- The electronic transmission of the information would be easier and more efficient for both industry and us than the current use of paper forms. For example, you would receive on-screen feedback if the information submitted was not complete, reducing errors and the time and cost of communicating with us. Similarly, electronic transmission of the information would reduce significantly the time and cost associated with our processing paper forms and communicating with industry concerning errors on those forms.

- Information search and retrieval time would be reduced, allowing quicker access to the information in the database.

The requirement to provide listing information to us electronically is consistent with the requirement to list in section 510(j)(1) of the act: ''Every person who registers with the Secretary * * * shall * * * file with the Secretary a list of all drugs * * *. Such list shall be prepared in such form and manner as the Secretary may prescribe * * *.'' The requirement to provide registration information to us electronically is consistent with section 510(p) of the act: ''Registrations * * * (including the submission of updated information) shall be submitted to the Secretary by electronic means, upon a finding by the Secretary that the electronic receipt of such registrations is

feasible * * *.'' Persons who register are also required to list drugs which are being manufactured, prepared, propagated, compounded, or processed for commercial distribution (21 U.S.C. 510(j)(1)).

2. What Was the Electronic Submission Pilot Project?

In the **Federal Register** of January 9, 2001 (66 FR 1684), we requested volunteers to participate in a pilot project involving the electronic submission of registration and listing information. In a September 2001 meeting/ teleconference with the pilot project volunteers, we provided information on the major functions of the electronic drug registration and listing system, including instructions on the installation, setup, and testing of the systems. The pilot test was held from October 19, 2001, through November 9, 2001, and approximately 28 industry representatives voluntarily participated.

As mentioned previously, our electronic drug registration and listing system is expected to be a Web-enabled, integrated system that provides controlled database access for you to register establishments and list drugs. A separate capability—an extranet—could be used that authenticates external users and controls their access to the our online registration and listing database. This system would allow you to create user accounts and manage additional users.

Industry representatives accessed the pilot test through our extranet to perform the following functions: (l) Initial company setup and establishment registration; (2) registration of additional establishments; (3) drug listing; (4) updates; and (5) system access, logoff, and exit. The pilot test included installation, setup, and operational testing of our electronic drug registration and listing system.

The pilot test was intended to get direct input from the pilot participants about the usability and functionality of the system. The pilot test provided feedback to us on:

- The pilot participants' experience in submitting and preparing registration and listing data.
- Web browsers used.
- Acceptability of proposed normal operating hours.
- Page layout and design.
- Ease of navigation within pages and between functions.
- Whether error messages provide sufficient information to resolve the error.
- The appropriateness of the style, content, and depth of detail of the onpage help.

The comments we received on our electronic drug registration and listing system were generally positive. Those who volunteered to participate in the pilot test were able to successfully access the system, set up a company account within the system, register establishments, and list drugs. Pilot participants encountered a few one-time difficulties that we will address, including minor password problems and difficulties completing the initial company setup and establishment registration process.

We are using information from the pilot program to develop our electronic system.

3. How Would the Electronic Drug Registration and Listing System Work?

Electronic format submissions of registration and listing information, as well as information required for an NDC number, would consist of the electronic transmission via the Internet of the required information from

manufacturers, repackers, relabelers, and drug product salvagers into our electronic drug registration and listing system.

Our electronic drug registration and listing system would be made available using an Internet-based data collection system accessed through our FDA Internet site.

- To use the Web site, you would need access to the Internet using a browser.
- You could arrange for Internet access through one of many available Internet Service Providers (ISPs).
- You would need an e-mail address so we can send you confirmation of submissions and other related information.
- This e-mail service could be provided by the ISP or by other sources.

Prior to accepting registration and listing information from this online system, we would authenticate the source (that is, the manufacturer, repacker, relabeler, or drug product salvager) providing the data.

- We could, for example, authenticate entry into the electronic drug registration and listing system by establishing user accounts based on current registration information.
- We anticipate that we may contact manufacturers, repackers, relabelers, and drug product salvagers to obtain contact information to establish an administration account.

To register and list electronically, to provide updated registration and listing information, and to provide information to obtain an NDC number, you would go to our Web site and follow the prompts.

- You could sign onto the system by entering the account number, user name, and password obtained by following the procedures in the guidance we

intend to issue on our electronic drug registration and listing system, as discussed in section IV.E.6 of this document.

- You would then be prompted to provide general information about your company and then specific information about each establishment and drug as required in proposed part 207.
- When all of the required information is provided, your official contact would receive confirmation electronically that the information has been received by us.
- If you provide information to obtain an NDC number, the number could be issued electronically.

4. What Are the Proposed Requirements for the Submission of Content of Labeling in Electronic Format?

Under proposed § 207.61(a)(2), the content of labeling would be provided to us in an electronic format. The electronic submission of the content of labeling would permit us to electronically review, compare, and extract data from the labeling.

The content of labeling would be submitted in electronic format for the following drugs:

- Human prescription drugs;
- Human OTC drugs, including those that the manufacturer regards as subject to section 505 of the act or section 351 of the Public Health Service Act as well as those regarded as not subject to sections 505 or 351; and
- Animal drugs, including those that the manufacturer regards as subject to section 512 of the act as well as those regarded as not subject to section 512.

The ''content of labeling'' is defined in proposed § 207.1 (and discussed in section IV.A.5 of this document) to mean:

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

The proposed requirement to provide the content of labeling electronically is consistent with (among other things) that part of the listing requirement in section 510(j)(1) of the act which states that ''Such list shall be prepared in such form and manner as the Secretary may prescribe.'' The proposed requirement to submit the content of labeling for human prescription drugs, human OTC drugs, and animal drugs is consistent with the statutory requirements of section 510(j)(1)(A), (j)(1)(B)(i), and (j)(1)(B)(ii) of the act. Section 510(j)(1)(A) of the act requires, among other things, the submission of

a copy of all labeling for drugs subject to sections 505 or 512 of the act. Section 510(j)(1)(B)(i) requires, among other things, the submission of a copy of all labeling for prescription drugs not subject to section 505 or 512 of the act. Section 510(j)(1)(B)(ii) requires, among other things, the submission of the label, package insert, and representative sampling of any other labeling for OTC drugs not subject to section 505 or 512 of the act.

We are proposing that manufacturers provide the NDC number electronically with the content of labeling during listing so that we can more easily link the content of labeling to the listed drug and, thus, expedite the listing process. The NDC number may accompany the content of labeling by being referenced, for example, in the transmittal message to us that contains the content of labeling. The NDC number does not need to be on the content of labeling.

As discussed in greater detail in section IV.D.4 of this document, we are proposing that you need not submit the content of labeling for human prescription or OTC drugs approved under section 505 of the act or section 351 of the PHS Act if you provide the application number when listing the drug or requesting an NDC number for the drug. Incorporating the content of labeling by reference to the application number would eliminate unnecessary duplication of effort and cost to industry.

The submission of the content of labeling in an electronic format would assist us in several ways:

- The use of computer technology to identify changes in different versions of the labeling would greatly enhance our accuracy and efficiency in updating our listing database.

- Our ability to protect the public health would be enhanced because electronic review and comparison of labeling files would provide a higher degree of certainty that all portions of the labeling are consistent and up to date.

- Our ability to protect the public health would be enhanced because we could provide and make easily accessible up-to-date product labeling through the DailyMed initiative, as described in section IV.C.2 of this document.

- Our ability to protect the public health would be enhanced by supporting the implementation of the electronic prescribing provisions of the Medicare Modernization Act. The product labeling information we would make available through DailyMed would be associated with the unique NDC number for each drug, supporting electronic prescribing.

- In the future, the electronic submission of the content of labeling would enable us to receive much of the drug listing information through the labeling, thus improving efficiency in the drug registration and listing system. Industry would be able to satisfy many drug listing requirements through the submission of the content of labeling.

The proposed requirement to provide the content of labeling would not significantly burden industry because labeling is maintained in electronic format by most manufacturers. In addition, our proposal seeks to limit industry costs by avoiding unnecessary duplication of effort—for example, as mentioned previously, if the content of labeling has already been submitted in an approved application, supplement, or annual report, the manufacturer would only have to reference the application number to comply with this listing requirement. In addition, only the manufacturer would be required to submit the content of labeling.

We would require, under proposed 207.61(a)(4), that the information in electronic format be submitted in a form we can process, review, and archive. We are prepared at this time to receive the content of labeling as a portable document format (PDF) file that is searchable. Using commercially available software, an electronic source document created by any number of programs (for example, word processors and desktop publishing programs) can be converted to a PDF file, preserving the fonts, formatting, and graphics of the source document, regardless of the application and platform used to create it. The PDF file can be copied onto a disk or CD–ROM and shared with other users who can use PDF reading software to view, navigate through, and print the document, as well as view, search, and print the file, and copy text, tables, and figures from the file.

However, to be responsive to technological advances, we may recommend in the future that new file formats such as extensible markup language and software applications be used to submit labeling electronically. The language in proposed § 207.61(a)(4), that electronic format submissions must be in a form that we can process, review, and archive, will provide us with the flexibility to recommend file formats or software other than PDF, if appropriate, such as SPL (described earlier in sections III.B and IV.C.2 of this document). We will provide advance notice, in accordance with FDA's good guidance practice regulations under § 10.115 (21 CFR 10.115), so that affected parties will have adequate time to convert to any new format or software. In addition, we expect that such format or software will be widely available before we switch to a new technology. Changes in format and/or software will

be identified in public docket number 92S–0251.[11] During any such transition, we will accept submissions using either file format or software.

