

DATE: September 1, 2006  
NOTE TO: FDA Dockets Management Branch  
DOCKET NO.: 2005N-0403  
SUBJECT: OMB Changes  
PUBLISHED: August 29, 2006

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The September 30, 1993, Executive Order 12866 (E.O.) --Regulatory Planning and Review sets forth the Administration's principles and requirements for the Federal regulatory process. Under section 6(a)(3)(E) of the E.O., for "significant regulatory actions," Federal agencies must make certain information available to the public after publication of the regulatory action in the Federal Register.

Pursuant to the E.O for significant regulatory actions, FDA has attached in this docket a copy of the rule showing the following information:

- 1) The draft regulatory action as submitted to the Office of Management and Budget's (OMB) Office of Information and Regulatory Affairs (OIRA) for review including any materials or assessments, required by the Executive Order, that accompanied the draft;
- 2) Substantive changes between the draft submitted to OIRA for review and the action subsequently published are shown by track change notations; and
- 3) Likewise, changes in the regulatory action that were made at the suggestion or recommendation of OIRA, are shown by track change notations.



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(HF-26)

Attachment(s)

2005N-0403

REF 1

OMB CHANGES

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].

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 number 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 detailed instructions on submitting comments and additional information on the rulemaking process, 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.

See section VII of this document for the address to which comments on the information collection requirements of this rule may be sent.

FOR FURTHER INFORMATION CONTACT:

For information concerning drugs regulated by the Center for Drug Evaluation and Research (CDER):

Herbert Gerstenzang or John W. Gardner,  
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5600 Fishers Lane,  
Rockville, MD 20857,  
301-827-8920,  
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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,  
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Rockville, MD 20852-1448,  
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[valerie.butler@fda.hhs.gov](mailto: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](mailto:lowell.fried@fda.hhs.gov) or [isabel.pocurull@fda.hhs.gov](mailto:isabel.pocurull@fda.hhs.gov).

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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;<sup>1</sup>
- 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;
- 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

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<sup>1</sup> "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).

- 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.<sup>2</sup> 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 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).

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<sup>2</sup> “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).

- 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.)

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- 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.<sup>3</sup>

Accordingly, we are proposing 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.

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<sup>3</sup> See footnote 1 of section 510 of the act.

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--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.

Proposed § 207.13(a) reorganizes and clarifies current § 207.10(a). It is generally consistent with current § 207.10(a), except as noted in the discussion below. Additional language has been added to proposed § 207.13(a)(1)(i) and (a)(1)(ii) to reflect the language in section 510(g)(1) of the act. 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)(1) 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--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).

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• 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

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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:

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- 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) 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

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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 801(d)(3) -- 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.

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The amendment to section 801(o) 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

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listing requirements -- either by virtue of importing into a foreign trade zone or by importing components under 801(d)(3) -- 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 801(d)(3) 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.

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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, 107th Cong. (2002), "Joint Explanatory Statement of the Committee of Conference," "Subtitle B--Protection of Drug Supply," (discussing section 322) (emphases added)). 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),<sup>4</sup> 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

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<sup>4</sup> 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.

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 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 (2) (21 CFR 202.1(l)(1) and (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.<sup>5</sup>

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<sup>5</sup> 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.

This proposed definition is consistent with how the term "content of labeling" is used in the final rule entitled "Requirements for Submission of 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.<sup>6</sup> 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 circular". We are

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<sup>6</sup> 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

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.

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- 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

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format the content of labeling required in 21 CFR parts 314 and 601.

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.

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All listing information required under the proposal is needed to identify the drug. 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.

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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 repackaging 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).

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## 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.1 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.

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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.

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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 repackers 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 (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	<ul style="list-style-type: none"> <li>○ Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ Drug's established name and proprietary name (if any)</li> <li>○ Package size and type</li> <li>○ Drug Master File number or Veterinary Master File number, if any, assigned to the active pharmaceutical ingredient</li> </ul>
§ 207.33(c)(2) (Manufacturer)	Drug other than an active pharmaceutical ingredient	<ul style="list-style-type: none"> <li>○ Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ Drug's established name and proprietary name (if any)</li> <li>○ Name and quantity of each active pharmaceutical ingredient or the approved U.S. application number</li> <li>○ 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</li> <li>○ Dosage form</li> <li>○ Package size and type, including immediate unit-of-use container</li> <li>○ Marketing status (e.g., prescription or OTC)</li> <li>○ Drug or drug product type (human drug or animal drug)</li> <li>○ Imprinting information</li> </ul>
§ 207.33(c)(3) (Manufacturer)	Active pharmaceutical ingredient for a private label distributor	<ul style="list-style-type: none"> <li>○ Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ Drug's established name and proprietary name (if any)</li> <li>○ Package size and type</li> <li>○ Drug Master File number or Veterinary Master File number, if any, assigned to the active pharmaceutical ingredient</li> <li>○ Private label distributor's name, address, telephone number, fax number, e-mail address, labeler code</li> <li>○ Drug's proprietary name (if any) as assigned by the private label distributor</li> </ul>

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)(3) (Manufacturer)	Drug other than an active pharmaceutical ingredient for a private label distributor	<ul style="list-style-type: none"> <li>○ Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ Drug's established name and proprietary name (if any)</li> <li>○ Name and quantity of each active pharmaceutical ingredient or the approved U.S. application number</li> <li>○ 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</li> <li>○ Dosage form</li> <li>○ Package size and type, including immediate unit-of-use container</li> <li>○ Marketing status (e.g., prescription or OTC)</li> <li>○ Drug or drug product type (human drug or animal drug)</li> <li>○ Imprinting information</li> <li>○ Private label distributor's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ Drug's proprietary name (if any) as assigned by the private label distributor</li> </ul>
§ 207.33(d)(1) (Repacker or relabeler)	Drug that is repacked or relabeled	<ul style="list-style-type: none"> <li>○ Repacker's or relabeler's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ NDC number assigned to the drug immediately before its receipt by the repacker or relabeler</li> <li>○ Type of operation performed for the drug (repacking or relabeling)</li> <li>○ Drug's established name and proprietary name (if any)</li> <li>○ Package size and type, including immediate unit-of-use container, if any (required for repackers only)</li> </ul>
§ 207.33 (d)(2) (Repacker or relabeler)	Drug that is repacked or relabeled for a private label distributor	<ul style="list-style-type: none"> <li>○ Repacker's or relabeler's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ NDC number assigned to the drug immediately before its receipt by the repacker or relabeler</li> <li>○ Type of operation performed for the drug (repacking or relabeling)</li> <li>○ Drug's established name and proprietary name (if any)</li> <li>○ Package size and type, including immediate unit-of-use container, if any (required for repackers only)</li> <li>○ Private label distributor's name, address, telephone number, fax number, e-mail address, and labeler code</li> <li>○ Drug's proprietary name (if any) assigned by the private label distributor</li> </ul>

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.