5. Would the Proposal Require Electronic Submission of Advertisements and Other Labeling?

Under proposed § 207.61(a)(3), advertisements and labeling, other than the content of labeling, required under proposed §§ 207.49(g) and (h) and 207.53(d) and (e) would be provided to us in paper or electronic format. Information on how and where to send labeling and advertisements that are not provided electronically will be described in the guidance document we intend to develop, as discussed in section IV.E.6 of this document. Although we are proposing to require that only registration and listing information, information submitted to receive an NDC number, and the content of labeling need be submitted in electronic format, we expect to identify in public docket number 92S–0251 copies and samples of labeling and advertisements as types of documents we accept in electronic format. Under the proposal, you would have the option of submitting advertisements and labeling either electronically or in paper.

The proposed requirement to submit advertisements is consistent with section 510(j)(1)(B)(i) of the act, which requires, among other things, the submission of a representative sampling of advertisements and, upon request, a copy of all advertisements for prescription drugs not subject to section 505 of the act. The proposed requirement to submit labeling is, as explained previously, consistent with the statutory requirements of section 510(j)(1)(A), (j)(1)(B)(i), and (j)(1)(B)(ii) of the act.

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[11] This docket may be accessed on the Internet at *http://www.fda.gov/ohrms/dockets*.

6. What Guidance Documents Do We Intend To Issue on Providing Registration and Listing Information Electronically?

We plan to publish draft guidance and technical specifications on the electronic submission of registration and listing information through our electronic drug registration and listing system (the draft guidance). The draft guidance and technical specifications will explain the electronic process for providing registration and listing information and for providing the information that would be required to obtain an NDC number, including step-by-step instructions on entering information required under proposed part 207. We are also planning to issue guidance on providing registration and listing information in electronic format (concerning the method of transmission, media, file formats, and preparation and organization of files), and this guidance will be updated regularly to reflect the evolving nature of the technology.

In addition to the draft guidance and the guidance on providing registration and listing information in electronic format under development, we have issued other guidances that explain the process for submitting information to us in electronic format. These guidance documents are available at FDA's Web site *http://www.fda.gov/cder/guidance/index.htm* under the heading ''Electronic Submissions.''

7. How Would Part 11 Apply to the Electronic Submission of Registration and Listing Information?

Under proposed § 207.61(a)(1), the submission of registration and listing information (except for the content of labeling and advertisements and labeling) and the information required to receive an NDC number would be made in accordance with part 11, except for the requirements under § 11.10(b),

(c), and (e) and the corresponding requirements under § 11.30. Under proposed § 207.61(a)(2) and (a)(3), the submission of the content of labeling, and advertisements and other labeling in electronic format, would be made in accordance with part 11, except for the requirements under § 11.10(a), (c) through (h), and (k), and the corresponding requirements under § 11.30. In the **Federal Register** of March 20, 1997 (62 FR 13430), we published regulations on electronic records and electronic signatures (part 11). Part 11 regulations, among other things, set forth the criteria under which records submitted to us may be submitted in electronic format in lieu of paper records. Section 11.2(b) states that, for records submitted to us, persons may use electronic records in lieu of paper records, in whole or part, provided the requirements of part 11 are met and the documents or parts of documents to be submitted have been identified by us in public docket number 92S–0251 as being the type of submission we are prepared to accept in electronic format.

Part 11 permits the widest possible use of electronic technology, compatible with our responsibility to promote and protect the public health (62 FR 13430). Part 11 helps to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records. Part 11 also helps to safeguard against the possible repudiation of those records. The controls in subpart B of part 11 are intended to further this purpose.

We recently announced in the **Federal Register** our current thinking on part 11. In the **Federal Register** of September 5, 2003 (68 FR 52779), we announced the availability of a guidance for industry entitled ''Part 11, Electronic Records; Electronic Signatures—Scope and Application'' (the part 11 guidance). The part 11 guidance explains our current thinking regarding the requirements and application of part 11 and states that we intend to

exercise enforcement discretion in the manner specified in the guidance with respect to the validation (§ 11.10 (a)), audit trail (§§ 11.10(e) and (k)(2)), record retention (§ 11.10(c)), and copies of records (§ 11.10(b)) requirements of part 11, and any corresponding requirements in § 11.30. In addition, we announced that we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of the part 11 guidance. Although we explain the relationship between the part 11 guidance and this proposal, as discussed below, you should refer to the guidance we intend to issue on electronic registration and listing for information on complying with part 11 when providing registration and listing information electronically. The part 11 requirements from which we propose exemptions in this proposal differ from the part 11 requirements for which we intend to exercise enforcement discretion, as described in the part 11 guidance. They differ because the proposed exemptions in this rule are specific to the electronic submission of registration and listing information, including information that must be submitted to receive an NDC number and the content of labeling, for drugs that would be covered under proposed part 207, whereas the part 11 draft guidance applies to the maintenance of all electronic records and to all electronic submissions subject to part 11.

With respect to the electronic submission of registration and listing information, including the information required to receive an NDC number but not including the content of labeling and advertisements and other labeling, as previously noted, we believe, as provided in proposed § 207.61(a)(1), that several of the requirements in subpart B of part 11 are not necessary to further

the goals of part 11. Because we control the electronic drug registration and listing system, certain controls for systems would not apply to the submission of registration and listing information, such as:

- The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency (§ 11.10(b));
- The protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10(c));
- The use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records (§ 11.10(e)); and
- The corresponding controls of § 11.30.

You would be exempt from these subpart B controls because our registration and listing database is designed to ensure the authenticity, integrity, and confidentiality of this information in several ways. For example, we would control the database, and you would only be able to enter and/or revise information in your own account. In addition, the database would contain records of registration and listing information, and we could generate accurate and complete copies of records.

With respect to the electronic submission of the content of labeling and advertisements and other labeling, as previously noted, we believe, as provided in proposed § 207.61(a)(2) and (a)(3), that several of the requirements in subpart B of part 11 are not necessary to further the goals of part 11. For the reasons described below, certain controls for systems would not apply to the submission of the content of labeling and advertisements and other labeling, such as:

- The validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records (§ 11.10(a));
- The protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10(c));
- Limiting system access to authorized individuals(§ 11.10(d));
- The use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records (§ 11.10(e));
- The use of operational system checks to enforce permitted sequencing of steps and events, as appropriate (§ 11.10(f));
- The use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand (§ 11.10(g));
- The use of device checks to determine, as appropriate, the validity of the source of data input or operational instruction (§ 11.10(h));
- The use of appropriate controls over certain systems documentation (§ 11.10(k));and
- The corresponding controls of § 11.30.

We are proposing to exempt the submission of electronic content of labeling from certain part 11 requirements because we believe these part 11 requirements are not critical to ensure the quality of the content of labeling that would be submitted under this proposed rule and we do not think it is necessary for industry to expend resources on controls that are not necessary to further the goals of part 11. For example, validation for the system used to generate the labeling record is not necessary because the manufacturer's

verification that the information in the labeling record is accurate serves the same objective. Our review of the content of labeling is based on the version of the labeling record submitted to us. Earlier versions of the record, as well as changes made to the earlier versions, are not relevant to our analysis. In addition, our registration and listing database is designed to ensure the authenticity, integrity, and confidentiality of this information. As mentioned, we would control the database, you would only be able to enter and/or revise information in your own account, and the database would contain records of the information from which we could generate accurate and complete copies. Thus, controls related to the creation, modification, and maintenance of the content of labeling are not needed.

For the content of labeling and advertisements and other labeling, we recognize that there are some differences with respect to the exemptions from part 11 requirements provided in this proposal (that is, § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30), and the part 11 requirements set forth in the part 11 guidance for which we intend to exercise enforcement discretion (that is, § 11.10(a) through (c), (e), and (k)(2), and any other corresponding requirements in § 11.30)). Although the proposal does not provide an exemption from § 11.10(b) for the content of labeling and advertisements and other labeling, the part 11 guidance announces that we intend to exercise enforcement discretion with respect to that section in the manner described in the guidance.

If this proposed rule is finalized, we intend to identify in docket number 92S–0251 the registration and listing information and the content of labeling specified previously as the types of records that we are prepared to accept in electronic format.

8. What Language Would Be Used to Provide Registration and Listing Information?

Under proposed § 207.61(b), we would require that all registration and listing information be submitted in the English language. We are also proposing that labeling be submitted in the English language except, as provided under current 21 CFR 201.15(c), when drugs are distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English. In those instances, the predominant language may be substituted for English. We are proposing § 207.61(b) because providing information in languages other than English would lead to problems using the registration and listing computerized database and problems with our review of registration and listing information and the content of labeling. Foreign establishments are currently required to submit all registration and listing information in the English language under current § 207.40(b). Because all domestic manufacturers, repackers, relabelers, and drug product salvagers currently submit this information in English, and because foreign establishments are already subject to this requirement, we do not believe the proposed requirement would increase the burden on industry.

9. Could the Electronic Format Requirements Be Waived?

Under proposed § 207.65, manufacturers, repackers, relabelers, and drug product salvagers may request a waiver from the proposed requirement in § 207.61(a) that information be provided to us in electronic format. This proposed waiver provision is consistent with the Medical Device User Fee and Modernization Act of 2002 (Public Law 107–250) which amended section 510 of the act to add section 510(p) to explicitly give the Secretary discretion to require the electronic submission of registration information upon a finding

that electronic receipt of such registration information is feasible, unless the Secretary grants a request for a waiver because the use of electronic means is not reasonable for the person requesting the waiver. Under proposed § 207.65, we may grant a waiver request if the manufacturer, repacker, relabeler, or drug product salvager does not have an e-mail address and access to a computer and an ISP that can access our Web-based registration and listing database and communicate with us. The request must include a telephone number and/or mailing address where we can contact the person making the request. We intend to provide the mailing address for submitting a waiver request in the draft guidance and technical specifications on the electronic submission of registration and listing information.

We do not anticipate many waiver requests because the expenses associated with owning a personal computer, obtaining an e-mail address, and subscribing to Internet access are low. If owning a computer is not possible, however, only access to a computer and an ISP as well as having an e-mail address would be needed to input information electronically in accordance with the registration and listing requirements under this part, including the requirements for obtaining an NDC number. There would be no need for you to maintain data files on disks or other formats; all data would be maintained in our database and accessed electronically via the Internet. We would control the database and the information contained in it, and you would only enter new information and/or revise your own previously submitted information.

In those instances when we grant a request for a waiver, we would provide information on how to submit registration and/or listing information. One option may be to make available a paper form for submitting the required

registration and listing information (including the information required to obtain an NDC number).

F. Miscellaneous

1. What Are the Proposed Requirements for an Official Contact and a United States agent?

Under proposed § 207.69(a), manufacturers, repackers, relabelers, and drug product salvagers that are subject to the registration requirements in proposed part 207 would designate an official contact for each establishment. The official contact would be responsible for:

- Ensuring the accuracy of registration and listing information; and
- Reviewing, disseminating, routing, and responding to communications from us.

We are proposing to require an official contact to facilitate communications between you and us and to help ensure compliance with the registration and listing requirements. On numerous occasions, we have found it difficult to contact certain manufacturers, repackers, relabelers, and drug product salvagers to discuss registration and listing issues.

In addition to the proposed requirement to designate an official contact, each foreign manufacturer, foreign repacker, foreign relabeler, and foreign drug product salvager would be required, under proposed § 207.69(b), to designate a single United States agent. The United States agent would be responsible for:

- Helping us communicate with the foreign manufacturer, foreign repacker, foreign relabeler, and foreign drug product salvager;
- Responding to questions concerning those drugs that are imported or offered for import to the United States; and

- Helping us schedule inspections.

We would not object if the same individual serves as both the United States agent and the official contact for a foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager, or if the same individual serves as the United States agent for more than one foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager.

We are proposing that each foreign manufacturer, foreign repacker, foreign relabeler, and foreign drug product salvager designate a single United States agent. (We note, however, the United States agent may be a company comprised of more than one person). As we explained in the final rule entitled ''Foreign Establishment Registration and Listing'' (66 FR 59138 at 59140), we interpret section 510(i) of the act as allowing only one United States agent for each foreign establishment because section 510(i) of the act refers to the United States agent in singular, rather than plural, terms. We also explained in that final rule (66 FR 59138 at 59141) that we interpret section 510(i) of the act as requiring that the United States agent must be in the United States. These proposed provisions are also consistent with the use of ''U.S. agent'' in the interim final rule entitled ''Registration of Food Facilities Under the Public Health Security and Bioterrorism Preparedness Act of 2002'' (68 FR 58894 at 58915, October 10, 2003).

Currently, the provisions concerning a United States agent, as well as other requirements for foreign manufacturers, foreign repackers, foreign relabelers, or foreign drug product salvagers, are set forth under § 207.40. In addition, current § 207.3(a)(11) defines United States agent as a person residing or maintaining a place of business in the United States whom a foreign

establishment designates as its agent. The definition states that ''United States agent'' excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present. We are proposing to revoke current §§ 207.3(a)(11) and 207.40 and include these requirements (as revised), for example, under proposed §§ 207.1, 207.9, 207.13, 207.17, 207.33, 207.41, 207.61, and 207.69.

Under proposed § 207.69(b)(2) through (b)(4), the United States agent would be required to reside or maintain a place of business in the United States. A United States agent may not be a mailbox, answering machine or service, or other place where a person acting as the United States agent is not physically present. If we are unable to contact the foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager directly or expeditiously, we may provide information or documents to the United States agent, which we would consider equivalent to providing the same information or documents to the foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager.

We are proposing the requirements for a United States agent to facilitate communications between you and us and to help ensure compliance with the registration and listing requirements. On numerous occasions, we have found it difficult to contact certain foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers, resulting in their drugs being detained because certain registration and/or listing issues have not been resolved.

2. What Legal Status Is Conferred by Registration and Listing?

Under proposed § 207.77(a), registration of an establishment or listing of a drug does not denote approval of the establishment, the drug, or other drugs

of the establishment, nor does it mean that a product may be legally marketed. Any representation that creates an impression of official approval or that a drug is approved or is legally marketable because of registration or listing would be misleading and would constitute misbranding under section 502 of the act. To clarify and consolidate current regulations, we are proposing to revise and move a similar provision in current § 207.39 to proposed §§ 207.77(a) and 207.37. Current § 207.39 states that registration of a drug establishment or drug wholesaler, assignment of a registration number, or assignment of an NDC number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of registration or possession of a registration number or NDC number is misleading and constitutes misbranding. The registration provisions in current § 207.39 would be included in proposed § 207.77(a), and the NDC number provisions in current § 207.39 would be included in proposed § 207.37. Proposed § 207.37(c) states that the NDC number must not be used to denote FDA approval of that drug. We are proposing to include in proposed § 207.77(a) that listing a drug would not denote approval of the drug and that any such representation would be misleading and constitute misbranding.

Under proposed § 207.77(b), assignment of an establishment registration number, inclusion of a drug in our database of drugs, or assignment of an NDC number does not denote approval of the establishment or the drug or any other drugs of the establishment, nor does it mean that the drug may be legally marketed. Any representation that creates an impression that a drug is approved or is legally marketable because it appears in our database of drugs, has been assigned a NDC number, or the establishment has been assigned an establishment registration number, is misleading and constitutes misbranding.

Failure to comply with proposed § 207.37 also constitutes misbranding. We are proposing to add this provision to clarify that a drug's marketing approval status is determined, for example, under section 505 or 512 of the act, section 351 of the PHS Act, and parts 314, 514 (21 CFR part 514), and 601 of the regulations, and not under section 510 of the act or part 207 of the regulations.

Under proposed § 207.77(c), neither registration nor listing constitutes a determination by FDA that a product is a drug as defined by section 201(g)(1) of the act. This provision reflects a revision and relocation of current § 207.20(e) to proposed § 207.77(c). Current § 207.20(e) states that registration and listing do not constitute an admission, agreement, or determination that a product is a drug as defined under section 201(g) of the act. Proposed § 207.77(c) also states that registration and listing may be evidence that a facility is manufacturing, repacking, relabeling, or salvaging drugs or that a product is a drug. Thus, the proposed rule revises current § 207.20(e) such that, while neither registration nor listing constitutes a determination by FDA that a product is a drug as defined by the act, registration and listing may be evidence that a facility is manufacturing, repacking, relabeling, or salvaging drugs or that a product is a drug.

FDA is proposing to delete the statement in current § 207.35(c) that validation of registration and the assignment of a drug listing number do not, in themselves, establish that the holder of the registration is legally qualified to deal in such drugs. As explained in sections IV.B and IV.C of this document, FDA is proposing to discontinue the validation of registration. As explained previously in this document, the provision on the legal status of registration and listing is included in proposed § 207.77, and proposed § 207.37(c) sets

forth restrictions pertaining to the use of the NDC number (e.g., the NDC number must not be used to denote FDA approval of the drug).

3. What Registration and Listing Information Would Be Made Available for Public Disclosure?

Current § 207.37 pertains to the public availability of registration and listing information. Proposed § 207.81 would revoke, in part, and revise current § 207.37. The heading ''Inspection of registrations and drug listings'' in current § 207.37 would be changed to ''What registration and listing information will we make available for public disclosure?'' This heading would more accurately describe the scope of the provision in that the provision relates to the type of registration and listing information that we intend to make available for public disclosure.

The proposal would revoke the introductory text of current § 207.37(a), which includes a description of the types of forms available for inspection, the addresses at which such forms can be inspected, and the addresses that requests for verification of registration numbers and requests for locations of registered establishments can be directed. We are proposing to revoke this introductory text because these forms would no longer be used under the proposed scheme. Instead, we intend to make most information that is available for public disclosure accessible via the Internet. This initiative would be consistent with the GPEA and would also help to reduce the number of Freedom of Information Act (5 U.S.C. 552) requests we receive for registration and listing information. Accordingly, we are also proposing to revoke current § 207.37(b), which sets forth the address to which requests for information about drug registration and listing can be directed. We note that persons may

still submit Freedom of Information Act requests to the agency for drug registration and listing information that is not available on the Internet.

Current § 207.37(a)(1) sets forth 11 categories of information that, when compiled, will be available for public disclosure. Proposed § 207.81(a) would simplify this section to reference the following information as generally available for public disclosure: All registration information and, after a drug is listed, all information obtained for that drug under proposed §§ 207.33, 207.49, 207.53, and 207.54, except for that information obtained under proposed §§ 207.33(d)(1)(ii) and 207.54(b)(1) or the information that would otherwise be exempt from disclosure under proposed § 207.81(b) or (c).

Proposed § 207.81(a) would add registration information to the list of the types of information that would generally be considered to be publicly available. Registration information is currently available for public inspection as referenced in § 207.37(a).

For various reasons, proposed § 207.81(a) would not include certain specific categories of information that are listed in current § 207.37. The provision relating to a list of all drug products arranged by labeled indications or pharmacological category would not be included in the proposal because we currently do not compile or index drug registration and listing information by labeled indication. The provisions related to a list of drug products newly marketed or for which marketing is resumed, a list of drug products discontinued, and information that has become a matter of public knowledge would be deleted because these categories of information would also be disclosable under the general provision of proposed § 207.81(a).

We are proposing to exempt proposed §§ 207.33(d)(1)(ii) and 207.54(b)(1) from proposed § 207.81(a) because this information may disclose a business

relationship between the manufacturer, repacker, relabeler, or drug product salvager and the business from which they obtained the drug, and may constitute commercial or financial information that is exempt from public disclosure under § 20.61(c). We are proposing to exempt from public disclosure the information collected under proposed § 207.33(d)(1)(ii), which would require that repackers or relabelers, to obtain an NDC number, must provide, among other things, the NDC number assigned to the drug immediately before the drug is received by the repacker or relabeler. We also are proposing to exempt from public disclosure the information collected under proposed § 207.54(b)(1), which would require that drug product salvagers, to list a drug, must provide, among other things, the NDC number assigned to the drug immediately before the drug is received by the drug product salvager.

In addition to these changes, the proposal would make some fundamental changes to the disclosure provision in current § 207.37. We are proposing to add one category of listing information to the list of information that would generally be regarded as publicly available information. Specifically, proposed § 207.81 generally would make available for public disclosure a drug product's inactive ingredients when provided under § 207.33(c)(2)(ii) and (c)(3). When the firm provides the approved application number, we can link to the application and retrieve the names of the inactive ingredients included in the approved application. We will then make the names of the inactive ingredients available to consumers unless they are subject to trade secret protection, as discussed below. Proposed § 207.81 would change the current provision in § 207.37(a)(2). Current § 207.37(a)(2)(ii) and (a)(2)(iii) provide that information on inactive ingredients will not be available for public disclosure (except that any of the information will be available for public disclosure if it has become

a matter of public knowledge or if we find that it would be inconsistent with the protection of the public health).

We are proposing, under § 207.33(c)(2)(ii), to give manufacturers the opportunity at the time of listing to identify inactive ingredients that they consider trade secret. Information identified by the applicant as trade secret would not be routinely posted on the Internet. Public disclosure of inactive ingredients not designated as trade secret at the time of listing would be authorized by the proposed regulations. We would evaluate claims of trade secret protection based on the definition of a trade secret in § 20.61(a) when making disclosure decisions in response to requests made under the Freedom of Information Act for this information and would withhold the information from public disclosure, when appropriate, under § 207.81(c). This evaluation is consistent with how FDA evaluates requests asking for inactive ingredient information that is included in approved U.S. applications. When manufacturers submit the approved application number instead of listing inactive ingredients under proposed § 207.33(c)(2)(ii), they similarly would need to identify any inactive ingredients they considered to be trade secret. Proposed §§ 207.33(c)(2)(ii), 207.81(a), and 207.81(c) would strike a balance between manufacturers' commercial interests and the fact that it would generally be inconsistent with protection of the public health to withhold inactive ingredient information. We expect that manufacturers would only avail themselves of the opportunity to claim trade secret protection in extremely limited circumstances. We note that information in a drug's labeling, including the names of inactive ingredients, is not trade secret information.

The proposal to add information about inactive ingredients to the list of categories considered to be public information is also consistent with section

510(f) of the act. Section 510(f) of the act generally provides that listing information shall be exempt from inspection unless the Secretary finds that such an exemption would be inconsistent with protection of the public health. We find that exempting, among other things, a list of inactive ingredients from public disclosure would be inconsistent with the protection of the public health. It is important for consumers to know the inactive ingredients of the drugs they might be taking because such information can be important in certain situations. For example, some inactive ingredients can trigger allergic reactions in patients. If a particular inactive ingredient appeared to trigger such reactions in an individual, and the name of the inactive ingredient was available to the public, individuals and their caregivers would be able to access such information to prevent potentially serious reactions. Additionally, some inactive ingredients may be particularly toxic to individuals with certain medical conditions and some may exacerbate a person's medical condition. If inactive ingredient information is available for drugs, individuals and their caregivers could get this information and avoid adverse reactions. We could also use inactive ingredients information to help us investigate possible drug contamination, counterfeiting, or adulteration. For example, if a drug appeared to be linked to an unexpected number of adverse drug events or seemed less effective than expected, an analysis of the drug showing the presence of unidentified (i.e., not previously listed) inactive ingredients in that drug could suggest that the drug was adulterated or counterfeit, or that the unidentified inactive ingredient may interfere with the drug's mode of action. Additionally, the presence of an unidentified inactive ingredient in a drug product may suggest contamination or that the drug was not manufactured by the legitimate manufacturer. Generally, we believe that knowing about a drug's inactive

ingredients and having such information readily available in an electronic database is consistent with protection of the public health.

We recognize that because we may make a large amount of registration and listing information publicly available under proposed § 207.81, there may be instances where some of the information authorized by this proposed rule for public disclosure could identify business relationships. We believe that many of these business relationships could be identified currently, but that the electronic registration and listing system may make it somewhat easier to do so. For example, a contractual relationship that might not otherwise be publicly disclosed may be revealed when a manufacturer of a sole source material provides the drug's established name under proposed § 207.33(c)(1)(ii) or when a manufacturer provides registration numbers of each establishment where manufacturing is performed under proposed § 207.49(d). Also, for example, business relationships between private label distributors and manufacturers, repackers, relabelers may be revealed when providing information under § 207.33(c) or (d)(2). However, we believe this would be a rare event and that exemption of the information required by these regulatory provisions from public disclosure would be inconsistent with protection of the public health. For example, we believe that we should not exempt from public disclosure the names of inactive ingredients that would be submitted under proposed § 207.33(c)(2)(ii) because of the remote possibility that the names, along with other information that may be disclosed under this proposal, could reveal a business relationship. We believe that the potential public health benefits of releasing the names of the inactive ingredients justify our decision not to exempt them from public disclosure because they outweigh the remote possibility that a business relationship could be revealed. Therefore we have

concluded that the public interest in disclosure of most registration and listing information supports the proposals in the rulemaking.

We also note that, for foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers, the name of each importer and the names of persons who import a drug or offer a drug for import would be required for registration and we are proposing that this information would be available for public disclosure. Disclosure of this information would be consistent with section 510(f) of the act, which requires that any registration filed be made available for inspection.

We invite comments on which specific registration and listing information should be available for public disclosure. We request that you identify the specific registration and listing information on which you are commenting and explain why you believe the information should or should not be publicly disclosed.

Proposed § 207.81(b) would make one other conforming change to the current disclosure provision. Current § 207.37(a)(2) sets forth three categories of information that will not be available for public disclosure (except that any of the information will be available for public disclosure if it has become a matter of public knowledge or if we find that confidentiality would be inconsistent with protection of the public health). Proposed § 207.81(b) would retain the category treating as nondisclosable any information submitted as the basis upon which it has been determined that a particular drug product is not subject to section 505 or 512 of the act. As explained previously in this document, we are moving two previously nondisclosable categories (now disclosable) regarding information on inactive ingredients to proposed § 207.81(a) that relate to information generally regarded as publicly available.

Those categories, in current § 207.37(a)(2)(ii) and (a)(2)(iii), would be disclosable under proposed § 207.81(a). Proposed § 207.81(c) would allow FDA to determine, in limited circumstances and on a case-by-case basis, that it would be consistent with protection of the public health and the Freedom of Information Act to exempt from public disclosure specific information in paragraph (a) of this section. As explained previously in this document, we are proposing, under § 207.33(c)(2)(ii), to give manufacturers the opportunity at the time of listing to identify inactive ingredients that they consider trade secret and therefore, prohibited from disclosure under § 20.61. There may be other appropriate reasons for exempting certain drug listing and registration information from public disclosure. For example, FDA may decide for security reasons, and consistent with the Freedom of Information Act, not to publicly disclose the manufacturing site location for certain drugs.

G. Conforming Actions

1. Withdrawal from Sale of Drugs with Approved Marketing Applications

We are proposing to revise our human drug regulations on applications for approval to market a new drug to make them consistent with proposed part 207. Under current § 314.81(b)(3)(iii)(*a*), holders of new drug applications must report to us the withdrawal from sale of a drug product. Under this provision, the information must be submitted on Form FDA 2657 within 15 working days of the drug product's withdrawal from sale. The following information must be submitted: The NDC number; the identity of the drug by established name and by proprietary name; the new drug application number or abbreviated application number; and the date of withdrawal from sale. The reason for withdrawal of the drug from sale is requested but not required to be submitted. Section 314.81(b)(3)(iii)(*b*) provides the address for submitting

the completed form, and § 314.81(b)(3)(iii)(*c*) states that reporting under § 314.81(b)(3)(iii) constitutes compliance with the requirements under current § 207.30(a) to report ''at the discretion of the registrant when the change occurs.''

We are proposing to revise this requirement to be consistent with the requirements in proposed §§ 207.57 and 207.61. Proposed § 314.81(b)(3)(iii)(*a*) would provide that within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are manufacturers, repackers, or relabelers subject to proposed part 207 would be required to submit certain information about the withdrawn drug in electronic format, in accordance with the applicable requirements described in § 207.61(a).

Under proposed § 314.81(b)(3)(iii)(*b*), applicants who are not subject to proposed part 207 would submit the information specified under proposed § 314.81(b)(3)(iii)(*a*) on the appropriate form, which would be submitted to the Drug Listing Branch, Food and Drug Administration, CDER Central Document Room, 5901B Ammendale Rd., Beltsville, MD 20705–1266. We are proposing to require applicants who are subject to proposed part 207 to submit the information specified under proposed § 314.81(b)(3)(iii)(*a*) in electronic format, in accordance with the applicable requirements described in proposed § 207.61(a). Consistent with the proposed requirements in § 207.61, and discussed in section IV.E.3 of this document, these applicants would be required to obtain an account number, user name, and password to sign onto the electronic drug registration and listing system. We are considering this requirement because we believe the electronic submission of this information would be more efficient for applicants than the preparation and mailing of paper forms. Electronic submission would also make our review and

processing of this information more efficient. We request comments on requiring applicants who are not subject to proposed part 207 to submit electronically the information specified in proposed § 314.81(b)(3)(iii)(*a*).

Currently, we do not have a provision in our regulations for reporting withdrawals from sale of biological products. We are proposing to revise our regulations to include such a provision. Under proposed § 601.2(f), holders of BLAs must report to us, electronically in accordance with part 207, the withdrawal from sale of licensed biological products. The information must be submitted to us within 30 working days of the biological product's withdrawal from sale. The following information would be submitted: The holder's name; product name; BLA number; the NDC number, if applicable; and the date of withdrawal from sale. The reason for the withdrawal of the biological product would be requested but not required.

2. Proposed Revisions to Other Regulations

In addition to the revisions of regulations discussed previously in this document, we are also proposing revisions to other FDA regulations as a result of this proposed rule. The proposed revisions are as follows:

- Section 20.100(c)(9): The reference to § 207.37 would be changed to § 207.81 to correspond to the proposed provision on disclosure of registration and listing information.
- Section 20.116: The reference to § 207.37 would be changed to § 207.81 to correspond to the proposed provision on disclosure of registration and listing information.
- Section 201.1(f): The reference to § 207.3(b) would be changed to § 207.1 to correspond to the proposed definitions section.

- Section 330.1(b): As explained in section IV.C.5 of this document, the NDC number would be required to appear on OTC drug labels.

- Section 514.111(a)(12): As explained in section IV.B.2 of this document, we would refuse to approve an NADA if the drug is manufactured in an establishment that is not registered.

- Section 515.10(b)(8): The reference to ''§§ 207.20 and 207.21'' would be changed to ''part 207'' as a result of the proposed reorganization and revision of part 207.

- Section 607.3(b): Current § 607.3(b) defines ''blood and blood product'' to mean a drug which consists of human whole blood, plasma, or serum or any product derived from human whole blood, plasma, or serum, hereinafter referred to as ''blood product.'' The current definition also states that ''blood and blood product'' also means those products that meet the definition of a device under the act and that are licensed under section 351 of the PHS Act. We are proposing to amend this definition to add the phrase ''as well as licensed biologic components used in the manufacture of a licensed device.'' This proposed revision is intended to clarify that licensed biologic components used in the manufacture of a licensed device are covered under the definition of ''blood and blood product'' and that manufacturers of licensed biologic components used in the manufacture of a licensed device are required to register and list under part 607. It is important that manufacturers of licensed biologic components used in the manufacture of a licensed device register and list because licensed devices are used to ensure the safety of blood and blood products.

- Section 607.3(k): We are proposing to define ''importer'' as a company or individual in the United States that is the owner, consignee, or recipient

of the foreign establishment's blood product that is imported into the United States.

- Section 607.7: Current § 607.7(a) states that all owners or operators of establishments that engage in the manufacturing of blood and blood products are required to register, and that registration and listing of blood and blood products must comply with part 607. Current § 607.7(a) also states that registration does not permit blood banks or similar establishments to ship blood products in interstate commerce. Current § 607.7(b) and (c) explain how the registration form for these establishments may be obtained from CBER and where the completed form should be mailed to.

We are proposing to delete current § 607.7(b) and (c) and explain where to obtain establishment registration forms and where to send completed forms in proposed § 607.22(b) (discussed below in this document). We are deleting these provisions from current § 607.7 to eliminate redundancy in part 607. We are proposing to redesignate paragraph (a) in § 607.7 as the introductory paragraph.

- Section 607.22: For clarity, we are proposing to revise the title of current § 607.22—''How and where to register establishments and list blood products''—to read ''How to register blood product establishments and list blood products.''

Current § 607.22(a) requires the first registration of an establishment to be on Form FDA 2830 (Blood Establishment Registration and Product Listing), provides the mailing address where the Form FDA 2830 may be obtained and submitted, states that FDA will furnish a Form FDA 2830 before November 15 of each year to establishments whose registration for that year was validated under § 607.35, and states that the completed form must be mailed to us before

December 31 of that year. Current § 607.22(b) states that the first and subsequent blood product listing updates shall be on Form FDA 2830.

We are proposing to reorganize and update current § 607.22 as follows: Initial and subsequent registrations and product listings by a blood product establishment for blood products would be on Form FDA 2830 (Blood Establishment Registration and Product Listing). Manufacturers may obtain, complete, and submit the form in the following ways:

- Complete the form online and submit electronically at *http://www.fda.gov/cber/blood/bldreg.htm*; this information must be submitted in accordance with part 11 of this chapter, except for the requirements in § 11.10(b), (c), and (e) and the corresponding requirements in § 11.30 (as discussed in section IV.E.7 of this document); or
- Download the form from the Internet at *http://www.fda.gov/cber/blood/bldreg.htm*, and mail the completed form to the address in § 607.22(e); or
- Request the form by mail using the address in § 607.22(e), or by e-mail at *bloodregis@cber.fda.gov*, and mail the completed form to the address in § 607.22(e).
- For subsequent annual registration renewals, we will furnish the establishment's most recent Form FDA 2830 before November 15 of each year. The updated Form FDA 2830 would be submitted to us before December 31 of that year.
- Forms may be requested from and mailed to: Center for Biologics Evaluation and Research (HFM–370), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

We are proposing these revisions to current § 607.22 to make the registration and blood product listing process for blood product establishments

more efficient by utilizing the latest technology for completing and submitting registration and listing forms.

- Section 607.25(b)(1): Current § 607.25(b) lists the information required for blood product listing. Currently, blood establishments that manufacture bulk product substances and finished dosage forms must list their products under part 607 and also under part 207 to receive a NDC number. We are proposing to revise current § 607.25(b)(1) to delete the phrase ''including bulk product substances as well as finished dosage forms'' because we are proposing to require these manufacturers to list only under part 207 to reduce their reporting burden. In addition, we are proposing to add the phrase ''if any'' after ''by proprietary name'' because not all of these products have a proprietary name. We are also proposing to delete the reference to Form FDA 2250 (National Drug Code Directory Input) because this form is no longer being used by CDER or CBER.

- Section 607.35: For clarity, we are proposing to revise the title of current § 607.35—''Notification of registrant; blood product establishment registration number and NDC Labeler Code''—to read ''Blood product establishment registration number.''

Current § 607.35(a) states that FDA will send a validated copy of Form FDA 2830 as evidence of registration to the registering establishment, and that FDA will assign a permanent registration number to each establishment. We are proposing to revoke the provision that we will send a validated copy of Form FDA 2830 to blood establishments. All registration information will be available to registered blood establishments on the Internet; therefore, to increase efficiency we will discontinue sending the validated copy of Form FDA 2830. Proposed § 607.35 would state only that we will assign a permanent

registration number to each blood product establishment registered in accordance with part 607.

Current § 607.35(b) states that if a registered blood product establishment has not previously participated in the NDC system or in the National Health Related Items Code system, the NDC numbering system must be used. We are proposing to revoke this section because blood product manufacturers that obtain a NDC number for their products will register under proposed part 207 and not under part 607. We are also proposing to delete reference to the National Health Related Items Code system because it is a voluntary system for medical device manufacturers that is managed by CDRH.

Current § 607.35(c) states that although establishment registration and blood product listing are required, validation of registration and the assignment of a NDC Labeler Code do not, in themselves, establish that the holder of the registration is legally qualified to deal in such products. We are proposing to incorporate into proposed § 607.39 the provision that validation of registration does not establish that the holder of the registration is legally qualified to deal in such products. We are proposing to revoke the provision concerning the assignment of a Labeler Code because the NDC number requirements would be covered under proposed part 207 and not proposed part 607.

- Section 607.37(a): Current § 607.37(a) states that a copy of Form FDA 2830 will be available for inspection under section 510(f) of the act at FDA headquarters and at each of the FDA district offices. In addition, current § 607.37(a) states that FDA will provide by mail verification of registration number and location of a registered establishment. Current § 607.37(a) also gives examples of the blood product listing information that will be available for public disclosure.

Under proposed § 607.37(a), information submitted on Form FDA 2830 would be available for inspection at *http://www.fda.gov/cber/blood/bldregdata.htm* and at the Department of Health and Human Services, Food and Drug Administration, Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

- Section 607.39: Current § 607.39 states that registration of an establishment or assignment of a registration number or assignment of a NDC number does not in any way denote approval of the firm or its products, and that any representation that creates an impression of official approval because of registration is misleading and constitutes misbranding.

We are proposing to revise current § 607.39 to delete the reference to the NDC number, to incorporate the provision from current § 607.35(c) that validation of registration does not establish that the holder of registration is legally qualified to deal in blood products, and to revise the title accordingly. Manufacturers of blood products that obtain a NDC number would not register under proposed part 607; therefore, it is not necessary to reference NDC numbers under this part. Proposed § 607.39 would state that registration of an establishment, validating registration, or obtaining a registration number does not in any way denote approval of the firm or its products nor does it establish legal authority for the holder of the registration number to market such products.

- Section 607.40: As discussed in section IV.A.2 of this document, we are proposing to revoke current § 207.40, establishment registration and drug listing requirements for foreign establishments, and revise and move the requirements elsewhere in proposed part 207. Consistent with the revisions

to proposed part 207, we are proposing to revoke certain provisions of current § 607.40(a) and (b). We are proposing to revoke the exemption in current § 607.40(a) relating to foreign establishments whose blood products enter a foreign trade zone and are reexported from that foreign trade zone without having entered United States commerce. We are also proposing to revoke, in part, current § 607.40(b), which allows for blood, blood components, Source Plasma, or Source Leukocytes, or a component or part, under section 801(d)(4) of the act, to be imported or offered for import into the United States even if the product is not listed and manufactured, prepared, propagated, compounded, or processed at a registered foreign establishment. We are proposing to eliminate these two exemptions because of certain statutory changes that have occurred since the publication of the final rule on foreign establishment registration and listing. Those changes include, as discussed in section IV.A.2 of this document, enactment of the Bioterrorism Act, which reflects Congress' desire to increase the Nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies. Consistent with the provisions of the Bioterrorism Act, we are proposing to amend § 607.40(c) to require each foreign establishment to submit the name of each importer of the foreign establishment's blood products that is known to the establishment, and the name of each person who imports or offers for import such blood products to the United States.

We are also proposing to amend §§ 607.40(d) and (d)(3) to require each foreign establishment to submit the telephone and fax numbers and e-mail address of its United States agent. The name, address, and phone number of the United States agent is required under current § 607.40(d). We are proposing to require the submission of the information on importers and persons who

import because the Bioterrorism Act requires foreign establishments to submit, among other things, the name of each importer of such blood product that is known to the establishment, and the name of each person who imports or offers for import such blood product to the United States for purposes of importation. In addition to the name, the proposal would require that the address, telephone and fax numbers, and e-mail address of each importer and of each person who imports or offers for import be provided to enable us to contact these persons. Proposed § 607.40(d)(3) would also require the foreign establishment to report changes in the United States agent's name, address, telephone and fax numbers, and e-mail address to FDA within 30 calendar days of the change. Currently, § 607.40(d)(3) requires notification to FDA within 10-business days.

Proposed § 607.40(e) would make electronic registration and listing mandatory for foreign establishments, consistent with proposed § 607.22(a). For those foreign establishments that are unable to register and list blood products using the electronic registration and listing system, we are proposing waiver provisions in § 607.40(f)(1). We may grant a request for a waiver from a foreign establishment if the foreign establishment does not have an e-mail address and access to a computer and an Internet service provider that can access the electronic registration and listing system. We are also proposing in § 607.40(f)(2) to require that waiver requests include a telephone number and/or mailing address where the agency can contact the foreign establishment. In addition, we are proposing to add § 607.40(f)(3) which states that if the agency grants the waiver request, the foreign establishment must register and list blood products in accordance with § 607.22(b) or (c).

- Section 607.65: Proposed § 607.65 would be amended by redesignating paragraph (f) as paragraph (g) and by adding new paragraph (f). Proposed § 607.65(f) would exempt certain blood product manufacturers from registration and product listing under part 607 because FDA is proposing that manufacturers of these products register and list only under part 207. Because these products routinely bear NDC numbers, FDA believes it is more efficient to have manufacturers of these products register and list under part 207. The products that would be included under proposed § 607.65(f) are all plasma derivatives such as albumin, Immune Globulin, Factor VIII, and Factor IX, bulk product substances such as fractionation intermediates or pastes, recombinant versions of plasma derivatives or animal derived plasma derivatives. Under current § 607.20, manufacturers of plasma derivatives such as albumin, Immune Globulin, Factor VIII, and Factor IX are required to register and list under part 607 and under part 207 to obtain an NDC number.

- Sections 1271.1(a), 1271.1(b)(2), and 1271.20: We are proposing to amend §§ 1271.1(a), 1271.1(b)(2), and 1271.20 by removing ''207.20(f)'' and by adding in its place ''207.9(c)(2)''.

- Section 1271.3: For consistency with parts 207 and 607, we are proposing to define ''importer'' at proposed § 1271.3(mm) to mean a company or individual in the United States that is the owner or consignee or recipient of the foreign establishment's HCT/P that is imported into the United States. For consistency with part 607, we are proposing to define ''United States agent'' at proposed § 1271.3(nn) to mean a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. The definition of ''United States agent'' would exclude mailboxes, answering machines or services, or other places where an individual acting

as the foreign establishment's agent is not physically present. The United States agent would be responsible for helping FDA communicate with you, responding to questions concerning your HCT/Ps that are imported or offered for import to the United States, and helping FDA schedule inspections.

- Section 1271.22: We are proposing to make electronic registration and listing mandatory for HCT/P establishments. As a result, we are proposing to revise current § 1271.22 as follows:

Replace ''Form FDA 3356'' in current § 1271.22(a) with ''the electronic registration and listing system at *http://www.fda.gov/cber/tissue/tisreg.htm*'';

Revise current § 1271.22(b) and (c) to implement the electronic registration and listing system at *http://www.fda.gov/cber/tissue/tisreg.htm* and remove references such as ''Form FDA 3356,'' mailing addresses, and telephone numbers.

In the **Federal Register** of January 19, 2001 (''Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing,'' (66 FR 5447)), FDA announced its intention to develop an electronic submission process for HCT/P registration and listing. The agency has developed such a system and it is currently in use on a voluntary basis.

Consistent with proposed § 207.61(a)(4), proposed § 1271.22(b) states that FDA will periodically issue guidance on how to provide registration and listing information in electronic format (for example, method of transmission, media, file formats, preparation, and organization of files) for HCT/Ps.

Consistent with proposed § 207.61(a)(1), proposed § 1271.22(c) states that HCT/P manufacturers must provide the information under § 1271.22(a) in accordance with part 11, except for the requirements in § 11.10(b), (c), and (e) and the corresponding requirements in § 11.30.

- Section 1271.23: Proposed § 1271.23 would permit HCT/P establishments that do not have an e-mail address and access to a computer and an Internet service provider that can access the Web-based FDA registration and listing database to request a waiver from electronic registration and listing. This is consistent with proposed § 207.65 and the Bioterrorism Act.

- Section 1271.25: We are proposing to amend § 1271.25, ''What information is required for establishment registration and HCT/P listing,'' as follows:

Delete the reference to ''Form FDA 3356'' in current § 1271.25;

Amend current § 1271.25(a)(2) and (a)(3) to require the submission of the telephone and fax numbers and an e-mail address;

Add § 1271.25(a)(5) to require each foreign establishment to also 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 for purposes of importation;

Add proposed § 1271.25(a)(6) to require each foreign establishment to also submit, the name, address, telephone and fax numbers, and e-mail address of its United States agent. Under proposed § 1271.25(a)(6), each foreign establishment would have only one United States agent, and that United States agent must reside or maintain a place of business in the United States. Upon request from FDA, the United States agent must assist us in communications with the foreign establishment, respond to questions concerning the foreign establishment's products that are imported or offered for import into the United States, and assist us in scheduling inspections of the foreign establishment. If we are unable to contact the foreign establishment directly

or expeditiously, we may provide information or documents to the United States agent. The foreign establishment would 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.

Add proposed § 1271.25(d) to clarify that if your HCT/P is regulated as a drug, device, and/or biological product under current § 1271.20, you must submit the information required under part 207 using the procedures under part 1271.

- Section 1271.26: For consistency with proposed § 207.29(a), we are proposing to amend current § 1271.26 to include a change in the United States agent's name, address, telephone and fax numbers, and e-mail address. All changes in proposed § 1271.26 would be reported within 30 calendar days instead of the current requirement to report the change within 5 days.

- Section 1271.37 would be revised to delete the reference to ''Form FDA 3356''.

3. Compliance Verification Reports

On November 26, 2004 (69 FR 68831), FDA withdrew its September 2, 1993, proposal (58 FR 46587; Docket Number 92N–0291) to amend part 207 to require the completion of ''compliance verification reports.'' These reports are printouts of information as reported to FDA on Form FDA 2657 or Form FDA 2658. FDA had periodically mailed to domestic establishments the compliance verification report for listed prescription drugs and requested that the establishments verify or correct the information and return it to the agency within 30 calendar days. The completion of the report served to satisfy, in most cases, the drug listing updates required under current § 207.30(a). FDA provided this service to increase the accuracy of its computerized drug listing

files. Because FDA is now proposing to require the electronic submission of all registration and most listing information, FDA in anticipation of this proposal has already withdrawn the September 2, 1993, proposal and has discontinued the use of the compliance verification reports. Electronic submission of registration and most listing information would make it easier for establishments to register and list. In addition, FDA's electronic registration and listing database would save registration and listing information that was submitted, thereby making it easier for establishments to access, review, and update information.

V. Legal Authority

We have the legal authority to amend our regulations on foreign and domestic establishment registration and listing for human drugs, including drugs that are regulated under a BLA, and animal drugs. The statutory basis for our authority includes sections 201, 301, 501, 502, 503, 505, 506, 506A, 506B, 506C, 510, 512, 513–516, 518–520, 701, 704, 721, 801, and 903 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 360, 360b, 360c–360f, 360h–360j, 371, 374, 379e, 381, and 393); 15 U.S.C. 1451–1561; the PHS Act; and section 122, Public Law 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

Section 510(c) of the act requires every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug to immediately register with the Secretary his name, place of business, and the establishment. The provisions in section 510(b) and (d) of the act require annual registration and registration of additional establishments, respectively. Section 510(i) of the act requires any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or

processing of a drug that is imported or offered for import into the United States to register with the Secretary by providing certain information. These provisions, together with section 701(a) of the act (among others), authorize us to require the submission of the registration information specified in the proposal. The information specified in this proposal would help us identify who is manufacturing, repacking, relabeling, or salvaging drugs and where those operations are being performed. In addition, some information (e.g., official contact information) would help us communicate with establishments more effectively and schedule inspections more efficiently.

Section 510(j)(1) of the act requires every person who registers to file with the Secretary, at the time of registration, a list of all drugs that are being manufactured, prepared, propagated, compounded, or processed by the registrant for commercial distribution. That list must be prepared in the form and manner prescribed by the Secretary and must be accompanied by a copy of labeling (or the label and package insert) and, in some cases, advertising. Section 510(j)(2) of the act requires listing information updates every June and December. This listing information gives us a current inventory of marketed drugs. These provisions of the act and others, together with section 701(a) of the act, provide authority for requiring the submission of listing information set forth in this proposal. The drug listing information specified in this proposal would help us: (1) Develop a more current, robust inventory of drugs as a counter-terrorism measure; (2) more effectively administer our postmarketing surveillance programs; (3) facilitate recalls of products; (4) identify drugs or ingredients in short supply in the event of a national emergency; and (5) identify drugs marketed in violation of the law.

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 RULE[1]

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

[1]Based 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 undertainty 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 x 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 x 0.167 hours x $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 x 2.5 hours x $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 x 1 hour x $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 products[12] 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 employees x $150) + (2 employees x 6 hours x $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 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.

(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:

§ 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.

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

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.

(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.

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.

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

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.

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;

(4) Submit any material changes in any information previously submitted pursuant to §§ 207.49, 207.53, 207.54, 207.55, or this section; or

(5) Certify that no changes have occurred if no changes have occurred since the last review and update. If a drug is discontinued and we have received the information required under paragraph (b)(2) of this section, no further certifications are necessary for the discontinued drug.

SUBPART E—ELECTRONIC FORMAT FOR REGISTRATION AND LISTING

§ 207.61 How is registration and listing information provided to FDA?

(a) *Electronic format.* (1) Manufacturers, repackers, relabelers, and drug product salvagers that are subject to the registration and listing requirements of this part must provide the following information to us by using our electronic drug registration and listing system, in accordance with part 11 of this chapter, except for the requirements in § 11.10(b), (c), and (e) and the corresponding requirements in § 11.30:

(i) Establishment registration information in §§ 207.25 and 207.29;

(ii) Information required for an NDC number in § 207.33; and

(iii) Drug listing information in §§ 207.49 (except paragraphs (g) and (h)), 207.53 (except paragraphs (d) and (e)), 207.54, 207.55, and 207.57.

(2) The content of labeling required under § 207.49(g)(1) through (g)(3) must be provided to us in an electronic format, in accordance with part 11 of this chapter, except for the requirements in § 11.10(a), (c) through (h), and (k) and the corresponding requirements in § 11.30. The NDC number must also be provided with the content of labeling for each drug.

(3) Advertisements and labeling (other than the content of labeling) required under §§ 207.49(g) and (h) and 207.53(d) and (e) may be provided to us in paper or electronic format in accordance with part 11 of this chapter, except for the requirements in § 11.10(a), (c) through (h), and (k) and the corresponding requirements in § 11.30. The NDC number must also be provided with such advertisements and labeling for each drug.

(4) The information provided in electronic format must be in a form that we can process, review, and archive. We may periodically issue guidance on how to provide registration and listing information in electronic format (for example, method of transmission, media, file formats, preparation and organization of files).

(b) *English language*. Registration and listing information must be provided in the English language. Labeling must also be provided in the English language, except as provided in § 201.15(c) of this chapter.

§ 207.65 How is a waiver from the electronic format requirement requested?

(a) If the information under § 207.61(a) cannot be submitted electronically, a waiver may be requested. We may grant a waiver request if the manufacturer, repacker, relabeler, or drug product salvager does not have an e-mail address and access to a computer and an Internet service provider that can access our electronic drug registration and listing system.

(b) Waiver requests must include a telephone number and/or mailing address where we can contact the manufacturer, repacker, relabeler, or drug product salvager.

(c) If we grant the waiver request, we will provide information on how to submit registration and/or listing information.

SUBPART F—MISCELLANEOUS

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

(a) *Official contact.* Manufacturers, repackers, relabelers, and drug product salvagers that are subject to the registration requirements of this part must designate an official contact for each establishment. The official contact is responsible for:

(1) Ensuring the accuracy of registration and listing information; and

(2) Reviewing, disseminating, routing, and responding to communications from us.

(b) *United States agent.* (1) Each foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager must designate a single United States agent. The United States agent is responsible for:

(i) Helping us communicate with the foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager;

(ii) Responding to questions concerning those drugs that are imported or offered for import to the United States; and

(iii) Helping us schedule inspections.

(2) The United States agent must reside or maintain a place of business in the United States.

(3) A United States agent may not be a mailbox, answering machine or service, or other place where a person acting as the United States agent is not physically present.

(4) If we are unable to contact a foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager directly or expeditiously, we may provide information or documents to the United States agent. We will consider such an action to be equivalent to providing the same information

or documents to the foreign manufacturer, foreign repacker, foreign relabeler, or foreign drug product salvager.

§ 207.77 What legal status is conferred by registration and listing?

(a) Registration of an establishment or listing of a drug does not denote approval of the establishment, the drug, or other drugs of the establishment, nor does it mean that a product may be legally marketed. Any representation that creates an impression of official approval or that a drug is approved or is legally marketable because of registration or listing is misleading and constitutes misbranding.

(b) Assignment of an establishment registration number, inclusion of a drug in our database of drugs, or assignment of an NDC number does not denote approval of the establishment or the drug or any other drugs of the establishment, nor does it mean that the drug may be legally marketed. Any representation that creates an impression that a drug is approved or is legally marketable because it appears in our database of drugs, has been assigned a NDC number, or the establishment has been assigned an establishment registration number, is misleading and constitutes misbranding. Failure to comply with § 207.37 also constitutes misbranding.

(c) Neither registration nor listing constitutes a determination by FDA that a product is a drug as defined by section 201(g)(1) of the act. Registration and listing may, however, be evidence that a facility is manufacturing, repacking, relabeling, or salvaging drugs or that a product is a drug.

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

(a) Except as provided in paragraphs (b) and (c) of this section, the following information will be made available for public disclosure upon request or at our own discretion:

(1) All registration information; and

(2) After a drug is listed, all information obtained for that drug under §§ 207.33, 207.49, 207.53, and 207.54, except for that information obtained under 207.33(d)(1)(ii) and 207.54(b)(1).

(b) Unless information is publicly available or we find that confidentiality would be inconsistent with the protection of the public health, we will not make publicly available any information submitted as the basis upon which it has been determined that a particular drug product is not subject to section 505 or 512 of the act.

(c) We may determine, in limited circumstances and on a case-by-case basis, that it would be consistent with the protection of the public health and the Freedom of Information Act to exempt from public disclosure specific information in paragraph (a) of this section. In such instances, a manufacturer, repacker, relabeler, or drug product salvager must demonstrate that specific information is exempt or is otherwise prohibited by law from public disclosure. If we agree, we will not make such information publicly available.

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

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

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

9. Section 314.81 is amended by revising paragraph (b)(3)(iii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(3) * * *

(iii) *Withdrawal of approved drug product from sale.*

(*a*) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are manufacturers, repackers, or relabelers subject to part 207 of this chapter must submit the following information about the drug in electronic format, in accordance with the applicable requirements described in § 207.61(a):

(*1*) The National Drug Code (NDC) number;

(*2*) The identity of the drug by established name and by proprietary name, if any;

(*3*) The new drug application number or abbreviated application number;

(*4*) The date of withdrawal from sale. We request that the reason for withdrawal of the drug from sale be included with the information.

(*b*) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are not subject to part 207 of this chapter must submit the information listed in paragraphs (*a*)(*1*) through (*a*)(*4*) of this section. The information must be submitted on the appropriate form, which must be submitted to the Drug Listing Branch, Food and Drug Administration, CDER Central Document Room, 5901B Ammendale Rd., Beltsville, MD 20705–1266.

* * * * *

§ 314.125 [Amended]

10. Section 314.125 is amended in paragraph (b)(11) by removing the words ‘‘or processed’’.

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

11. The authority citation for 21 CFR part 330 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

12. Section 330.1 is amended by revising paragraph (b) to read as follows:

§ 330.1 General conditions for general recognition as safe, effective, and not misbranded.

* * * * *

(b) The establishment(s) in which the drug is manufactured is registered, and the drug is listed, in compliance with part 207 of this chapter. The appropriate National Drug Code (NDC) number must appear on the drug's label in accordance with §§ 201.2, 207.33, and 207.37 of this chapter.

* * * * *

PART 514—NEW ANIMAL DRUG APPLICATIONS

13. The authority citation for 21 CFR part 514 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e, 381.

14. Section 514.111 is amended by adding paragraph (a)(12) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(12) The drug will be produced in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and part 207 of this chapter.

* * * * *

PART 515—MEDICATED FEED MILL LICENSE

15. The authority citation for 21 CFR part 515 continues to read as follows:

Authority: 21 U.S.C. 360b, 371.

§ 515.10 [Amended]

16. Section 515.10 is amended in paragraph (b)(8) by removing the phrase ''§§ 207.20 and 207.21'' and by adding in its place the phrase ''part 207''.

PART 601—LICENSING

17. The authority citation for 21 CFR part 601 continues to read as follows:

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

18. Section 601.2 is amended by adding paragraph (f) to read as follows:

§ 601.2 Applications for biologics licenses; procedures for filing.

* * * * *

(f) *Withdrawal from sale of approved biological products.* A holder of a biologics license application (BLA) must report to FDA, electronically in accordance with part 207 of this chapter, the withdrawal from sale of an approved biological product. The information must be submitted to FDA within 30 working days of the biological product's withdrawal from sale. The following information must be submitted: The holder's name; product name; BLA number; the National Drug Code number, if applicable; and the date of withdrawal from sale. The reason for the withdrawal of the biological product is requested but not required to be submitted.

PART 607—ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS

19. The authority citation for 21 CFR part 607 continues to read as follows:

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

20. Section 607.3 is amended by revising the second sentence in paragraph (b), and by adding new paragraph (k) to read as follows:

§ 607.3 Definitions.

* * * * *

(b) * * * For the purposes of this part only, blood and blood product also means those products that meet the definition of a device under the Federal Food, Drug, and Cosmetic Act and that are licensed under section 351 of the Public Health Service Act, as well as licensed biologic components used in the manufacture of a licensed device.

* * * * *

(k) *Importer* means a company or individual in the United States that is the owner, consignee, or recipient of the foreign establishment's blood product that is imported into the United States.

21. Section 607.7 is revised to read as follows:

§ 607.7 Establishment registration and product listing of blood banks and other firms manufacturing human blood and blood products.

All owners or operators of establishments that engage in the manufacturing of blood products are required to register, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act. Registration and listing of blood products shall comply with this part. Registration does not permit any blood bank or similar establishment to ship blood products in interstate commerce.

22. Section 607.22 is revised to read as follows:

§ 607.22 How to register blood product establishments and list blood products.

Initial and subsequent registrations and product listings by a blood product establishment for blood products must be on Form FDA 2830 (Blood Establishment Registration and Product Listing). Manufacturers may obtain, complete, and submit the form in the following ways:

(a) Complete the form online and submit electronically at *http://www.fda.gov/cber/blood/bldreg.htm*; this information must be submitted in accordance with part 11 of this chapter, except for the requirements in § 11.10(b), (c), and (e), and the corresponding requirements in § 11.30; or

(b) Download the form from the Internet at *http://www.fda.gov/cber/blood/bldreg.htm*, and mail the completed form to the address in § 607.22(e); or

(c) Request the form by mail using the address in § 607.22(e), or by e-mail at *bloodregis@cber.fda.gov*, and mail the completed form to the address in § 607.22(e).

(d) For subsequent annual registration renewals, FDA will furnish the establishment's most recent Form FDA 2830 before November 15 of each year. The updated Form FDA 2830 must be submitted to FDA before December 31 of that year.

(e) Forms may be requested from and mailed to: Center for Biologics Evaluation and Research (HFM–370), 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

23. Section 607.25 is amended by revising paragraph (b)(1) to read as follows:

§ 607.25 Information required for establishment registration and blood product listing.

* * * * *

(b) * * *

(1) A list of blood products by established name as defined in section 502(e) of the act and by proprietary name, if any, which are being manufactured for commercial distribution and which have not been included in any list previously submitted on Form FDA 2830 (Blood Establishment Registration and Product Listing).

* * * * *

24. Section 607.35 is revised to read as follows:

§ 607.35 Blood product establishment registration number.

A permanent registration number will be assigned to each blood product establishment registered in accordance with this part.

25. Section 607.37 is amended by revising the introductory text of paragraph (a) to read as follows:

§ 607.37 Inspection of establishment registrations and blood product listings.

(a) Information submitted on the Form FDA 2830 (Blood Establishment Registration and Product Listing) will be available for inspection under section 510(f) of the act, on the Internet at *http://www.fda.gov/cber/blood/bldregdata.htm*, and at the Department of Health and Human Services, Food and Drug Administration, Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. The following information submitted under the blood product listing requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

* * * * *

26. Section 607.39 is revised to read as follows:

§ 607.39 Misbranding by reference to establishment registration, validation of registration, or to registration number.

Registration of an establishment, validation of registration, or assignment of a registration number does not in any way denote approval of the firm or its products nor does it mean that the products may be legally marketed. Any representation that creates an impression of official approval because of establishment registration, validation of registration, or possession of a registration number is misleading and constitutes misbranding.

27. Section 607.40 is amended by revising paragraphs (a), (b), (c), the introductory text of (d), and (d)(3), and by adding new paragraphs (e) and (f) to read as follows:

§ 607.40 Establishment registration and blood product listing requirements for foreign blood product establishments.

(a) Every foreign blood product establishment must comply with the requirements for domestic blood product establishments in subpart B of this part, unless exempt under subpart D of this part.

(b) No blood product may be imported or offered for import into the United States unless it complies with the blood product listing requirements in subpart B of this part and is manufactured, prepared, propagated, compounded, or processed at a registered foreign establishment. Blood products imported or offered for import under the investigational use provisions of part 312 of this chapter are not subject to the requirements in subpart B of this part. All establishment registration and blood product listing information must be in the English language.

(c) Each foreign establishment required to register under paragraph (a) of this section must, as part of the establishment registration and blood product listing, submit the name and address of the establishment, the name of each

importer of the foreign establishment's blood products that is known to the establishment, the name of each person who imports or offers for import such blood products to the United States, and the name of the individual responsible for submitting establishment registration and blood product listing information. Any changes in this information must be reported to FDA at the intervals specified for updating establishment registration information in § 607.26.

(d) Each foreign establishment required to register under paragraph (a) of this section must submit the name, address, telephone and fax numbers, and e-mail address of its United States agent as part of its initial and updated registration information in accordance with subpart B of this part. Each foreign establishment must designate only one United States agent.

* * * * *

(3) The foreign establishment or the United States agent must report changes in the United States agent's name, address, telephone and fax numbers, and e-mail address to FDA within 30 calendar days of the change.

(e) Each foreign establishment required to register under paragraph (a) of this section must register and list blood products using the electronic registration and listing system, in accordance with § 607.22(a).

(f)(1) If the foreign establishment cannot submit the information electronically under § 607.40(e), the establishment may request a waiver. FDA may grant a waiver request if the foreign establishment does not have an e-mail address and access to a computer and an Internet service provider that can access the electronic registration and listing system.

(2) Waiver requests must include a telephone number and/or mailing address where the agency can contact the foreign establishment.

(3) If the agency grants the waiver request, the foreign establishment must register and list blood products in accordance with § 607.22(b) or (c).

28. Section 607.65 is amended by redesignating paragraph (f) as paragraph (g) and by adding new paragraph (f) to read as follows:

§ 607.65 Exemptions for blood product establishments.

* * * * *

(f) Persons who engage solely in the production of any plasma derivative, such as albumin, Immune Globulin, Factor VIII and Factor IX, bulk product substances such as fractionation intermediates or pastes, or recombinant versions of plasma derivatives or animal derived plasma derivatives. This paragraph does not exempt such persons from registration and listing under part 207 of this chapter.

* * * * *

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

29. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

30. Section 610.60 is amended by revising paragraph (a)(2) to read as follows:

§ 610.60 Container label.

(a) * * *

(2) The name, address, license number of the manufacturer, and the NDC number in accordance with part 207 of this chapter.

* * * * *

31. Section 610.61 is amended by revising paragraph (b) to read as follows:

§ 610.61 Package label.

* * * * *

(b) The name, address, license number of the manufacturer, and the NDC number in accordance with part 207 of this chapter.

* * * * *

PART 1271—HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

32. The authority citation for 21 CFR part 1271 continues to read as follows:

Authority: 42 U.S.C. 216, 243, 263a, 264, 271.

§ 1271.1 [Amended]

33. Section 1271.1 is amended in paragraphs (a) and (b)(2) by removing ''207.20(f)'' and by adding in its place ''207.9(c)(2)''.

34. Section 1271.3 is amended by adding paragraphs (mm) and (nn) to read as follows:

§ 1271.3 How does FDA define important terms in this part?

* * * * *

(mm) Importer means a company or individual in the United States that is the owner, consignee, or recipient of the foreign establishment's HCT/P that is imported into the United States.

(nn) United States agent means a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. This definition excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present.

§ 1271.20 [Amended]

35. Section 1271.20 is amended by removing ‘‘207.20(f)’’ and by adding in its place ‘‘207.9(c)(2)’’.

36. Section 1271.22 is added to read as follows:

§ 1271.22 How do I register and submit an HCT/P list?

(a) You must use the electronic registration and listing system at *http://www.fda.gov/cber/tissue/tisreg.htm* in accordance with § 1271.25 for:

(1) Establishment registration,

(2) HCT/P listings, and

(3) Updates of registration and HCT/P listing.

(b) FDA will periodically issue guidance on how to provide registration and listing information in electronic format (for example, method of transmission, media, file formats, preparation, and organization of files).

(c) You must provide the information under paragraph (a) of this section in accordance with part 11 of this chapter, except for the requirements in § 11.10(b), (c), and (e) and the corresponding requirements in § 11.30.

37. Section 1271.23 is added to part 1271 to read as follows:

§ 1271.23 How is a waiver from the electronic format requirements requested?

(a) You may request a waiver from the requirement in § 1271.22 that information must be provided to FDA in electronic format if you do not have an e-mail address and access to a computer and an Internet service provider that can access the Web-based FDA registration and listing database.

(b) Requests for a waiver must include a telephone number and/or mailing address where FDA can contact the person making the request.

(c) If FDA grants the request for a waiver, FDA will inform you how to submit your registration and/or listing information.

38. Section 1271.25 is amended by revising introductory paragraph (a), paragraphs (a)(2) and (a)(3), and by adding new paragraphs (a)(5), (a)(6), and (d) to read as follows:

§ 1271.25 What information is required for establishment registration and HCT/P listing?

(a) Your establishment registration must include:

* * * * *

(2) Each location, including the street address, telephone and fax numbers, email address, and the postal service zip code of the establishment;

(3) The name, address, telephone and fax numbers, e-mail address, and title of the reporting official;

* * * * *

(5) Each foreign establishment must also submit the name, 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 for purposes of importation; and

(6) Each foreign establishment must also submit the name, address, telephone and fax numbers, and e-mail address of its United States agent. Each foreign establishment must designate only one United States agent.

(i) The United States agent must reside or maintain a place of business in the United States.

(ii) Upon request from FDA, the United States agent must assist FDA in communications with the foreign establishment, respond to questions concerning the foreign establishment's products that are imported or offered for import into the United States, and assist FDA in scheduling inspections of the foreign establishment. If the agency is unable to contact the foreign establishment directly or expeditiously, FDA may provide information or

documents to the United States agent, and such an action must be considered to be equivalent to providing the same information or documents to the foreign establishment.

(iii) The foreign establishment or the United States agent must report changes in the United States agent's name, address, telephone and fax numbers, and e-mail address to FDA within 30 calendar days of the change.

* * * * *

(d) In addition, if your HCT/P is described under § 1271.20, you must submit the information required under part 207 of this chapter using the procedures under this subpart.

39. Section 1271.26 is revised to read as follows:

§ 1271.26 When must I amend my establishment registration?

If the ownership or location of your establishment changes, or if there is a change in the United States agent's name, address, telephone and fax numbers, and e-mail address, you must submit an amendment to registration within 30 calendar days of the change.

§ 1271.37 [Amended]

40. Section 1271.37 is amended in the introductory text of paragraph (a) by removing the phrase ''Form FDA 3356'' and adding in its place the phrase ''registration and listing information''.

Dated: August 22, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

BILLING CODE 4160–01–S